Serotonin

Edited by Ying Qu

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Meet the editor

Dr. Ying Qu is a multi-disciplinary scientist, currently working in Leulan Bioscience, USA. She received her BS and MS in Chemistry from Lanzhou University, China and her PhD in Neuroscience from the Catholic University of Leuven, Belgium. Dr. Qu has spent part of her career at the National Institutes of Health, USA, studying depression mechanisms underlying serotonin post-receptor regulated signaling transduction. She is also involved in a drug discovery program at Johnson and Johnson in the USA developing novel dual-acting antidepressants with selective serotonin reuptake inhibitors. In 2002, she received a Sevier Young Investigator Award from the Serotonin Club at the International Union of Basic and Clinical Pharmacology (IUPHAR) Satellite Meeting on Serotonin. She has published over 30 peer-reviewed papers, 40 abstracts and two book chapters in the fields of neuropsychopharmacology and bioanalysis.

Contents

Preface

Serotonin is a monoamine neurotransmitter in the central nervous system (CNS), whose well-known biological functions include modulating cognition, sleep, emotion, learning, memory, and numerous physiological processes.

At any given time, over 4% of the global population suffers from a major depressive disorder. Among approved depression treatments are selective serotonin reuptake inhibitors (SSRIs). These are based on the serotonin hypothesis, which holds that low levels of extracellular serotonin causes depression; consequently, increasing extracellular serotonin can treat depression. Since the introduction of SSRIs, many books about serotonin have been published.

I started my neuroscience career by measuring serotonin in the brain of different animals during my PhD study. Later on, I became involved in depression mechanisms research and drug discovery. This scientific journey brought me from Lanzhou in China, Leuven in Belgium, Bethesda in the USA, all the way to San Diego.

Sometimes I pick up an assortment of scattered seashells while walking along the beautiful Torrey Pines Beach in San Diego. Likewise, this book contains an assortment of discussions of different aspects of serotonin to enrich our knowledge and understanding of this neurochemical.

Ying Qu, PhD
Leulan Bioscience,
San Diego, CA

Introductory Chapter: From Measuring Serotonin Neurotransmission to Evaluating Serotonin Post-Receptor Signaling Transduction

Ying Qu

1. Introduction

Serotonin or 5-hydroxytryptamine (5-HT) is a well-established monoamine neurotransmitter in the central nervous system (CNS). The discovery of 5-HT dates as far back as 1868 and can be traced to its presence in the blood and in the gastrointestinal tract [1]. Its well-known biological functions include modulating cognition, sleep, emotion, learning, memory, and numerous physiological processes. 5-HT is primarily found in the enteric nervous system located in the gastrointestinal tract [2], where it
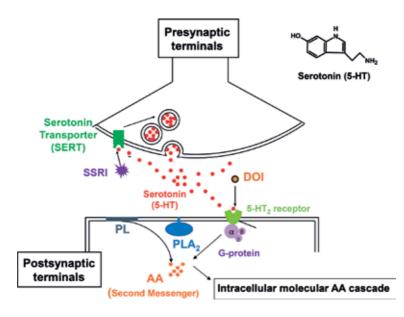
Figure 1.
Model explaining PLA_2 activation in response to serotonergic drugs. Under normal conditions, the 5-HT that is released from presynaptic vesicles into the synaptic cleft binds to postsynaptic 5-HT receptors coupled via a G-protein to PLA_2, thus hydrolyzing arachidonic acid (AA) from membrane phospholipids (PL). Administration serotonergic drugs activate PLA and increase incorporation of AA by different routes. (1) $5\text{-}HT_{2A/2C}$ agonist, DOI directly binds to $5\text{-}HT_2$ receptors to activate this signal; (2) fluoxetine (SSRI) inhibits 5-HT uptake, thus increasing 5-HT in the synaptic cleft so as to increase PLA activation and AA release. This figure adapted from [23].

regulates intestinal movements [2], and the remainder is synthesized in the serotonergic neurons of the CNS, where it has various functions such as the regulation of mood, appetite, and sleep. Modulation of 5-HT at synapses is thought to be a major action of several classes of pharmacological antidepressants. Among these, selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine and citalopram, are the most important class of antidepressant in the treatment of major depressive disorder (MDD) and anxiety disorders [3]. The exact mechanism of action of SSRIs is not fully revealed. SSRIs are able to increase the extracellular level of the neurotransmitter 5-HT by inhibiting its reuptake into the presynaptic terminal, increasing the level of 5-HT in the synaptic cleft available to bind to the postsynaptic 5-HT receptor (as shown in **Figure 1**). SSRIs have different degrees of selectivity for the other monoamine transporters, and the most selective SSRI has weak affinity for the norepinephrine and dopamine transporters. They are the most widely prescribed antidepressants in many countries, and their efficacy in mild or moderate cases of depression has been disputed [4] and may be outweighed by side effects [3]. I have been involved in 5-HT research for two decades. This chapter summarized my research on 5-HT-related projects from measuring 5-HT concentration, attempting to discover a new generation of SSRIs to investigate 5-HT-regulated post-receptor signaling transduction. This chapter also discusses some perspectives research that is important for SSRI and depression treatment.

2. Measuring serotonin in CNS system

In the early 1990s, liquid chromatography (LC) with an electrochemical detector (ED) had been widely used for the measurement of neurochemicals [5]. The first 5-HT project that I worked with was to develop a method for measuring 5-HT concentration in chicken brain tissue [6]. An isocratic LC-ED for the determination of L-3,4-dihydroxyphenylalanine, dopamine, norepinephrine, epinephrine, 5-HT, and their major metabolites, 3,4-dihydroxyphenylacetic acid, 4-hydroxy-3-methoxyphenylacetic acid, and 5-hydroxyindole-3-acetic acid in chicken brain tissue was developed in our lab. The method was applied to study the influence of food restriction on the concentration of 5-HT and other monoamine neurotransmitters in different brain areas, known to be involved in the feeding and reproductive behavior of female broiler chickens. In the experiment, two to six micropunches from 20 different brain areas on 300 μm cryostat brain section were punched out and expelled into Eppendorf for homogenization and extraction. Supernatant was injected onto LC-ED, and over 1000 micro-punched tissue samples from ad libitum fed and food-restricted female broiler chickens were analyzed. Tissue pellets were dissolved in PBS buffer for protein content determination to express the results as pg monoamine/μg protein. Although the concentration of monoamines in the brain is not high, multiple tissue micropunches made enough amount of monoamine and 5-HT to match the sensitivity of the assay. Our results provided a possible role for catecholamines and indolamines in the altered feeding and reproductive behavior of the broiler chicken [6]. To finish my Ph.D. thesis, I modified this method to measure 5-HT and other monoamine neurotransmitters in cat visual cortex [7]. The role of monoaminergic neuromodulators in the reorganization of cortical topography following limited sensory deprivation in the adult cat was investigated in this study [8]. The total concentrations of dopamine, noradrenaline, 5-HT, and their major metabolites were measured in the visual cortex of both control and experimental animals using this microbore LC-ED method. The sensory deprivation cats were subjected to a binocular retinal lesion corresponding to the central 10 degrees of vision and sacrificed 2 weeks post-lesion. The deprivation was confirmed in area 17 by measuring immediate-early gene if-268 messenger RNA expression. The total concentration

of 5-HT was significantly lower in the deprived cortex, and the metabolite of 5-HT, 5-hydroxyindole-3-acetic acid, was significantly higher in the nondeprived cortex than in deprived cortex and normal cortex. The levels of noradrenaline and dopamine were significantly higher in the nondeprived cortex of retinal lesion cats than in the deprived cortex of retinal lesion cats and the cortex of normal animals. This pattern follows the release of the excitatory neurotransmitter glutamate under the same conditions. These results suggest that the modulation of 5-HT, noradrenaline, and dopamine is regulated by visual afferent activity [8].

To switch my scientific career to the pharmaceutical industry, I joined the CNS drug discovery team for making a new generation dual function SSRI [9] for depression treatment. Fluoxetine (Prozac) [10] is the first SSRI and widely used for the treatment of depression which was used as reference compounds for new SSRI discovery. Fluoxetine exerts its behavioral and clinical therapeutic effect by blocking the transport of 5-HT at the serotonin reuptake transporter (SERT), thereby increasing extracellular level of 5-HT in the serotonergic synaptic cleft of many brain regions as shown in **Figure 1**. In vivo microdialysis has been extensively used to document the changes of extracellular level of 5-HT in the rat brain after administration of fluoxetine [11]. Therefore, we designed a 21-hour in vivo microdialysis experiment and the effect of acute systemic administration of fluoxetine (3 and 10 mg/kg s.c.) on extracellular level of 5-HT in the frontal cortex of freely moving rats was analyzed by LC with ESA CoulArray coulometric detector (an electrochemical detector) [9, 12]. In this experiment, the guide cannula was implanted on rats' brain by surgery and secured in place with skull screws and dental cement. Animals were allowed at least 3 days to recover from surgery prior to experimentation. Dialysis probes were perfused with artificial cerebral spinal fluid (aCSF, 47 mM NaCl, 4 mM KCl, 0.85 mM $MgCl_2$, 2.3 mM $CaCl_2$, pH 7.4) at a flow rate of 1 μL/min. Samples were collected every 60 min. Microdialysates were analyzed by LC-ED. Separation was performed on a C18 column. All values for microdialysis studies were calculated as percentage change at each time point compared with the average of three baseline values. Due to the limitation of low recovery of microdialysis probe (less than 20% in average) and low concentration of 5-HT in the frontal cortex of rat brain (about 100 fg/μL in this microdialysates), high sensitivity analytical tool is required. LC-ED was the most popular method to measure 5-HT. In recent years, liquid chromatography with tandem mass spectrometry (LC-MS/MS) was also used for this purpose [13].

Pharmacokinetic (PK) characterization and in vivo pharmacological properties of new chemical entities are important components during lead compound selection and optimization in the drug discovery process. Accordingly, reliable techniques are needed that can generate the requisite pharmacokinetic/pharmacodynamic (PK/PD) information for an increased number of compounds. When dealing with compounds targeting the central nervous system (CNS), biophase PK may differ significantly from plasma PK, because blood-brain barrier (BBB) transport and brain distribution often do not occur instantaneously and to a full extent. In vivo microdialysis technique can be used to collect not only the extracellular endogenous substances but also the extracellular free drug in the same local interstitial environment, which may reflect the amount of drug available at the pharmacological target. However, the application of this technique was highly limited by the lack of the proper sensitive analytical methods to determine the endogenous substance and exogenous drug. LC-MS/MS technique improvement provides a direct, structural-specific measurement of individual components with very high sensitivity. The mass spectrometer has minimal baseline drift and can be equilibrated very rapidly. For this purpose, we have developed a series of LC-MS/MS methods, which enable us to monitor drug, citalopram, and 5-HT in the same

microdialysis samples [13]. These applications demonstrated in vivo microdialysis coupled with LC-MS/MS is a very important tool to evaluate the PK/PD relationship by comparing the time course of free drug versus biomarker. LC-MS/MS method measuring 5-HT concentration in the brain is possible, but not widely applied [13].

