Premature ejaculation and serotonergic antidepressants-induced delayed ejaculation: the involvement of the serotonergic system

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Abstract

Premature ejaculation has generally been considered a psychosexual disorder with psychogenic aetiology. Although still mainly treated by behavioural therapy, in recent years double-blind studies have indicated the beneficial effects of some of the serotonergic antidepressants (SSRIs) in delaying ejaculation. We describe here the neurophysiology and the peripheral neuroanatomy of ejaculation and provide a review of the involvement of serotonin in the central nervous system in relation to serotonergic nuclei and their projections. A hypothesis of the role of 5-HT1A and 5-HT2C receptors in premature ejaculation is postulated. © 1998 Elsevier Science B.V. All rights reserved.

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1. Introduction

Premature ejaculation is defined as a persistent or recurrent ejaculation with minimal sexual stimulation before, on or shortly after penetration and before the person wishes it [4]. Generally, premature ejaculation was and still is considered a psychosexual disturbance [1,41]. This led to the idea that the main option for treating premature ejaculation were behavioural therapies such as the stop-start technique [44], the squeeze technique [33] and other psychotherapeutic interventions [47]. However, in two longitudinal studies [17,27] it was shown that the initial positive effects of behavioural techniques disappear after 3 years.

Pharmacotherapy was also used to delay the ejaculation time. Initially, local anesthetic ointments were recommended [5,16,13], but later case reports and open trials described the beneficial effects of monoamine-oxidase inhibitors [6], clomipramine [24,23,3,26] and benzodiazepines [42]. However, the use of pharmacotherapy was considered as ‘only’ suppressive for the disorder. The ‘real’ etiology was still thought to be psychogenic, which is probably one of the reasons that a neurobiological view regarding etiology and pathogenesis is still lacking.

The beneficial effects of the recently introduced selective serotonergic re-uptake inhibitor antidepressants (SSRIs), such as fluoxetine [15,55], paroxetine [55,52,54], and sertraline [34,55] for treating premature ejaculation, clearly indicates that the classical psychological view of premature ejaculation is no longer tenable as the only pathogenetic theory. Possibly, serotonin plays a role in the ejaculation process. It might as well be that genetic factors play a role in the etiology of premature ejaculation [56].

This paper first describes the peripheral nervous pathways associated with the ejaculation process, then reviews the SSRl-induced ejaculatory retardation and describes some essential features of the serotonergic system.
system. Finally, it will be postulated which serotonin receptor subtypes might be involved in premature ejaculation.

2. Neurophysiology and peripheral neuroanatomy of ejaculation

Ejaculation occurs in two stages [7]. In the first stage, the emission phase, sympathetic impulses produce peristaltic smooth muscle contractions of the epididymis and vas deferens, moving sperm to the posterior (prostatic) urethra. At the same time, the seminal vesicles and prostate contract rhythmically, expelling seminal and prostatic fluid to mix with sperm. Finally, all these fluids mix with mucus already secreted by the bulbourethral glands. The combination of these fluids is known as semen [46]. The emission is subjectively experienced as ejaculatory inevitability, because at this point ejaculation cannot be stopped. It is immediately followed by the second phase, the expulsion or ejaculation proper, in which semen is expelled out of the urethra by rhythmic contractions of pelvic floor muscles.

The (preganglionic) sympathetic nerves, involved in the emission phase, originate from the intermediolateral columns of the spinal thoracolumbar cord from T10 to L2 [32] and travel via the sympathetic chain and hypogastric nerve (postganglionic) to the pelvic plexus (inferior hypogastric plexus) or via the sympathetic chain and pelvic nerve (nervi erigentes) to the pelvic plexus [18]. From the pelvic plexus the sympathetic nerves are mediated via the cavernous nerve to