3. Evaluating PK/PD profile of the dual function SSRI

The World Health Organization (WHO) estimates that more than 300 million individuals of all ages suffer from depression [14]. SSRIs have been the drugs for depression treatment. These drugs increase 5-HT levels in the synaptic cleft by inhibiting its reuptake into the presynaptic neuron through blockade of the SERT. Although many patients experience relief after treatment with one of the many marketed SSRIs, efficacy is noticeable only after weeks of treatment. Many physicians are reported to co-prescribe stimulants with SSRI to provide subjective relief during the beginning weeks of antidepressant therapy [15]. Most of these stimulants are increased dopamine release and produced robust behavioral activation, which had the risk of allowing patients to act on their suicidal ideation. It is very important to choose other classes of molecules that have been shown to produce wakefulness in animals without releasing dopamine or producing behavioral activation. Wake-promoting agents such as modafinil are used in the clinic as adjuncts to antidepressant therapy in order to alleviate lethargy. Histamine H_3 receptor antagonist has been demonstrated having the wake-promoting action in numerous animal studies and may therefore be a viable strategy for use as an antidepressant therapy in conjunction with SSRIs. Therefore, some potential antidepressant molecules were created, which combined the wake-promoting effect of a histamine H_3 receptor antagonist with 5-HT reuptake blockage effects of SERT inhibitor [9]. The synthetic approach and structure-activity relationships associated with this effort have been studied [16–18]. In vivo microdialysis experiments were used to examine whether a compound was capable of inducing a robust and persistent increase in 5-HT level over baseline. One of these molecules, JNJ-28583867 (2-methyl-4-(4-methylsulfanyl-phenyl)-7-(3-morpholin-4-yl-propoxy)-1,2,3,4-tetrahydro-isoquinoline), is a selective and potent histamine H_3 receptor antagonist (Ki = 10.6 nM) and inhibitor of the SERT (Ki = 3.7 nM), with 30-fold selectivity for SERT over the dopamine and norepinephrine transporters [9]. After subcutaneous administration, JNJ-28583867 significantly increased cortical extracellular levels of 5-HT as shown in **Figure 2A**. Baseline measurements of 5-HT levels were performed for 4 h prior to administration of JNJ-28583867. At all doses, 5-HT levels remained elevated for the duration of the experiment up to 18 h after dosing. JNJ-28583867 was also tested in a classical test of antidepressant activity, the mouse tail suspension model. As was expected based on the neurochemical profile of JNJ-28583867, an increase in struggling time was observed. Some PK characterization of JNJ-28583867 was carried out in the rat. The behavioral experiments had indicated good oral bioavailability and this was confirmed. The half-life correlates well with the observation that effects could be observed up to 24 h after a single oral dose, as was the case in the head twitch test. The plasma and brain levels of JNJ-28583867 are sustained and correlated reasonably well with efficacy for an extended period of time as shown in **Figure 2B** [9]. Similar PK/PD profiles were observed from norfluoxetine, which is the metabolite of reference SSRI, fluoxetine [12]. Norfluoxetine is the most important active metabolite of the widely used antidepressant fluoxetine. Following subcutaneous administration of fluoxetine in rats, plasma, and brain PK of fluoxetine and norfluoxetine were monitored, respectively, by LC-MS/MS. The extracellular level of 5-HT in the frontal cortex was measured by microdialysis as a PD endpoint. Norfluoxetine when directly
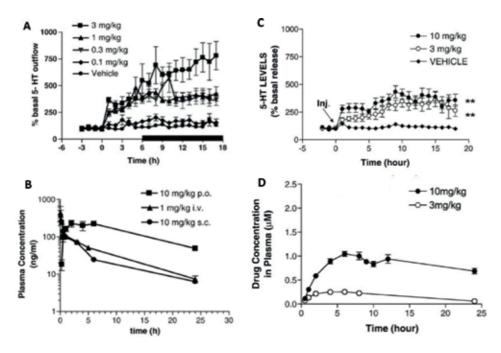
Figure 2.
*(A). Effect of JNJ-28583867, administered s.c., on extracellular 5-HT levels in the frontal cortex of male Sprague-Dawley rats. Microdialysis time course. Results are expressed as the average ± S.E.M. of n = 3–6 rats per group. (B). Plasma levels of JNJ-28583867 after oral (10 mg/kg, square), intravenous (1 mg/kg, triangle), and subcutaneous (10 mg/kg, circle) administration to the rat. Results are shown as the average ± S.D. of n = 2–3 samples. (C). Effect of norfluoxetine on the extracellular level of 5-HT in the frontal cortex of free moving rat. Values are mean ± S.E.M. of extracellular 5-HT levels and expressed as a percentage of the average of three baseline samples (defined as 100%). Two-way ANOVA-post-hoc Duncan's multiple range tests were used for comparison. Control (n = 5), 3 mg/kg (n = 6), and 10 mg/kg (n = 6) norfluoxetine were subcutaneously administrated. Asterisks indicate significance of overall effect of drug treatment versus vehicle, P < 0.01. (D). Time course of plasma concentrations of fluoxetine and norfluoxetine. Plasma concentrations (mean ± S.E., n = 10) of norfluoxetine were measured following subcutaneous administration of 3 or 10 mg/kg fluoxetine. **Figure 4A** and **B** was adapted from [9]; **Figure 4C** and **D** was adapted from [12].*

administered to rats caused a significant increase in the extracellular level of 5-HT in the frontal cortex and maintained for 18 hours as shown in **Figure 2C**. This result is correlated well with higher plasma and brain concentration and longer plasma and brain retention time of norfluoxetine (as shown in **Figure 2D**) [12]. In summary, these studies have shown that the combination of histamine H_3 receptor antagonism with SSRI activity in a single molecule results in a pharmacology consistent with the combination of either class of molecule alone. JNJ-28583867 can be a prototype of such a compound to improve current SSRI efficacy and safety profiles [9].

4. Serotonin-mediated post-receptor signaling transduction

Although antidepressants are generally effective in the treatment of MDD, side effects still exist. Serotonin syndrome is a potentially life-threatening adverse drug reaction that results from therapeutic drug use and a predictable consequence of excess serotonergic agonism of CNS and peripheral serotonergic receptors [19]. In 2002, the Toxic Exposure Surveillance System, which receives case descriptions from office-based practices, inpatients settings, and emergency department, reported 26,733 incidences of exposure to SSRIs that caused significant toxic effects in 7349 persons and resulted in 93 deaths [19, 20]. The development mechanism of serotonin syndrome is unknown. It is hypothesized that the level of 5-HT elevation

in blood plasma has to be 10–15% above the baseline levels to result in 5-HT toxicity [21]. Several lines of evidence converge to suggest that agonism of 5-HT$_{2A}$ receptors contributes substantially to the condition [22].

To address this question, we studied 5-HT-mediated post-receptor signaling transduction [23]. The 5-HT$_2$ receptor is G protein-coupled receptor and is recognized to be coupled to the phospholipase A$_2$ (PLA$_2$) signaling pathway, stimulating the release of the second messenger, arachidonic acid (AA). This signaling pathway is illustrated in **Figure 1**. PLA$_2$ activation can be initiated by serotonergic 5-HT$_2$ receptors via a G-protein. The in vivo fatty acid methods were developed in our lab to measure regional brain incorporation of a radiolabeled fatty acid, including [5,6,8,9,11,12,14,15-^{3}H] arachidonic acid (^{3}H-AA) in conscious rats. Tracer incorporation, represented as the incorporation coefficient k*, reflects PLA$_2$-mediated AA release. Activation of PLA$_2$ in the brain is revealed as increments in k* in different receptors or to change serotonergic neurotransmission (**Figure 1**). The fatty acid method can be used to evaluate serotonergic neurotransmission mediated by PLA$_2$ in awake rats. It can quantify and localize brain PLA$_2$ signaling in response to different drugs administered acutely or chronically.

In rats, 2,5-dimethoxy-4-iodophenyl-2-aminopropane (DOI), which is a 5-HT$_{2A/2C}$ receptor agonist, provokes head twitches, skin jerks, and forepaw tapping, behaviors that are considered part of a "5-HT syndrome" [24]. The responses usually appear at a dose of 1.0 mg/kg and peak at 2.5 mg/kg. In one of our studies, DOI, when administered to unanesthetized rats, produced widespread and significant increases, of the order of 60%, in k* for arachidonate, particularly in neocortical brain regions reported to have high densities of 5-HT$_{2A}$ receptors [25]. The increases could be entirely blocked by chronic pretreatment with mianserin, a 5-HT$_2$ receptor antagonist, which is an atypical antidepressant [25]. The results suggest that the 5-HT$_2$ syndrome involves widespread brain activation of PLA$_2$ via 5-HT$_{2A}$ receptors, leading to the release of the second messenger, arachidonic acid. Chronic mianserin, a 5-HT$_2$ antagonist, prevents this activation [25]. In another study, brain PLA$_2$-mediated signal transduction in response to acute fluoxetine administration in unanesthetized rats had been imaged [26]. By inhibiting presynaptic 5-HT reuptake, fluoxetine is thought to act by increasing 5-HT in the synaptic cleft, thus 5-HT binding to postsynaptic 5-HT$_{2A/2C}$ receptors, activates PLA$_2$ pathway, and releases the second messenger AA from synaptic membrane phospholipids. To image this activation, fluoxetine (10 mg/kg) or saline vehicle was administered i.p. to unanesthetized rats, and regional brain incorporation coefficients k* of intravenously injected radiolabeled AA were measured after 30 min. Compared with vehicle, fluoxetine significantly increased k* in prefrontal, motor, somatosensory, and olfactory cortex, as well as in the basal ganglia, hippocampus, and thalamus. Many of these regions demonstrate high densities of the SERT and of 5-HT$_{2A/2C}$ receptors. The brain stem, spinal cord, and cerebellum, which showed no significant response to fluoxetine, have low densities of the transporters and receptors. The results show that it is possible to image quantitatively PLA$_2$-mediated signal transduction in vivo in response to fluoxetine [26]. Fluoxetine's therapeutic action when chronically administered has been ascribed to desensitization of pre-synaptic 5-HT$_{1A}$ and 5-HT$_{1B}$ auto-receptors, further augmenting extracellular 5-HT [27]. We thereby conducted a study to see if this signaling process in rat brain would be altered by chronic administration of fluoxetine followed by 3 days of washout of this SSRI [28]. [^{3}H] AA was intravenously injected in unanesthetized rats and used quantitative autoradiography to determine the incorporation coefficient k* for AA (regional brain radioactivity/integrated plasma radioactivity), a marker of PLA$_2$ activation, in each of 86 brain regions. k* was measured following acute i.p. saline or DOI (1.0 mg/kg i.p.), in rats injected for 21 days with 10 mg/kg i.p. fluoxetine or saline daily, followed by 3 days without injection. As shown in **Figure 3**,

acute DOI produced statistically significant increments in k* in brain regions with high densities of 5-HT$_{2A/2C}$ receptors, but the increments did not differ significantly between the chronic fluoxetine- and saline-treated rats. Additionally, chronic fluoxetine is compared with saline widely and significantly increased baseline values of k*. These results suggest that 5-HT$_{2A/2C}$ receptor-initiated AA signaling is unaffected by chronic fluoxetine plus 3 days of washout in the rat, but that baseline AA signaling is nevertheless upregulated. This upregulation likely occurs because of significant active drug in the brain, considering the long brain half-lives of its metabolite, norfluoxetine [12]. To further understand SERT regulate brain serotonergic transmission and its mediated signaling transduction, we measured PLA$_2$ activation in SERT knockout mice (SERT−/−) and their littermate controls (SERT+/+). Following administration of 1.5 mg/kg s.c. DOI to unanesthetized mice injected intravenously with radiolabeled AA, PLA$_2$ activation, represented as the regional incorporation coefficient k* of AA, was determined with quantitative autoradiography in each of 71 brain regions. As shown in **Figure 4**, in SERT+/+ mice, DOI significantly increased k* in 27 regions known to have 5-HT$_{2A/2C}$ receptors, including the frontal, motor, somatosensory, pyriform and cingulate cortex, white matter, nucleus accumbens, caudate putamen, septum, CA1 of the hippocampus, thalamus, and hypothalamus. In contrast, DOI did not increase k* significantly in any brain region of SERT−/− mice. Head twitches following DOI, which also were measured, were robust in SERT+/+ mice but were markedly attenuated in SERT−/− mice. These results show that a lifelong elevation of the synaptic 5-HT concentration in SERT−/− mice leads to downregulation of 5-HT$_{2A/2C}$ receptor-mediated PLA$_2$ signaling via AA and of head twitches, in response to DOI. Compared with wild-type mice, DOI-induced k* increments were reduced in
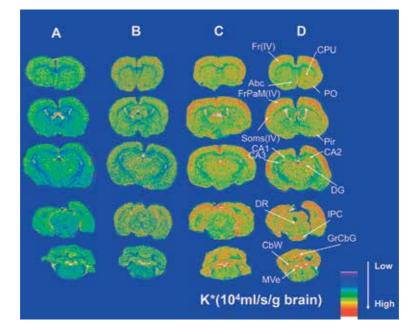
Figure 3.
Coronal autoradiographs demonstrating arachidonic acid incorporation coefficients k. Brain of (A) control rat given acute saline 3 days after receiving i.p. saline for 21 days; (B) control rat given acute DOI (1.0 mg/kg i.p.), 3 days after receiving i.p. saline for 21 days; (C) rat given fluoxetine (10 mg/kg i.p. daily) for 21 days, followed by 3 day washout, and then i.p. Saline on day 24; (D) rat given fluoxetine (10 mg/kg i.p. daily) for 21 days, followed by 3 day washout, and then acute DOI (1.0 mg/kg i.p.). k is color-coded. Abbreviations: Fr (IV), frontal cortex, layer IV; FrPaM (IV), frontal motor (layer IV); Soms, somatosensory cortex; IPC, interpeduncular nucleus; CPU, caudate putamen; CA1, CA2, CA3, DG, regions of the hippocampus; Pir, pyriform cortex; PO, olfactory cortex; GrCbG, granular layer, cerebellar gray; CbW, cerebellar white; DR, dorsal raphe; MVe, medial vestibular nucleus; Abc, nucleus accumbens. This figure adapted from [28].
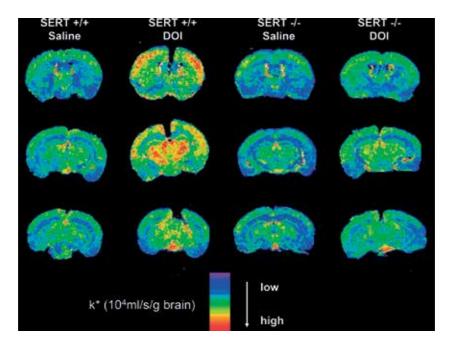
Figure 4.
Coronal autoradiographs demonstrating incorporation coefficients k* for arachidonic acid, from brain of SERT+/+ mouse given saline s.c.; SERT +/+ mouse given DOI (1.5 mg/kg s.c.); SERT−/− mouse given saline; SERT+/+ mouse given DOI. k* is color coded. This figure adapted from [29].

SERT knock out mice [29], but there was no significant effect of 3 weeks of fluoxetine plus washout on DOI-induced k* increments in compared with baseline of chronic fluoxetine treated rats. The difference suggests that a life-long, but not a 3-week, elevation of synaptic 5-HT will downregulate 5-HT$_{2A/2C}$ receptor signaling involving PLA$_2$.

In summary, these studies suggest that labeled AA can be used to examine in vivo brain PLA$_2$ signaling initiated by a serotonergic drug. Eventually, brain 5-HT$_{2A/2C}$-mediated signaling coupled to PLA$_2$ might be imaged in such subjects with positron emission tomography [30].

5. Monitoring therapeutic SSRI in patients

Depression is among the most prevalent psychiatric disorders with a highly variable treatment response and up to one-third of patients not achieving response [31]. SSRIs are the most commonly prescribed antidepressants and the best overall treatments for depression patients. However, therapeutic outcomes of SSRIs are often far from satisfactory for both patients and prescribing physicians [32]. Therefore, after having focused clinical research on the development of new drugs, growing evidence suggests that an improved application of available drug may still bring substantial benefit to patients [33, 34]. Moreover, there is a gap between the available pharmacological knowledge and its utilization in health care. The newest initiative to bridge this gap is "Precision Medicine." It considers individual variability to build the evidence base needed to guide clinical practice [35]. Therapeutic drug monitoring (TDM) is a patient management tool for precision medicine [36]. It enables tailoring the dosage of the medications to the individual patient by combining the quantification of drug concentration in blood, information on drug properties, and patient characteristics [37]. Because patients differ in their ability

to absorb, distribute, metabolize, and excrete drug due to concurrent disease, age, concomitant medication or genetic abnormalities, the drug's steady-state concentration in the body may have a more than 20-fold interindividual variation when the same dose of drug is administrated [38, 39]. TDM quantifies the drug's concentration in plasma or serum to adjust the dosage of individual patients, which increases probability of response and decreases risk of adverse drug reactions/toxicity [40, 41]. Moreover, TDM has the potential to enhance the cost-effectiveness of antidepressant therapy [42–44]. The benefits of TDM for optimization of pharmacotherapy, however, can only be obtained when the method is adequately integrated into the clinical treatment process. Current TDM use in depression care is often suboptimal as demonstrated by systematic studies [45–47]. The suboptimal use of TDM wastes laboratory resources and bears the risk of misleading results that will adversely influence clinical decision making. Studies on TDM for antidepressant will further specify the information on the imperfect use of TDM [48].

Among SSRIs, citalopram is the most SSRI [13], and some studies reported that it is more effective and better tolerated than other drugs for depression but has been associated with suicidality and worsening depression especially in adolescents and young adults [49]. Citalopram is strongly recommended for TDM by the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie (AFNP) guidelines and was recently upgraded into the level 1 recommendation drug [37, 50]. Its reported therapeutic reference ranges (50–110 ng/mL) are established and have been quantified. Controlled clinical trials have known beneficial effects of TDM, reports on decreased tolerability or intoxications [50]. Fluoxetine strongly inhibits 5-HT uptake with minimal effects on other neurotransmitter uptake system [51]. Norfluoxetine, an active metabolite of fluoxetine, contributes to the long elimination half-life (3-15 days) and overall clinical effect of fluoxetine [12]. TDM of fluoxetine is listed as "useful" AFNP guidelines [37, 50]. The therapeutic reference range of 120–500 ng/mL includes the quantification of fluoxetine and its long-lasting active metabolite, norfluoxetine. The total concentration of fluoxetine and norfluoxetine in plasma is needed to be determined. Thus, there is a clinical demand for the detection of fluoxetine and norfluoxetine when patients are receiving fluoxetine. The clinical service for TDM of antidepressants needs to be established.

Acknowledgements

Author details

Ying Qu
Leulan Bioscience, San Diego, California, USA

*Address all correspondence to: yingqu68@gmail.com

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Serotonin Reuptake Inhibitors and Their Role in Chronic Pain Management

Adela Hilda Onuțu, Dan Sebastian Dîrzu
and Cristina Petrișor

Abstract

Serotonin has a particular place in the modulation of pain. Experimental studies have described 5-HT1–7 receptors and their effects on facilitation or inhibition of nociceptive input. Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors showed efficient and safer than tricyclic anti-depressants in neuropathic pain. Although there is evidence regarding the beneficial impact of SSRIs in the multimodal acute pain management, studies are still searching for the potentially favorable effect of these drugs in the prevention of chronic postoperative pain. The scope of this chapter would be to update the knowledge regarding serotonin involving in pain pathways and to highlight the importance and contribution of serotonin reuptake inhibitors in the multimodal pain management schemes.

Keywords: serotonin, pain, SSRIs, SNRIs, pain management

1. Introduction

Chronic pain is recognized today as a disease [1], affects almost 20% of the population [2], and represents a significant cause of disability bringing along high secondary social costs. The management of chronic pain involves pharmacological and interventional tools and become a priority for healthcare systems. This chapter aims to summarize the role of serotonin reuptake inhibitors (SRI) in the treatment of chronic pain. SRI includes selective serotonin reuptake inhibitors (SSRI) and serotonin-norepinephrine reuptake inhibitors (SNRI).

2. Chronic pain conditions

Defined as the pain that lasts more than 3 months, frequent after the disappearance of the causal factor, chronic pain shows numerous risk factors (socio-demographic, biological, clinical, and psychological). Thus, most affected are females, older people, and people with low socio-economic level. A significant risk for developing chronic pain is the pain itself (acute and chronic at other sites), and also are incriminated the geographical background, occupational factors, and the history of abuse and violence. Neuroimaging studies have already proved the changes in the

brain with severe pain, reversible with proper treatment, and also suggested its importance for preventing the chronicization of pain [3]. The treatment of chronic pain is multi/interdisciplinary and multimodal, targeting different mechanisms of pain. We summarized some critical pain syndromes, which benefit from the SRI medication.

2.1 Diabetic neuropathy

Diabetes mellitus affects billions of people worldwide. The painful diabetic neuropathy (PDPN) occurs in 20% of diabetes patients during the disease. Risk factors include age, hypertension, obesity, alcohol abuse, and smoking.

Pathogenesis implies endoneurial microangiopathy and axonal loss, especially in sensory nerves. Aldose reductase activation by increasing polyol flux and the deposition of advanced glycated end-products are the primary determinants of PDPN. Secondary ischemia leads to enhanced oxidative stress and high production of free radicals, which leads to nerve damage [4].

Clinical PDPN may present as burning, stabbing, dull and aching, or sharp pain. In some instances, allodynia (painful response to a normally non-noxious stimulus) might accompany pain. PDPN is symptomatic mainly in the lower limbs and progresses proximally. Patients with PDPN show skin changes and loss of sensory that could lead further to diabetic ulcers.

The medication of painful diabetic neuropathy includes duloxetine, venlafaxine, tricyclic antidepressants (TAD), oxcarbazepine, and tapentadol. Overall, the quality of life in patients with PDPN is poor [5].

2.2 Fibromyalgia

Fibromyalgia (FM) is a syndrome composed of widespread chronic pain, muscle fatigue, and functional symptoms. It shows a genetic predisposition, but environmental factors play a prominent place during the disease. FM pathogenesis involves modified inflammatory response and oxidative stress [6].

Diagnosis is difficult because of the variety of clinical symptoms—75% of these patients do not meet the inclusion criteria, thus often they lack the diagnosis. Besides, these patients develop sleep disturbances and sexual dysfunction, altering further the quality of life.

The current evidence suggest for FM management antidepressants, cardiovascular exercise, and cognitive behavioral therapy [7]. Meta-analysis results agree that the medication approved by FDA—milnacipran—and duloxetine are effective in FM while there are concerns that the results showed only a moderate effect on pain and sleep, and no impact on fatigue [8].

2.3 Tension-type headache

Tension-type headache (TTH) is a typical headache (up to 78%), caused by the contractions of muscles of the scalp, neck, and jaw, and triggered mainly by stress and emotional conflicts. It is described as a moderate pressure applied to the frontal area, around the head or neck, and according to its frequency is classified as infrequent, frequent, and chronic.

Chronic TTH results as a consequence of sensitization of the pain pathway due to persistent pericranial myofascial nociceptive input. This TTH shows a frequency of at least 15 days/month for at least 3 months. If nausea and vomiting are present, exclude the diagnosis of TTH. Photophobia may occur in TTH.

Treatment of the acute episodes of TTH includes nonsteroidal anti-inflammatory drugs and acetaminophen, while their prevention associates pharmacologic and non-pharmacologic (physical and psychologic therapy) interventions. Tricyclic antidepressants (amitriptyline) are the most studied drugs in TTH, but new studies showed efficacy for other antidepressants including SRI—citalopram, sertraline, venlafaxine, and paroxetine [9].

2.4 Somatoform pain

Somatoform pain (SP) is the primary symptom in an ambiguous and unclarified category called somatization spectrum disorders (SSD), defined as the displaying of somatic complaints as a result of social stress. It shows a growing incidence (up to 60%) and is a symptom generally unexplained by the medical condition of these patients (which must be ruled out). The symptomatology—headache and musculo-skeletal pain—overlaps with other chronic pain syndromes and may be associated with psychiatric symptoms (depression, anxiety, personality disorders) and thus makes the diagnosis difficult. The mechanism of this condition is a subject of debate, but a genetic predisposition plus an altered interpersonal relationship in childhood and adolescence are the determining factors [10].

Treatment is focused on psychotherapy and modulation of interpersonal relations, by learning to develop robust, safe, and supportive social relationships. Besides, acupuncture and massage proved efficacy. Medication includes TADs and SSRIs [11].

3. Selective serotonin reuptake inhibitors in chronic pain management

Due to the association between chronic pain states and depression and also due to the continuous need and search for effective analgesic drugs, antidepressants have long been considered for the treatment of chronic pain. Some antidepressants are useful in the management of pain syndromes showing analgesic effects, but not all antidepressants have analgesic properties [12]. TADs are recognized to have analgesic effects in doses lower than the antidepressant ones. However, frequent side effects preclude their widespread use.

Consequently, newer generations of antidepressants, like SSRIs and SNRIs, have been studied in chronic pain management. For SSRIs, efficiency in chronic pain conditions has been debated, and results are still inconclusive. It is felt that antidepressants with both noradrenergic and serotoninergic activities are superior analgesics compared to drugs that possess only serotoninergic activity [13].

Currently available SSRIs are fluoxetine, sertraline, paroxetine, citalopram, and escitalopram. Fluvoxamine is approved for the treatment of obsessive-compulsive disorders but has sometimes been used off-label for the treatment of depression. SSRIs are currently approved and used for the treatment of a wide range of diseases: depression, anxiety and panic disorders, obsessive-compulsive disorders, post-traumatic stress disorder, premenstrual dysphoric syndrome, dysthymia, irritable bowel syndrome, eating disorders, alcohol abuse, and some personality disorders [14].

SSRIs utility for the treatment of chronic pain has been questioned but seems attractive due to their better side-effect profile compared to first-generation antidepressants like TADs, as SSRIs selectively block serotonin reuptake (reabsorption in the synaptic cleft).

How could SSRIs be useful in chronic pain management? Do they possess both antidepressant and intrinsic analgesic properties?

Even though widely prescribed, the mechanism of action of SSRIs is not yet fully understood. The traditional theories claim the fact that antidepressant drugs act by influencing certain brain neurotransmitters [15]. Serotonin (5-HT) is one of the neurotransmitters which carry signals between neurons. The monoamine signaling theory of depression explains how SSRIs and other antidepressants work at the synaptic level by inhibiting the reuptake of one or several neurotransmitters, an effect which is almost immediate and leads to the increase of the extracellular level of the mediator. SSRIs are selective inhibitors of the presynaptic 5-HT reuptake transporter (SERT) that leads to an acute increase in serotonin concentrations in the synaptic cleft. This effect does not explain why antidepressant drugs work 2–4 weeks after treatment commencement, which might be better explained by receptor downregulation and delayed desensitization of presynaptic serotonin receptors [16]. Recent findings also suggest changes in brain-derived neurotrophic factor expression, which might even lead to SSRI antidepressant effect. Another newer theory suggests that SSRIs impact brain levels of allopregnanolone, enhancing gamma-amino butyric functions in the brain [14]. Apart from monoamine neurotransmitter's imbalance, the inflammatory theory of depression claims the increased serum levels of proinflammatory mediators in the depressed patients [17]. As inflammation is the well-known cause of acute and some type of chronic pain, proinflammatory mediators play the capital role in initiating nociception and peripheral sensitization. *In vitro* experimental studies and early *in vivo* studies suggested that SSRIs could inhibit the release of TNF-α, interferon γ, interleukin 1β, and free radical superoxide [16, 18]. Probably one of the most plausible humoral links between chronic pain conditions and depression is inflammation. If SSRIs have intrinsic anti-inflammatory and anti-oxidative properties and could modulate inflammatory processes, then this could be an explanation for their therapeutic effect in chronic pain management. The detailed specificity of action for this mechanism remains unknown [19]. Intrinsic antihyperalgesic effects in animal models have recently been described for SSRIs [20–23].

Possible side effects observed during antidepressant treatment with SSRIs also need to be considered when prescribing SSRIs for chronic pain management.

These side effects include [12, 14, 24]:

- Drowsiness, dry mouth, blurred vision, dizziness

- Gastrointestinal effects: nausea, diarrhea or constipation, vomiting

- Central nervous system effects: insomnia, agitation or restlessness, headache, tremors, increased sweating, rarely extrapyramidal symptoms, anorexia

- Syndrome of inappropriate antidiuretic hormone secretion with hyponatremia, somnolence, delirium, confusion

- Sexual dysfunction

- Weight gain

- Platelet dysfunction and increased risk of bleeding

- Drug interactions due to the concomitant hepatic metabolism involving the cytochrome P450

- Safety issues in pregnancy

- Serotonin syndrome

Suicide might be a risk occurring early in the treatment, even though larger epidemiological studies do not confirm this assumption [14].

SSRIs discontinuation syndrome is characterized by sensory and gastrointestinal symptoms, dizziness, lethargy, and sleep disturbances [25].

3.1 Individual SSRIs and their efficiency in chronic pain conditions as highlighted in clinical trials

3.1.1 Fluoxetine

Fluoxetine (Prozac™, Sarafem™) has been one of the first SSRIs available for the treatment of depression. Its use for chronic pain management has been highlighted in several clinical trials including modest numbers of patients (**Table 1**). For chronic tension-type headache, fluoxetine administered in 20 mg daily dose is equally efficient to desipramine [26]. For the treatment of painful diabetic neuropathy, fluoxetine is no more effective than placebo and ameliorates pain in 48% of the patients, especially the depressed ones [27]. For somatoform pain disorders, the analgesic effect is related to treatment duration and is related to its antidepressant effect as depressive patients show greater improvement compared to non-depressed ones [28]. Fluoxetine was found to be efficient for the treatment of fibromyalgia when compared to placebo or amitriptyline [29, 30].

3.1.2 Fluvoxamine

Fluvoxamine (Luvox™) is currently used for the treatment of obsessive-compulsive disorders, and the therapeutic dose varies widely between 50 and 300 mg. Non-depressed patients with severe chronic tension-type headache respond to fluvoxamine 50–100 mg daily [31], and it is efficient in central post-stroke pain, cancer pain, and osteoarthritis [32–34]. However, for chronic cancer pain, its beneficial effect has not yet been proven [35].

	Study	Chronic pain condition	Dose used for chronic pain (mg)	No patients	Comparator	Efficiency
Fluoxetine 10–80 mg/day for depression [14]	Walker et al. [26]	Chronic tension-type headache	20	25	Desipramine	Equally efficient
	Max et al. [27]	Diabetic neuropathy	40	46	Placebo	Equally efficient
	Luo et al. [28]	Somatoform pain disorders	20	80	Placebo	Efficient for depressed patients
	Goldenberg et al. [29]	Fibromyalgia	20	19	Amitriptyline	Effective
	Arnold et al. [30]	Fibromyalgia	45 ± 25	60	Placebo	Effective

Table 1.
Randomized controlled trials for fluoxetine in chronic pain management.

3.1.3 Sertraline

Sertraline (Zoloft™) is recommended in single daily doses of 50–200 mg for the treatment of depression. In small sample size studies, it has proven to be efficient in non-cardiac chronic chest pain and chronic pelvic pain of prostatic origin in men [36, 37], but not in women with chronic pelvic pain [38].

3.1.4 Paroxetine

Paroxetine (Paxil™, Seroxat™) is one of the most extensively studied SSRI for chronic pain management (**Table 2**). For tension-type daily headache, two studies failed to prove any beneficial effect [39, 40]. Foster et al. suggested that by extending treatment periods up to 3–9 months, patients may benefit [41]. For chronic low back pain, doses of 20 mg are less efficient than maprotiline, and the effects are similar to placebo [42, 43]. In fibromyalgia, paroxetine improves overall symptomatology, but the effect on pain is less robust [44]. Paroxetine has been shown to be useful for the treatment of diabetic peripheral neuropathy, but not more efficient than imipramine [45]. In a mixed study comparing paroxetine and citalopram versus gabapentin, the comparable efficiency of these two SSRIs with gabapentin was shown [46].

	Study	Chronic pain condition	Dose used for chronic pain (mg)	No of patients	Comparator	Efficiency
Paroxetine 10–50 mg daily for depression [14]	Langemark and Olesen [39]	Chronic tension-type headache	20–30	50	Sulpiride	Less efficient
	Holroyd et al. [40]	Chronic headache, non-responding to amitriptyline	Up to 40	31	Placebo	Modest effect
	Foster and Bafaloukos [41]	Chronic daily headache	10–50	48	Placebo	Efficient when used for 3–9 months
	Dickens et al. [42]	Chronic low back pain	20	91	Placebo	Not efficient
	Atkinson et al. [43]	Chronic low back pain	20	74	Maprotiline	Less efficient
	Patkar et al. [44]	Fibromyalgia	12.5–2.5 mg	116	Placebo	Inconclusive
	Sindrup et al. [45]	Diabetic peripheral neuropathy	40	29	Placebo and imipramine	Efficient compared to placebo, less efficient compared to imipramine
	Giannopoulos et al. [52]	Diabetic peripheral neuropathy	20–40	101	Citalopram or paroxetine *versus* gabapentin	Comparable efficiency

Table 2.
Randomized controlled trials for paroxetine in chronic pain management.

	Study	Chronic pain condition	Dose used for chronic pain (mg)	No of patients	Comparator	Efficiency
Citalopram 10–80 mg for depression [14]	Nørregaard et al. [46]	Fibromyalgia	20–40	43	Placebo	No effect
	Anderberg et al. [47]	Fibromyalgia	20–40	40	Placebo	Inconclusive
	Aragona et al. [48]	Somatoform pain disorder	20	35	Reboxetine	Moderate effect
	Bendsten et al. [49]	Chronic tension-type headache	20	40	Placebo and amitriptyline	No significant effect
	Viazis et al. [50]	Gastroesophageal reflux disease	20	63		Efficient when administered with proton pump inhibitors
	Roohafza et al. [51]	Pediatric functional abdominal pain	20	86	Placebo	Effective
	Giannopoulos et al. [52]	Diabetic peripheral neuropathy	20–40	101	Citalopram or paroxetine *versus* gabapentin	Comparable efficiency

Table 3.
Randomized controlled trials for citalopram in chronic pain management.

3.1.5 Citalopram

Citalopram (Celexa™, Cipramil™) is administered in 10–80 mg dose once daily for the treatment of depression (**Table 3**). It has been investigated for the treatment of fibromyalgia and chronic tension-type headache, with no beneficial results [47–49], while for somatoform pain disorders it has only moderate analgesic effect [50–52].

3.1.6 Escitalopram

Escitalopram (Cipralex™, Lexapro™) has antidepressive effects in 10–20 mg daily dose. For chronic low back pain, citalopram has similar results compared to duloxetine [53]. It has pain-relieving effects in painful diabetic neuropathy and somatoform disorders [54, 55]. For the treatment of pain symptoms associated with depression, escitalopram is equally effective with nortriptyline [56].

4. Serotonin norepinephrine reuptake inhibitors in pain management

SNRIs are first-line antidepressants known to inhibit the reuptake of serotonin and norepinephrine almost exclusively by binding to their transporters (SERT and NET). This category includes drugs with very different chemical structure and includes venlafaxine, desvenlafaxine, duloxetine, milnacipran, and levomilnacipran.

SNRIs show different pharmacokinetics and dynamics and also different affinity to SERT and NET with consequences on their therapeutic actions (**Table 4**).

SNRI	Bioavailability (%)	Elimination half life	Elimination	SERT affinity	NAT affinity	Active metabolite
Venlafaxine	45	5 h (IR) 11 h (ER)	Renal	High	Low	Yes
Duloxetine IR	50	12 h	Renal + feces	High	High	No
Milnacipran	85	8 h	Renal (55% unchanged)	Moderate	Moderate	No
Desvenlafaxine	80	11 h (IR) 13–14 h (ER)	Renal (45% unchanged) at 72 h	High	Low	No
Levomilnacipran	92	12 h	Renal 58% unchanged	Low	High	No

SERT, serotonin transporter; NAT, noradrenaline transporter; IR, immediate release; ER, extended release.

Table 4.
SNRIs pharmacokinetics and pharmacodynamics.

Side effects of SNRIs are common to all antidepressants, but these drugs add dry mouth and constipation due to increased levels of noradrenaline. The risk of withdrawal because of side effects, in patients with chronic pain, was highest for milnacipran and followed by venlafaxine and duloxetine [57].

4.1 Venlafaxine

Venlafaxine (Effexor™) is an SNRI with mixed action on amine reuptake. When administrated in low doses, it inhibits SERT and at higher doses NAT. It is indicated for major depressive disorder (MDD) and also for anxiety, panic disorders, and social phobia management.

An experimental study showed its antihyperalgesic effect after a single administration in a diabetic neuropathic pain model, a result reversed by pretreatment with yohimbine and chloroamphetamine, but not by naloxone [58].

Long ago, a short case report raised attention to the potential beneficial effect of venlafaxine in chronic pain management [59], and later others confirmed its beneficial effects in managing neuropathic pain: peripheral neuropathy, postherpetic neuropathy, headache, and multiple sclerosis. In a systematic review on neuropathic pain, the authors found four trials (high quality evidence): two with positive results at doses of 150–225 mg venlafaxine ER daily and two with negative results (lower doses). The number needed to treat (NNT) was 6.4 and the number needed to harm (NNH) was 11.8 [60].

In elderly patients with low back pain and depression, 150 mg venlafaxine showed efficacy, but the authors suggested that patients who did not respond to small doses may benefit from dose augmentation after a 2-week period [61].

Venlafaxine may be useful in the treatment of spinal cord injury (SCI) associated with MDD because this medication improved SCI-related disability and pain. Still, further trials are needed to determine optimal doses and efficiency in patients with SCI without MDD [62, 63].

Studies in patients with taxane-oxaliplatin-induced neurotoxicity showed clinical improvement after venlafaxine (37.5 mg bid) [64], and further studies are in progress [65].

Venlafaxine had good results in acute pain; in patients with cancer breast surgery, the preoperative administration of 37.5 mg venlafaxine reduced the postoperative opioid consumption and the incidence of chronic postoperative pain at 6 months [66].

A former Cochrane meta-analysis reported little evidence to support the recommendation of venlafaxine in neuropathic pain management and noted that venlafaxine promoted fatigue, nausea, dizziness, and somnolence with a low incidence [67].

Eventually, two recent reviews (11 and 13 trials) found that venlafaxine was beneficial in neuropathic pain management with good tolerability claiming the necessity for further research to expand these findings [68, 69]. There are contradictory findings in these recent reviews, but there is need for further good quality evidence.

4.2 Desvenlafaxine

Desvenlafaxine (Pristiq™) is the third SNRI with FDA approval and only indication for MDD management (50–400 mg daily). The daily recommended dose is 50 mg. Desvenlafaxine is the salt of an active metabolite of venlafaxine, and the ER form allows 1 day administration. It presents a good bioavailability (**Table 4**) and shows a low binding to plasma proteins (30%). Desvenlafaxine binds to SERT 10 times more than to NAT and also has a weak affinity for dopamine transporter. Adverse effects are dose-dependent and typical to all antidepressants. Doses of 200–400 mg showed efficacy in DPN management, with effect sizes similar to duloxetine [70] and with increased side effects at higher doses. At the moment, there is a lack of evidence to support the use of desvenlafaxine in chronic pain management.

4.3 Duloxetine

Duloxetine (Cymbalta™; DLX) is probably the most used drug from this class of antidepressants. Aside from MDD and urinary incontinence, duloxetine is indicated for anxiety disorder, chronic pain in diabetic neuropathy, fibromyalgia, musculoskeletal pain, and osteoarthritis. DLX is a potent SNRI, with a high affinity for both SERT and NAT. It has a moderate bioavailability, with an elimination half-time of 12 h. It is metabolized in the liver and does not possess any active metabolite. Duloxetine exerts antihyperalgesic and allodynic effects, by impairing nociception at a peripheral level (blocks NaV 1.7 current) and by inhibiting neuronal firing [71]. With acute administration, DLX leads to elevated levels of NA and 5-HT, and with chronic treatment, it does not affect further basal levels of these monoamines [72]. Even if the significant pain-relieving effect was found after 7 weeks of treatment [73], others showed that patients treated with DLX for OA knee pain or low lumbar pain who have <10% reduction in pain after 4 weeks treatment have low chance to reach moderate pain reduction by the end of 12 weeks [74]. DLX's recommended dose for the first week is 30 mg, raising the dose to 60 mg in the second week in order to avoid a high incidence of side effects.

Because of interfering with platelet function, it is indicated to stop its administration 4 days before surgery.

Data from animal pain models and clinical studies on DLX administration in perioperative setting (spine, knee, breast surgery) suggested its analgesic effects. Pre- and postoperative duloxetine reduced 24-h opioid consumption, delayed first analgesic requirement, and reduced incidence of chronic postoperative pain at 6 months, being of primary interest for patients with preoperative chronic pain and spine surgery [75–77]; results from ongoing studies will respond to questions remained unanswered. Duloxetine shows good tolerability with dizziness and nausea, dry mouth, and constipation, as more frequent side effects [78].

Study	Pathology	No trials	Number of patients	Findings
Lunn et al. [79] 60 mg	Diabetes fibromyalgia	14 8-DPN; 6-FM	6407	In both category showed efficacy DPN-NNT 5 FM-NNT 8
Quilici et al. [80]	Diabetes	11	679	Effective in DPN NNT = 5 Good toleration Superior to placebo Discontinuation due to AE
Wang et al. [81] 60/120 mg (QD)	Knee osteoarthritis	3	1011	Significant pain reduction Improved function Reported "acceptable" AE
Lee and Song [82]	Fibromyalgia	9	5140	Results showed equal efficacy and tolerability
Hauser et al. [83]	Fibromyalgia	10	6038	Small benefit over placebo

QD, quaque die; DLX, duloxetine; MLC, milnacipran; DPN, diabetes polyneuropathy; NNT, number needed to treat; FM, fibromyalgia; AE, adverse effect.

Table 5.
Meta-analysis for duloxetine in chronic pain management.

While duloxetine proved its efficacy in chronic nociceptive/neuropathic pain [79–83] (**Table 5**), it is yet unrevealed its possible impact on acute postoperative pain and chronic postoperative pain.

4.4 Milnacipran

Milnacipran (Savella™) described in 1998 by Briley as a potent SNRI that showed similar inhibition on both monoamine re-uptakes, in vitro and in vivo, was approved in Europe for the treatment of depression. It did not link to alpha adrenoreceptors, muscarinic cholinergic, and histaminic receptors and showed no effect on beta-adrenergic receptors sensitivity, thus having reduced side effects. The drug has an excellent bioavailability with a mean peak plasma concentration reached between 0.5 and 4 h after the oral administration. About 13% binds to plasma proteins and is wholly eliminated after 36 h [84]. Studies on the efficacy of milnacipran in psychiatric patients revealed its significant superiority when compared to SSRIs. Most frequent adverse effects were nausea, dry mouth, and headaches [85]. Milnacipran has FDA approval for the management of fibromyalgia.

In 2006, Obata et al. found that intrathecal administration of milnacipran reduced allodynia in a rat neuropathic pain model [86].

Other experimental data confirmed these findings regarding milnacipran's antiallodynic and antihyperalgesic effects [87] and showed its effectiveness in treating allodynia in vincristine-induced neuropathic pain [88].

In a Cochrane meta-analysis, Cording et al. analyzed six studies (4238 patients) that compared milnacipran 100/200 mg with placebo in fibromyalgia. By using a "conservative" method of analysis, they found 26% positive response with milnacipran as compared to 19% for placebo and an increased rate of side effects [89].

Despite the evidence that milnacipran (100 or 200 mg) was found to be useful in neuropathic pain, as compared with placebo, Derry et al.'s meta-analysis did not

obtain enough data to confirm former data and support its recommendation in chronic neuropathic pain [90]. Future trials are needed to establish milnacipran's possible favorable effects in pain management.

4.5 Levomilnacipran

Levomilnacipran (Fetzima™) is the enantiomer of milnacipran with the highest activity, and its primary indication is MDD. At usual doses, this drug is known to possess a higher potency for norepinephrine (twofold) reuptake inhibition, as compared with 5-HT [91]; but with higher doses, it showed equal efficacy in increasing 5-HT and NE levels [92].

Regarding tolerability, the most frequently recorded adverse effects were nausea, constipation, and sweating, although a small proportion (3–6%) of patients recorded increased blood pressure and heart rate [93]. We have not found any data regarding its use in chronic pain patients.

5. Double function serotonin reuptake inhibitors

A particular category of drugs includes SRIs with double mechanism: 5-HT reuptake inhibition and interaction with 5-HT receptors. Animal studies have suggested that these receptors are included in the descending pain inhibitory systems [94, 95], and their activation is involved in reducing the acute nociceptive and neuropathic pain [96].

5.1 Trazodone

Trazodone (Desyrel™, Oleptro™) is the first non-tricyclic antidepressant approved for the treatment of MDD (1981), and it is also used to treat anxiety, alcohol dependence, insomnia, and chronic pain (off-label). It was developed for the treatment of "mental pain," which was recognized to occur in depression [97]. It acts as a SRI, antagonist of 5-HT$_{A2}$ receptor, and a partial agonist for 5-HT$_{A1}$ receptors. Secondary acts as an antagonist to α_1-adrenergic receptors and lacks any effect on cholinergic receptors. The drug shows a 65% oral bioavailability, 90% plasma protein binding capacity, and is metabolized in the liver (via CYP3A4) to an active metabolite—mCPP. The main excretion route is renal, and the biological half-time is 7 h. Side effects are not only shared with the other antidepressants but also list dry mouth, orthostatic hypotension, cardiac arrhythmias, and priapism.

Trazodone showed some efficacy in several chronic pain conditions represented in **Table 6**, but future studies are needed.

5.2 Nefazodone

Nefazodone (Serzone™) is related to trazodone but with fewer side effects. Doses of 300–600 mg are indicated for the treatment of MDD, panic disorders, and aggressive behavior. It acts as an antagonist of 5-HT$_{A2}$ and 5-HT$_{C2}$ receptors and serotonin, norepinephrine, and dopamine reuptake inhibitor. Its effects on the mentioned receptors enhance neurotransmission by an increased binding on the 5-HT$_{A1}$ receptors. Nefazodone shows an affinity for α_1 and less for β-adrenoreceptors and does not interact with muscarinic cholinergic receptors. It has low bioavailability; it is metabolized in the liver (CYP3A4) and has four metabolites (mCPP active). Nefazodone has a biological half-time between 2 and 4 h and is excreted in urine. Frequent side effects are dry mouth, dizziness, and sleepiness, and rare, severe liver damage [98].

Murine studies yielded the capacity of nefazodone to potentiate opioid analgesia by acting through μ_1 and μ_2 receptors without affecting mortality [99]. Other results indicated that rats treated with nefazodone have shown an increased expression of μ-opioid receptors in the area of the central nervous system related to pain perception and modulation [100].

Even if it shows an excellent clinical profile, at this time we found only a two-center open-label study on the efficacy of nefazodone on preventing chronic daily headache. The study included 52 patients who received nefazodone between 100 and 450 mg (300 mg median) for 12 weeks. The results showed significantly lower incidence and intensity of daily headache and a good tolerance for nefazodone [101].

5.3 Vilazodone

Vilazodone (Viibryd™) approved by FDA (2011) for the treatment of MDD is a partial agonist to the 5-HT$_{A1}$ receptor, GABA agonist, and SRI. Currently is presumed that it increases serotoninergic neurotransmission and it shows fast onset and good effect at daily doses between 10 and 40 mg. Vilazodone has 72% bioavailability when it is taken with food, is metabolized in the liver (via CYP3A4), and it did not possess active metabolites. It is excreted in urine and feces and has a biological half-time of 25 h [102]. Side effects include nausea, vomiting, diarrhea, and insomnia (>5%). Sexual adverse reactions and low influence on weight-gain were reported [103]. Even if it presumed that vilazodone should add value in the treatment of patients with the depression-pain syndrome, there are not yet available data on its efficacy in pain states.

Study	Chronic pain condition	Dose	Number of patients	Comparator	Efficiency
Wilson [103]	Diabetic neuropathy	50–100 mg	31	—	Effective
Ventafridda et al. [104]	Deafferentation pain	—	45	Amitriptyline	Equal efficacy
Goodkin et al. [105]	Chronic low back pain	201 mg (average)	42	Placebo	Similar effect
Morillas-Arques et al. [106]	Fibromyalgia	50–300 mg	66	—	Effective
Calandre et al. [107]	Fibromyalgia	50–300 mg trazodone + 75–450 mg pregabalin	41	—	Pregabalin enhanced the favorable effects of trazodone
Davidoff et al. [108]	Dysesthetic pain following spinal cord injury	150 mg	18	placebo	Similar effect
Battistella et al. [109]	Migraine (pediatric 7–18 years)	1 mg/kg	40	placebo	Effective
Frank et al. [110]	Rheumatoid arthritis	1.5 mg/kg	47	—	No effect

Table 6.
Trials for trazodone in chronic pain management.

6. Conclusions

SSRIs seem to be effective in most chronic pain conditions, and they are well tolerated [41]. The efficacy of SSRIs might be comparable to TADs and SNRIs, but their tolerability and safety are superior [30]. For some chronic pain conditions, valuable, while for others their utility is limited:

- For migraine, SSRIs are not better than placebo for reducing the number of attacks, and results of studies on migraine are conflicting [24, 111].

- Patients with chronic tension-type headache seem to benefit from SSRIs [24].

- There are conflicting results regarding the use of SSRIs for pelvic pain.

- Non-cardiac chest pain might benefit from SSRIs.

- Low back pain does not seem to respond well to SSRIs.

- The effects of SSRIs on fibromyalgia are uncertain [112].

- Diabetic neuropathy looks to improve from SSRIs treatment.

- Post stroke central pain might improve with fluvoxamine.

- Evidences support that antidepressants are useful for the treatment of irritable bowel syndrome [113].

- There is no evidence from randomized controlled trials to recommend antidepressants to treat chronic non-cancer pain in children and adolescents [114] or adults.

Even though several clinical trials were published, the results remain inconclusive. That happens because the sample sizes are quite modest rendering the studies slightly underpowered. Primary outcomes are variable: self-reported pain scores, effect on pain symptoms observed by the physician, complex pain questionnaires, and effects on quality of life and functionality. Current drug classes available for chronic pain treatment include anti-inflammatory drugs, opioids, gabapentinoids along with interventional or surgical management, and physical activity. Heterogeneity of the chronic pain syndromes, many currently available drugs and treatment modalities, and drug-drug and drug-interventional management associations should be considered when designing future larger scale trials.

In conclusion, compared to all other antidepressants in the management of chronic pain, for SSRIs, the data are still inconclusive, and studies are fewer in number. For depression, SSRIs are considered first-line agents due to a favorable side-effect profile and good tolerability. However, they have not yet entered first-line use for neuropathic pain conditions [12]. Probably, it would be advisable to restrict their use for those patients failing to respond to other medications or who do not tolerate side effects.

From SNRIs category, in particular duloxetine is already a first-line treatment for DPN and other chronic pain syndromes (fibromyalgia, musculoskeletal pain, and osteoarthritis), showing good results and an acceptable safety profile. It also showed favorable effects on chronic postoperative pain and life quality with the perioperative administration in surgery with a high incidence of chronic pain

(spine, breast). Venlafaxine is a drug of choice for the treatment of fibromyalgia. Milnacipran proved antiallodynic and antihyperalgesic effects and might show further positive results in chronic pain management; well-designed trials are still required.

SRIs seem to play their role through the spinal modulation pain pathways being less involved in reducing nociception, and that is probably why their effects are more evident in patients with chronic pain states.

Conflict of interest

Nothing to declare.

Author details

Adela Hilda Onuțu[1]*, Dan Sebastian Dîrzu[2] and Cristina Petrișor[1,2]

1 Emergency Clinic County Hospital, Cluj-Napoca, Romania

2 Anaesthesia and Intensive Care II Department, "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania

*Address all correspondence to: adela_hilda@yahoo.com

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Chapter 3

Serotonin and Emotional Decision-Making

Sara Puig Pérez

Abstract

Serotonin is one of the most important neurotransmitters involved in emotional regulation, which affect decision-making. In fact, specific genes regulate the transporter protein of serotonin, making people prone to show or not higher amygdala activation. Higher activation of specific components of the limbic system, such as amygdala, results in a higher susceptibility to make decision taking into account the environmental and emotional aspects and not only rational elaborations of the facts. It makes the response of decision-making more visceral or emotional in contrast to people with lower amygdala activation. Therefore, the importance of serotonin regulations impacts on daily and important decisions.

Keywords: serotonin, amygdala, decision-making, behavior

1. Introduction

Nowadays, decision-making has been considered as one of the most complex cognitive functions that use other superior processes such as learning, memory, and feedback sensibility [1]. Theoretically, when people have to make a decision, they are placed on a continuum of uncertainty being "complete ignorance" one pole and "certainty" the other one [2]. In this case, there are difficulties to identify the level of uncertainty (ambiguity), it could be impossible to determine the probability of gain or loss, regardless of the fact that consequences are established and clearly known. In contrast, in those situations where there is risk of uncertainty, although the consequences are stable and clearly known too, gain of fail result can be calculated. So, accordingly, decisions can be made considering as key construct the range of ambiguity or risk of uncertainty [2, 3].

The cognitive-experiential theory supported by Epstein's group [4] distinguishes between two qualitative systems of information processing in decision-making: the rational and the experiential system. The rational style of thinking is characterized by a free emotional perspective, which results in a more analytic, conscious, and effortful process. In contrast, the experiential system is based on emotions, being more automatic, effortless, imaginative, and unconscious (Epstein, 2010). Interestingly, the way people process the inputs from the environment and make decisions is considered in two ways: analytical and intuitive [5]. So, the thinking styles and the decision-making styles probably share an important background. But, decision-making is considered independently from emotional processes and brain neurochemical balance. In this chapter, we will summarize the physiological overlapping between emotional and decision-making processes and the effect of serotonin neurotransmitter on the modulation of these cognitive functions.

2. Main brain regions involved in emotions and decision-making

The main brain structure involved in decision-making is the prefrontal cortex (PFC), which is considered nowadays as the main location of executing cognitive functions. In fact, it has been considered the PFC as the central key structure for cognitive functions as attention for relevant environmental stimuli, objective selection, cognitive control, planning, and monitoring performance [6, 7]. For goal-directed behavior [8] and attention [9–11], subcortical and thalamic regions are involved together with the PFC leading to a complex top-down cognitive control network. In this line, behaviors controlled by other subcortical or cortical areas out of PFC control network become habits or inflexible behaviors, mostly dependent on simple sensory motor associations [12].

It is important to take into account that the PFC region is controlled by subcortical regions involved in emotional processing such as amygdala or nucleus accumbens (NAc) [13, 14]. Both are considered key structures in processing the signal of the environmental stimuli, taking into account the emotional valence, in order to classify them as appetitive or aversive [15–17]. At the same time, PFC is connected with the orbitofrontal cortex (OFC) in voluntary choices and to the anterior cingulate cortex (ACC) in monitoring the outcome of our choices [18, 19]. These connections support the well-known effect of emotions on decision-making. In fact, lesion model studies performed with rats and nonhuman primates showed that NAc injury affects negatively response inhibition and cognitive flexibility [20–22]; meanwhile, amygdala inactivation or lesion affects the selection of relevant information, which is needed in situations with emotional value to coordinate cognitive, physiological, and behavioral responses [17, 23, 24].

Interestingly, although the dorsolateral prefrontal cortex (DLPFC) has been considered as the cognitive brain region per excellence [25, 26], there is growing evidence suggesting that DLPFC plays an important role in emotional regulation and motivated behavior [27–32].

3. Physiological overlapping between emotions and decision-making

When someone has to choose between doing something or not, he balances the immediate reward of doing it as well as the risk of incurring future negative consequences. This fact is known as the concept of willpower, which involves two brain systems' activation: the impulsive system and the reflective system [33] (see **Figure 1**). According to that, the decision-making process will mainly depend on neural substrates, which are affected by emotions because of the modulation that feelings make on neurotransmitter systems.

Main structures involved in the impulsive system are amygdala and striatum [33], which are the structures involved in short lived and very quick responses [34]. As we explained above, amygdala is responsible for attributing affective or emotional value to stimuli perceived evoked through hypothalamus and autonomic brainstem nuclei, which produce changes in internal milieu and visceral structures (e.g., *striatum* and periaqueductal gray) [35]. Amygdala plays a role in emotional decision-making, even in stimuli with an affective value learned by experience (e.g., money or drugs). It has been shown that autonomic response to the gain or loss of important amounts of money depends on the amygdala integrity [1]. In the same line, in addicts, it has been show an exacerbated autonomic response similar to monetary gains [36], which could be related to abnormal activity in the amygdala-ventral striatum system that probably would result in a heightened reward perception of the stimuli [37].
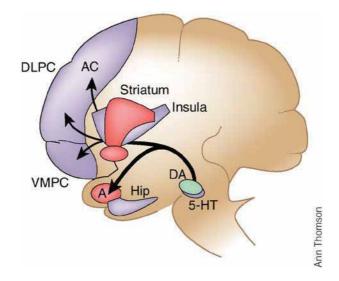
Figure 1.
Diagram from key structures involved in the impulsive (red) and reflective system (blue). A: amygdala, VMPC: ventromedial prefrontal cortex, AC: anterior cingulate, DLPC: dorsolateral prefrontal cortex, hip: hippocampus, DA: dopamine, and 5-HT: serotonin. Extracted from Ref. [33].

In contrast, the reflective system involves hippocampus, insula, AC, and PFC structures (ventromedial prefrontal cortex—VMPC, lateral orbitofrontal, inferior frontal gyrus, and DLPFC) [33]. The VMPC is crucial to induce affective states from recall to imagination, because it is responsible to reactivate the pattern of the affective state experienced in the past of reward or punishment that was developed from the brainstem nuclei [35] and to which the brain preserves the neural pattern [1]. In fact, patients with damage or people with functional abnormalities in VMPC [1] (Erns and Paulus, 2005) show impairments in decision-making. However, the normal function of the VMPC depends on the integrity of other neural systems. The insula, hippocampus, DLPFC, and somatosensory cortices need to be preserved for representing patterns of emotional or affective states and memory, but they need to preserve their integrity for the correct functioning of the VMPC too. Impairments in decision -making in patients with right parietal damage [1] and in people with functional abnormalities (Erns and Paulus, 2005), including the insula and somato-sensory cortex, have been observed. Same difficulties in decision-making have been observed in patients with damage on DLPFC (Clark, Cools and Robbins, 2004). For these reasons, it can be concluded that the decision-making process depends directly on the correct functioning of other brain systems involved in memory and emotional regulation [33]. This neural overlapping suggests a functional interconnection between memory, emotions, and decision-making cognitive processes, being all con-nections between these brain systems are located in VMPC [1] (Clark et al., 2004).

In line with those exposed above, Rolls [38] highlights the importance of emo-tions in decision-making processes giving the fact that the resulting behavior of a decision is the consequence of two brain systems (see **Figure 2**). On the one hand, the emotional system is responsible for the behavior directed to reward or avoidance of punishment in terms of aptitude to natural selection [39–41]. OFC and amygdala have been related to the reward process [39], giving a reward/affective value of the stimulus processed firstly by sensorial main structures (see **Figure 2**). In contrast, the cognitive system depends on the frontoparietal network and responds to declarative knowledge and explicit goals [38]. The main contribution of Rolls [38, 39] was the stablishment of the role of lateral PFC, which is considered the hub of modulation of emotion circuity able to bias our behavior and conduct it agreeing to our explicit goals.
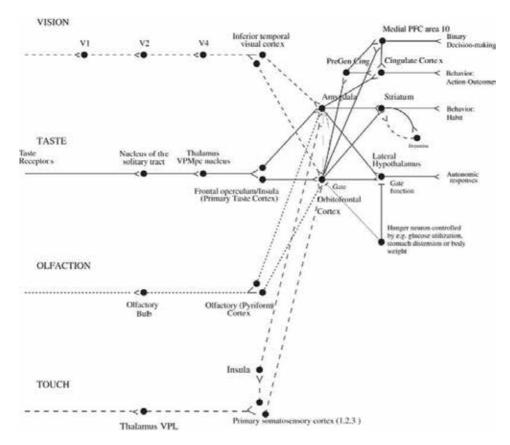
Figure 2.
Schematic diagram showing some of the connections of the taste, olfactory, somatosensory, and visual pathways in the brain. V1, primary visual (striate) cortex; V2 and V4, further cortical visual areas. PFC, prefrontal cortex. VPL, ventroposterolateral nucleus of the thalamus, which conveys somatosensory information to the primary somatosensory cortex (areas 1–3). VPMpc, ventro-postero-medial nucleus pars parvocellularis of the thalamus, which conveys the taste information to the primary taste cortex. Pregen Cing, pregenual cingulate cortex. For the purpose of description, the stages can be described as Tier 1, representing what object is present independently of reward value; Tier 2 in which reward value is represented; and Tier 3 in which decisions between stimuli of different values are taken, and in which the value is interfaced to behavioral output systems. Extracted from Rolls [39].

4. Serotonin as key neurotransmitter in emotional decision-making

Why is serotonin the hub of decision-making? Considering the neural correlation explained above which regulates emotions and decision-making, the following question to consider is which neurotransmitter regulates these networks.

Neuroanatomical studies described the brain regions mainly regulated by serotonin. It has been stated that serotoninergic neurons are located mainly in the brainstem raphe nuclei [42] and project to numerous cortical and subcortical regions. The innervation of serotoninergic neuron from this area projects to the PFC, amygdala, and NA as well as to the ventral tegmental area (VTA), which have been related to reward processes, emotions, and decision-making [13, 14, 43]. Interestingly, the medial areas from PFC play a top-down regulation from these serotoninergic regions acting as a self-feedback regulation mechanism [44]. But there is a big amount of brain regions sensible to the serotonin neurotransmitter, the effect of which depends on the receptor located in the region. Specifically, 5-HT$_{1A}$ receptors are found mainly at hippocampus, hypothalamus, and septum

which are part of the brain networks suggested as part of the different ways of decision-making process [45]. In contrast, 5-HT$_{1B}$ receptors are found mainly on deep subcortical structures as globus pallidus, substantia nigra, ventral pallidum, and dorsal subiculum [46, 47]. The 5-HT$_{2A}$ receptors from medial PFC are located practically exclusively on dendrites of local neuron circuits and spines of pyramidal neurons [48]. Moreover, 5-HT$_{2A}$ receptors can be found on amygdala, hippocampus, and frontal, piriform and entorhinal cortices, as it happens with 5-HT$_{2C}$ [49]. Finally, 5-HT$_6$ receptors are mainly expressed on the cerebral cortex, NA, striatum, and hippocampus [50].

Apart from neuroanatomical evidence highlighting the sensitivity from brain structures related to emotional processing and decision-making processes, one of the most important evidence of the key role of serotonin in these processes is using drugs to regulate serotonin release [51]. For example, the use of serotonin reuptake inhibitors (SSRIs) is one of the most important antidepressants used in depression and obsessive compulsive disorder [52, 53]. Interestingly, there are evidence that SSRI treatment, being effective reducing depressive symptom, improves decision-making and the sensitivity to positive feedback [54]. In this line, serotonin helps to predict future punishment [55] and affects the process of positive stimuli [54]. Increasing serotonin levels can block the uptake of serotonin released in synaptic space using, for example, SSRIs. These drugs, applied acutely, increase serotonin concentration in terminal regions, as well as reduce serotonin concentrations in raphe nuclei due to the activate 5-HT$_{1A}$ receptor [56, 57]. Although these drugs have been considered one of the most efficient ways to increase serotonin levels, it has been observed negative effects on brain development when they have been used in young individuals [58], and to several alterations of the balance of other neurotransmitter systems [59].

Interestingly, there is a big amount of studies interested on genetic basis of serotonin, mood disorders, and cognitive functioning. Along the different genetic studies done about serotonin, it can be highlighted the role of 5-HTTLPR s-allele, which has been strongly related to anxiety traits, poor SSRI treatment response and increase of prefrontal activity [60]. C(−1019)G 5-HT1A polymorphism increases the risk of depressive disorder as well as reduces the efficacy of SSRI drug treatment [61]. And in the case of G-697C, polymorphism from 5-HT$_{2C}$ is related to suicide [62]. Regarding 5-HT$_{3A}$ and 5-HT$_{3B}$, which show a large variety of polymorphisms, they have been related to major depressive disorder [63].

Regardless of the evidence showed till now, recent studies are still trying to clarify the role of serotonin in the decision-making process. In fact, decision-making should be considered as a complex sequence of different superior process, making difficult to deeply understand the role of serotonin in each phase of brain subtasks that involves the decision-making process. In fact, the main subprocesses of decision-making with serotonin that has been considered key moderator are reversal learning, attentional set shifting, reinforce devaluation, delay discounting, and response inhibition (see [51]). In fact, Homberg [51] concluded that serotonin acts as an integrating internal and external information, affecting cognitive functioning: when serotonin is high, there is a high vigilance behavior increasing therefore the top-down PFC control which leads to an improved reversal learning, attentional set shifting, and response inhibition meanwhile decreases delay discounting. In contrast, when serotonin is low, the top-down PFC is low too leading to an impaired reversal learning, reduced attentional set shifting as well as decreased response inhibition; meanwhile, delay discounting turns high. In conclusion, serotonin regulation affects brain region functioning involved in the subtask, which depends on the decision-making process.

Author details

Sara Puig Pérez

Health Sciences Department, Valencian International University, Valencia, Spain

*Address all correspondence to: sara.puig@campusviu.es

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Chapter 4

Clinical Aspects Related to Plasma Serotonin in the Horse

Katiuska Satué Ambrojo, Juan Carlos Gardon Poggi and María Marcilla Corzano

Abstract

Serotonin (5-HT) is a neurotransmitter that has important functions such as the physiological regulation of hemostasis, blood clotting, bone metabolism, cardiovascular growth, contractile activity and gastrointestinal motility, renal function, and stress and sexual behavior, among others. In this review, we consider the potential of 5-HT to contribute to the development of various pathological conditions, including metabolic, vascular, and nervous disorders in horses. The values of 5-HT in circulation are modified under common pathological conditions. Thus, laminitis, endotoxemia, surgical cramps, recurrent airway obstruction, Cushing's syndrome, central fatigue, and certain behavioral alterations such as stereotypes and other acute or chronic conditions can cause increased levels of 5-HT.

Keywords: horse, pathology, plasma serotonin

1. Introduction

Serotonin (5-hydroxytryptamine, 5-HT) is an important neurocrine messenger that is synthesized from tryptophan (TRP) by tryptophan hydroxilase in the brain and mastocytes and enterochromaffin (EC) cells in the gastrointestinal (GI) tract [1]. TRP is able to cross the blood-brain barrier and metabolize into 5-HT in the raphe nuclei within the brain stem. In the intestinal tract, 5-HT is produced by EC and to a lesser extent by serotonergic neurons and released upon mucosal stimulation. The synthesis of 5-HT is identical in the central nervous system (CNS) and in the gut, where TRP is first converted to 5-hydroxytryptophan (5-HTP) via tryptophan hydroxylase (TPH), the rate-limiting enzyme in the biosynthesis of enzyme. 5-HT is eliminated from the interstitium by 5-HT transporters on enterocytes and neurons; 5-HT overflow from the gut reaches the intestinal lumen and portal circulation. In the circulation, it is quickly removed from the plasma by uptake into platelets (PLTs) or metabolized by monoamine oxidase (MAO) into 5-hydroxy-indoleacetic acid (5-HIAA) in hepatic and lung endothelial cells. Plasma 5-HT is quickly transported into the PLTs via 5-HT reuptake transporter (5-HT transporter; SERT) on the PLT membrane. PLTs accumulate, store, and release 5-HT in an analogous manner to central serotoninergic synaptosomes. The free plasma 5-HT exerts important systemic functions, modulating PLT aggregation, and has been reported to be also involved in vasomotor function [1, 2].

In GI tract, 5-HT interacts with receptors on afferent neurons, initiating peristaltic, secretion, and secretory reflexes. On the other hand, 5-HT induces smooth

muscle cell contraction and proliferation but stimulates endothelial cells to release vasodilating substances and acts as a "helper agonist" of PLT aggregation [2, 3].

Measurement of 5-HT in whole blood gives a reasonable approximation of 5-HT in PLTs [4], and the free 5-HT/whole blood-5-HT (f-5HT/WB-5-HT) ratio may be a marker of PLT activation [5]. The concentration of free 5-HT is typically measured in PLT-poor plasma (PPP), produced by prolonged or high-speed centrifugation of plasma and containing <10,000 PLTs/µl [6]. Several researchers reported PPP 5-HT values in healthy horses range from 2.5 ng/ml to 90 ng/ml, with a majority varying between 3 ng/ml and 30 ng/ml [7–16]. Plasma 5-HT is the fraction which shows the equilibrium state between synthesis by EC cells, the inactivation by liver and lung by MAO and PLT uptake.

5-HT plasma concentrations in horses are subject to physiological variations such as age [17, 18], exercise [7–9], stress [19], seasonal, circadian and nycthemeral rhythms [15, 20], altitude [21], reproductive status [22], and type of anticoagulant and laboratory technique [23–25]. In addition, these factors also influence the analytical results of this neurotransmitter. Even in healthy horses, reported reference values for 5-HT are not consistent, which hampers further research into the role of 5-HT in equine diseases. One possible explanation for this inconsistency is the use of different biological samples and analytical methods for 5-HT determination. Indeed, to determine the concentrations of 5-HT in whole blood high-pressure liquid chromatography (HPLC) [7] and in serum, commercially available enzyme-linked immunosorbent assays (ELISA) or radioimmunoassays (RIAs) [19] have been used. Torfs et al. [24] showed that for accurate determination of plasma levels of 5-HT, it is essential to use PPP. It is believed that 5-HT in PPP reflects the amount of 5-HT synthesized and recently secreted in EC cells. Although ELISA [23] and HPLC [18, 21] have been used, the tandem chromatographic mass spectrometry (LC-MS/MS) method is suitable for determining the plasma reference values of 5-HT and analyzing changes in 5-HT associated with pathological conditions.

2. Role of serotonin in the equine clinic

In horses, changes in 5-HT levels are associated with gastrointestinal pathologies such as ileus, colic or endotoxemia, vascular dysfunctions such as digital hypoperfusion causing laminitis, recurrent airway obstruction and endocrine disruption such as intermediate equine pituitary dysfunction (PPID) or Cushing syndrome, and behavioral alterations such as stereotypes [26, 27].

2.1 Gastrointestinal diseases: ileus, colic, and endotoxemia

In the intestine, there are three types of cells that produce 5-HT, such as immune cells, nerve cells and EC cells [26]. Free plasma 5-HT concentration is a potential predictive parameter for postoperative ileus, since it may reflect intestinal integrity, as well as the circulatory effects associated with inflammation or endotoxemia. Therefore, 5-HT quantitation might be an aid in prognosticating the outcome in horses with postoperative colic. The knowledge of plasma 5-HT changes in colic horses is also important in the quest for an effective treatment for ileus, since certain classes of prokinetic drugs target 5-HT receptors [26]. A risk of receptor desensitization [27] might exist when these drugs are used in patients with already elevated 5-HT levels.

5-HT contractile receptors have been identified in the longitudinal and circular layers of the smooth muscle [28] and myenteric neurons of descending colon, ileum and submucosal neurons of ileum, and duodenum in horses [29, 30], in which 5-HT

exerts local actions, causing the activation of intrinsic and extrinsic afferent neurons. This initiates secretory and peristaltic responses to transmit the information to the CNS [27]. While the interaction of 5-HT with 5-HT_2, 5-HT_3, and 5-HT_4 receptors stimulates contractibility, 5-HT_1 and 5-HT_7 receptors induce relaxing effects in the GI tract [31]. Among these types of receptors, 5-HT_4 exerts important control over intestinal motility. Indeed, a prokinetic effect occurs following the administration of 5-HT_4 agonists, such as Tegaserod and Mosapride [32].

In horses with intestinal hypomotility, the agonist of 5-HT_4 receptor Prucalopride can increase motor contractility of the duodenum, cecum, and colon, 30–90 minutes after oral administration. This motor activity is maximal in the duodenum, with a minimal increase in the cecum and left colon related with other intestinal segments [33]. Tegaserod is other selective agonist of 5-HT_4 receptor that induces increase in the frequency and amplitude of contractions in equine ileum and pelvic flexion [34], speeding up GI transit time and increases frequency of bowel sounds and defecation [29]. In this way, Tegaserod can offer therapeutic potential in horses suffering from impaction or paralytic ileus. Cisapride is an indirect cholinergic prokinetic agent that acts by promoting the release of acetylcholine from intramural nerve terminals (myenteric plexus) through stimulation of 5-HT_4 receptors [35]. Mosapride is other selective agonist of 5-HT_4 receptors. The use of this agonist improves gastric, jejunal, and cecal motility in horses [36]. A disadvantage of this medication is the oral administration route. This complicates the use in horses with postoperative ileus. Unfortunately, the availability of this drug is also limited. On the other hand, Tegaserod with a higher risk of cardiac events in humans has been suspected (as for cisapride), its availability is limited, as well as its application in equine practice, explaining the lack of more clinical reports. This drug is a potent dopamine D2 receptor antagonist, a moderate 5-HT_3 receptor antagonist, and 5-HT_4 receptor agonist [29] that increases the contractility of smooth muscle [37] and improved *in vivo* motility of the jejunum [36].

The final effects of 5-HT in the intestine will depend on plasma concentrations and the balance between activation and desensitization of these receptors. The concentrations of 5-HT in the intestinal mucous membrane and its association with postoperative bowel recovery may better reflect the net effects of 5-HT on intestinal motility [38].

5-HT is a very potent proinflammatory, vasoconstrictor, and immunomodulatory agent. Although Delesalle et al. [11] reported an increase in plasma concentrations of 5-HT in horses with intestinal strangulation, Ayala et al. [19] showed a decrease in serum concentration of 5-HT in horses with acute abdominal pain.

Several authors have observed higher concentrations of 5-HT after ischemia-reperfusion in the peritoneal fluid intestinal lumen and mesenteric, portal, and hepatic veins [11, 39]. Increased plasma of 5-HT can have important consequences in colic horses. It has been shown *in vitro* and *in vivo* that 5-HT is an important and very powerful vasoconstrictor agent [16]. The accumulation of 5-HT in the systemic circulation of horses that have colic may reinforce continuous intestinal ischemia. Both local lesions in the intestinal wall and the associated inflammatory and endotoxemic systemic reactions promote the development of ileus. The concentration of free 5-HT in plasma is a possible predictive parameter in cases of postoperative ileus, as it may reflect the integrity of the intestine, as well as the circulatory effects associated with inflammation or endotoxemia. For this reason, the quantification of 5-HT in horses could be an important tool to predict postsurgical evolution as a consequence of colic [26, 40].

Coagulation of circulating PLTs, as well as EC from necrotizing intestinal segments, could serve as a source of 5-HT. In horses, it is argued that intestinal ischemia makes the mucosa more permeable. This event leads to an important

translocation of endotoxins and amines from the diet, among which 5-HT passes from intestinal contents to systemic circulation [28]. Indeed, Davis et al. [41] showed liver lesions in horses suffering from proximal duodenitis-jejunitis. In addition to the lesion caused by the ascending bile duct infection, these authors also propose the absorption of endotoxins or inflammatory mediators of portal circulation. In addition, hepatic hypoxia resulting from systemic inflammation and endotoxemic shock may be possible causes of liver injury.

Intestinal microorganisms are also important for the 5-HT synthesis. Yano et al. [42] estimated that 90% of peripheral 5-HT is produced by the intestinal microbiota. These authors found that in germ-free mice, the production of 5-HT was approximately 60% less in comparison to mice with normal intestinal bacteria. Indeed, when bacterial colonies were restored in the intestines of germ-free mice, 5-HT levels are recovered. Several metabolic byproducts of the intestinal microbiota are controlled by the mixture of spore-forming bacteria acting on EC to alter 5-HT production. However, bacteria are capable to produce 5-HT on their own. In fact, *Lactobacillus spp*. produce acetylcholine and GABA; *Bifidobacterium spp*. produce GABA, *Escherichia* produce norepinephrine, 5-HT, and dopamine; and *Streptococcus* and *Enterococcus* produce 5-HT. *Bacillus* species have also been shown to produce norepinephrine and dopamine [43].

Torfs et al. [24] showed that the plasma concentrations of 5-HT are significantly lower in horses with small bowel surgical colic compared to healthy animals. In addition, it was demonstrated that 5-HT concentrations remained low until at least the first morning after surgery. A previous study on horses with signs of acute colic showed significantly lower concentrations of 5-HT compared to healthy ones [19]. However, this earlier study focused on serum concentration of 5-HT used the ELISA method of analysis. This situation complicates the comparison of these results with the current ones. In contrast to these achievements, Delesalle et al. [11] indicated an increase in plasma concentrations of 5-HT, measured by HPLC, in a small group of horses undergoing small bowel surgery. In addition to the analytical differences between these studies, there are multiple possible physiological and pathological explanations for variations in the results obtained.

2.2 Vascular dysfunctions: Laminitis

The GI flora produces relatively high concentrations of dietary amines by fermenting the consumed amino acids [44, 45]. It is thought that the link between the GI system and the equine foot occurs through dietary amines.

The bacteria responsible for the fermentation of carbohydrates produce enzymes (amino acid decarboxylase) that convert free amino acids to monoamines. Then, the fermentation of large amounts of carbohydrates in the large intestine is associated with a greater number of Gram-positive bacteria (*Streptococci* and *Lactobacilli*) and elevated production of dietary amines [12]. These bacteria increase in the production of lactate, which is responsible for the decrease in intraluminal pH causing death of Gram-negative bacteria and therefore an increase in endotoxin release (lipopolysaccharide, LPS). Tryptamine is the most potent amine in the cecum. It causes vasoconstriction both *in vitro* and *in vivo* through direct activation of serotonergic receptors and 5-HT displacement of PLTs. Monoamines found in the horse's cecum could potentially induce hemodynamic disturbances in the hoof resulting in lamellar ischemia and therefore laminitis [46–50]. Besides, these monoamines present in the cecum can also be detected at much lower concentrations in blood plasma.

Leukocytes can be indirectly activated by PLTs and mainly by LPS. Therefore, endotoxin may contribute to the initiation of early inflammatory changes observed in experimental models of acute laminitis [13]. This may occur because the amines

are able to mimic and potentiate the effects of the biogenic amines (5-HT, epinephrine, norepinephrine, and dopamine) in the circulation. Gut-derived amines mimic the actions of the endogenous biogenic amines by displacing 5-HT from PLTs or norepinephrine from sympathetic nerve ending or by directly activating the receptors for these amines on the vasculature [49]. The potentiation of the action of endogenous amines is produced by two processes: inhibition of absorption in endothelial cells and PLTs [47, 48] or by competition between amines derived from the intestines and endogenous amines by the metabolism of the enzyme amine oxidase [12, 47, 48].

Dietary amines are similar to substances normally produced by the body, including catecholamines and 5-HT. Since 5-HT is a potent vasoconstrictor that is mainly stored in PLTs, it helps to maintain low plasma concentrations that reduce its effects. Bailey et al. [46] reported that the absorption of 5-HT by PLTs is a saturable process in horses. The most efficient way to work is at substrate concentrations below the micromole. The noncompetitive inhibition of 5-HT absorption by other natural monoamines may result in increased plasma concentrations of 5-HT and endotoxin release. The amines present in the diet inhibit the uptake of 5-HT from the PLTs. As a result, plasma concentration of 5-HT would increase above the level at which digital vasoconstriction occurs [44, 51]. However, other peripheral blood vessels are unaffected, since digital vessels are much more sensitive to the vasoconstriction effects of 5-HT [52, 53]. Dietary amines can also cause digital vasoconstriction directly [49]. The overall result is the digital ischemia and subsequent reperfusion, which could lead to the activation of metalloproteinases.

Endotoxins act as a mechanism that triggers laminitis. These substances activate the coagulation cascade directly through the Hageman factor (factor XII, in the intrinsic coagulation pathway). They are called the contact factor because the activation occurs by contact with nonendothelial and foreign surfaces. In addition, endotoxins are the initial stage of intrinsic plasma coagulation. They also cause damage to endothelial cells and favor the addition of PLTs, thereby establishing a blood profile compatible with disseminated intravascular coagulation (DIC). As a result, peripheral vasoconstriction initially results in decreased capillary perfusion of the hoof with some degree of ischemia [47, 48].

The aggregation of PLTs and the formation of microthrombi in the capillaries of the hull contribute to maintain vascular occlusion ischemia. In addition, a potent vasoconstrictor such as thromboxane A2 is released from PLTs, which adds to increase the process. At the same time, the inflammatory response begins with the release of autacoids such as histamine, 5-HT, bradykinin, prostanoids, leukotrienes, and interleukin 1. Histamine plays a very important role in acute inflammation. It has a vasodilatory action on arterioles, but the role in inflammation is more important, since it improves the action of other mediators such as histamine and bradykinin. This results in arteriolar dilation, increased capillary permeability, and hyperalgesia. Leukotriene B4 is also involved in the passage of leukocytes to inflammatory exudate [16].

The relationship between the appearance of digital hypoperfusion and increases in plasma concentration of 5-HT is consistent. This is because PLTs-derived mediators are associated with LPS-induced laminitis. These experimental data support the use of antiPLT therapy in the prevention of laminitis related to endotoxemic diseases [16].

2.3 Endocrine diseases: pituitary pars intermedia dysfunction

Pituitary pars intermedia dysfunction (PPID) or Cushing's disease is characterized by hypertrophy and hyperplasia of the Pituitary Pars Intermedia and is argued

to be due to a reduction in dopamine synthesis or degeneration of periventricular pituitary dopaminergic neurons [54]. PPID is more frequent in adult horses and result of a progressive loss of the neurotransmitter at central and peripheral level as result of the degeneration of the pineal gland [15].

The role of 5-HT in the regulation of the PPID it is not clear. Treatment of PPID in horse includes 5-HT antagonists [55], such as cyproheptadine. Antagonist of 5-HT is potent secretagogue of ACTH in pituitary rat tissue, and it was used effectively in human Cushing's disease. Cyproheptadine decreases the 5-HT-induced stimulation to the pituitary pars intermedia, the synthesis of pro-opiomelanocortin (POMC), and finally, ACTH secretion. Cyproheptadine (0.25–0.5 mg/kg PO, SID, or BID) was used for the treatment of PPID result in an improvement in clinical status and normalization of laboratory parameters within 1–2 months of treatment initiation, being effective in 28–60% of cases [56]. However, similar improvements were achieved with improved nutrition, preventive care, and management alone [57].

Additionally, Bailey et al. [46] measured peripheral plasma concentrations of 5-HT in summer, autumn, winter, and spring in clinically normal ponies and those predisposed to laminitis, and no significant differences were observed. Although light/dark differences were not investigated in the latter work, nycthemeral increases in serum 5-HT in the healthy, athletic horse have been reported [20]. Later, Haritou et al. [15] reported seasonal changes in circadian peripheral plasma concentrations of melatonin, 5-HT, dopamine, and cortisol in aged horses with PPID. Six horses and ponies with PPID were matched with six controls to test the hypothesis that aged horse responds differently to changes in season because of deficiency in melatonin production. They also examined the link between the presence or absence of the clinical signs of PPID and peripheral plasma concentration of 5-HT, dopamine, and cortisol. Results showed that the 24-h pattern of plasma melatonin concentrations during the four seasons of the year was similar in both groups, indicating that impaired melatonin output is unlikely to play a role in PPID. However, 5-HT profiles were affected by season, with lower 5-HT detected in PPID horses in the summer and winter. Although the reasons for this reduction remain unknown, enhanced conversion of 5-HT to melatonin could account, at least in part, for the lowered circulating level. The total amount of dopamine released was dependent on season and markedly lower in PPID horses versus controls. These results implicate both serotonin and dopamine in the pathogenesis of the disease [15].

2.4 Behavioral alterations: stereotypes

Most frequently observed stereotypies in domestic horses are crib biting, weaving, box walking, wind sucking, and wood chewing. However, there is no scientific consensus as to whether wood chewing is definitely a stereotypy [58]. More recently, some morphological variations of these stereotypic activities have also been identified as equine stereotypies, such as licking the environment, lip licking, sham chewing or teeth grinding, self-biting, and rubbing self, as well as locomotion stereotypies, including pawing, tail swishing, door kicking or box kicking, and head tossing/nodding [59]. The most common forms of equine stereotypies are within two general categories, oral and locomotion stereotypic behaviors.

The neurobiological consequences of equine stereotypies focus on neurotransmitter systems, specifically the serotonergic and dopaminergic pathways [59, 60]. 5-HT is implicated in the underlying pathology of stereotypies. Indeed, Lebelt et al. [61] found a trend for lower basal 5-HT levels in crib-biting compared to nonstereotypic horses, suggesting that the serotonergic system of crib-biters may differ from

that of noncrib biting horses (mean 201.5 vs. 414.3 nmol/l). The precise role of 5-HT in the development or maintenance of the behavior remains unclear however, and the results obtained by these authors have yet to be confirmed or refuted through additional experimental studies of the serotonergic system in crib-biting horses.

However, blood levels of 5-HT in horses with weaving is more than triple compared to healthy horses. Thus, 5-HT is recognized as the "happiness hormone" or "pleasure hormone" [62]. It can be assumed that during the demonstration of stereotypical disorder, horses are "happy," and that repetitive disturbance is a means of increasing 5-HT levels in the blood and therefore the feeling of comfort [63].

Serotonin reuptake inhibitors (SRI) are a type of drug which acts as a reuptake inhibitor of the neurotransmitter serotonin (5-hydroxytryptamine (5-HT)) by blocking the action of the serotonin transporter (SERT). This in turn leads to increased extracellular concentrations of serotonin and, therefore, an increase in serotonergic neurotransmission. Although administration of SRIs drugs has been associated with the reduction of stereotypies, it was dubious if such medications decreased stereotypic behaviors due to general sedative effects or selectively influenced stereotypic behavior. These uncertainties were due to general sedative effects or selective influence on the type of behavior. As previously expressed, the specific role of 5-HT in the development or maintenance of behavior remains uncertain [60, 61, 64, 65], and further studies are needed to provide a more accurate interpretation of stereotypes.

Pharmacological preparations containing TRP are marketed worldwide as relaxing agents for treating excitable horses. The few studies in which TRP has been administered to horses suggest that low doses cause mild excitation. However, high doses reduce endurance capacity and cause acute hemolytic anemia when given orally due to the presence of a toxic metabolite in the intestine [65, 66]. Despite questions about its effectiveness, TRP is marketed as an equine sedative and is related to sedation, inhibition of aggression, fear, and stress.

Because TRP competes with other amino acids to bind to protein transport and cross the blood-brain barrier, researchers are now using a ratio of TRP with other large neutral amino acids (ANNALs) to estimate the production of 5-HT in the CNS [67]. Besides, previous researchers showed that the age, breed, and gender modify the response of serotoninergic system due to changes in dietary TRP [17, 68]. While all of these factors may play a role in the permeability of the blood-brain barrier, the effectiveness of supplemental TRP on 5-HT biosynthesis, it is also worth considering that these types of treatments may be most effective in horses with dysfunctioning serotoninergic system.

Although the safety of TRP doses should be confirmed, there is no evidence to suggest that a single dose is an effective analgesic in horses. In fact, given that TRP continues to be used as a tranquilizer, there is an urgent need for research to confirm its efficacy and establish a range of safe therapeutic doses. In the meantime, available data suggest that it would be unwise to rely on the TRP to calm the excitable horse. Instead, more efforts should be made to identify the underlying causes of excitability and explore other more appropriate nonpharmacological solutions. Indeed, when evaluating the use of calming supplements or drugs, it is important to consider the welfare of the horse. While calmative compounds may be beneficial in alleviating short-term stress and anxiety, the cause of such emotions should also be evaluated. Horses kept in unnatural environments, managed poorly, or asked to perform beyond their level of training may show signs of stress and anxiety. Chronic health issues, such as ulcers or lameness, may also be the culprit. Sedative drugs and supplements are often utilized to limit unwanted behaviors such as spooking, bolting, rearing, or bucking. Looking into the potential causes of unwanted behaviors should be the first step before owners turn to calming drugs or

supplements. Providing more training, turnout time, or treatment for an underlying disease or condition could result in a more sustainable way to reduce a horse's unwanted behaviors and could improve welfare for the animal [65].

Equine self-mutilation syndrome (ESMS) includes glancing or biting at the flank or pectoral areas, bucking, kicking, vocalizing, rubbing, spinning, or rolling. Eight flank-biting horses with ESMS were enrolled for a behavioral study, and the effects of drugs that either stimulate or inhibit central opioid, dopamine, norepinephrine, and 5-HT neurotransmitter systems were reported. Behaviors were recorded hourly during the study and were compared with those of a saline control baseline to determine whether there were significant differences among the treatments. The suppression of ESMS activities with Buspirone (0.5 mg/kg) suggests a role for serotonergic modulation of the behavior. However, the clomipramine, a preferential 5-HT reuptake blocker, does not produce any significant effect on ESMS behavior in horses [69].

Horses with compulsive disorder may help the fluoxetine at dose of 0.25–0.5 mg/kg/day PO. Fluxetine is a selective serotonin reuptake inhibitor (*SSRI*) that increases 5-HT levels within CNS by preventing the reuptake of 5-HT at level of the presynaptic neuron. This allows 5-HT to accumulate in the synaptic cleft and affect the postsynaptic neuron. While no cases of fluoxetine-induced colic have been reported in horses being treated for behavior problems and because there are many 5-HT receptors in the gut, it is advisable to begin administering the drug at the lowest dose and increase it gradually in horses that do not improve and have not exhibited adverse effects [70].

The ability to train and control horses is an important behavioral trait for the handling and training of animals. Hori et al. [71] inform that horses carrying allele A located at c. 709G > A had a lower capacity to be handled. These results provide the first evidence that a polymorphism in a 5-HT-related gene may affect the management of horses with a partially different sex-related effect.

2.5 Recurrent airway obstruction

Based on the results reported in humans, in which PLTs contribute to the pathogenesis of allergic airway disease, Hammon et al. [14] compared PLT aggregation induced by the activating factor PLTs (PAF), thromboxane (Tx), plasma Tx, and 5-hydroxytryptamine (5-HT) production in ponies with recurrent airway obstruction (RAO) before and after antigen exposure. Plasma 5-HT was significantly higher in ponies with RAO but did not increase more by exposure to the antigen. There were also no differences between the aggregation of PLTs induced by PAF or the production of Tx or plasma Tx before or after exposure. These evidences suggest that there may be a difference between 5-HT uptake of PLTs in RAO and normal ponies. However, they do not provide evidence of PLTs activation after exposure to the antigen. This bronchoconstriction can be mediated by 5-HT. However, the effect or pathway of 5-HT may be deactivated during the development of small airway disease [72].

2.6 Central fatigue

Accordingly, the synthesis and metabolism of 5-HT in the CNS increase in response to exercise [73]. Increased 5-HT concentration in the brain is associated with central fatigue markers, such as decreased motivation, lethargy, fatigue, or loss of motor coordination [74].

It has been shown that nutritional status can alter cerebral neurochemistry, especially carbohydrates and 5-HT [75]. Therefore, it has been hypothesized that

infusion of TRP may increase the ratio of fTrp (free TRP) and fTrp to BCAA while decreasing the resistance of endurance horses to treadmill. Therefore, central fatigue may limit resistance in horses, and by manipulating fTrp and BCAA, exercise capacity could be altered in a predictable way [76]. However, TRP infusion results are consistent with the central fatigue hypothesis where an increase in plasma fTrp concentration is related to the early onset of fatigue during prolonged exercise [77]. Piccione et al. [20] reported that if exercise is performed at the time of the rhythmic acrophase of the TRP (18:45, 18:16), it is likely that exercise performed at the time of the acrophase of the TRP rhythm (18:45, 18:16) affects the onset of physiological fatigue, thus turning on the body's exercise adaptation mechanisms in order to maintain better physical performance.

2.7 Other conditions

Virus of Borna's disease (BDV) can enter into the brain and infect neurons, often the limbic system. It can also remain active for long periods of time in the CNS without generating neuronal lysis. The BDV virus is unique in the order of mononegavirals because it replicates in the cell nucleus. Alterations include falling, tremor, abnormal posture, hyperactivity or hypoactivity, increased aggression, and paralysis. In some rodent species, BDV can cause mild or asymptomatic symptoms, while in other animal species such as horses, it can cause severe CNS symptoms that often lead to death. In humans, a common treatment for psychiatric illnesses such as depression or anxiety disorders is the use of SSRIs. The function of these drugs is to increase extracellular 5-HT. Interestingly, there are viruses that can exert the opposite action and reduce levels of 5-HT and therefore theoretically have an opposite effect to SSRI [78].

Equine hepatic encephalopathy is caused by direct damage to the liver or by toxins derived from the intestine that overwhelm or evade this organ. These toxins act on the CNS, giving rise to signs of encephalopathy. Secondary hepatic encephalopathy in horses occurs more often than liver failure. This may be due to megalocytic liver disease caused by ingestion of plants containing pyrrolizidine alkaloid (*Senecio, Crotalaria and Amsinckia*), Theiler's or Tyzzer's disease, cholangiohepatitis, chronic active hepatitis, liver neoplasia, toxic liver disease, and portosystemic shunts [79]. Because the liver is incapacitated, normal detoxification activities cannot be performed in all these conditions. Therefore, toxins derived from IG enter the CNS through the bloodstream.

In horses, hyperammonemia has been linked to clinical signs of encephalopathy without evidence of liver disease, which promotes the formation of Alzheimer's cells II [80]. It is also suggested that alteration of amino acid metabolism with upward regulation of aromatic amino acids and downward regulation of BCAA lead to direct neuronal inhibition secondary to effects on CNS. Alteration of *gamma aminobutyric acid* (GABA) and glutamate during liver failure plays an important role in the physiopathology of hepatic encephalopathy. Liver impairment leads to an increase in substances similar to endogenous benzodiazepines that inhibit neuronal excitation. Therefore, the most likely scenario is that there are multiple mechanisms working in synergy with each other to create signs of encephalopathy.

3. Conclusions

Serotonin is a neurotransmitter associated with important physiological, digestive, and vascular functions of the central nervous system. This review describes the involvement of serotonin in the most common pathological processes of equine

clinic. Deficiencies or excesses in plasma serotonin concentrations may predispose to endocrine, vascular, or nervous disorders in the horse. Therefore, new additional studies are needed to continue showing the physiopathological mechanisms with implications of serotoninemia in other organs of the horse.

Author details

Katiuska Satué Ambrojo[1*], Juan Carlos Gardon Poggi[2] and María Marcilla Corzano[1]

1 Department of Animal Medicine and Surgery, Cardenal Herrera University, Spain

2 Department of Animal Medicine and Surgery, Faculty of Veterinary and Experimental Sciences, Catholic University of Valencia "San Vicente Mártir", Valencia, Spain

*Address all correspondence to: ksatue@uchceu.es

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Edited by Ying Qu

My scientific journey brought me from Lanzhou in China, Leuven in Belgium, Bethesda in the USA, all the way to San Diego. Sometimes I pick up an assortment of scattered seashells while walking along the beautiful Torrey Pines Beach in San Diego. Likewise, this book contains an assortment of discussions of different aspects of serotonin to enrich our knowledge and understanding of this neurochemical. The book contains four different chapters: 1. Introductory chapter: From Measuring Serotonin Neurotransmission to Evaluating Serotonin Post-Receptor Signaling Transduction; 2. Serotonin Reuptake Inhibitors and Their Role in Chronic Pain Management; 3. Serotonin and Emotional Decision-Making; and 4. Clinical Aspects Related to Plasma Serotonin in the Horse.

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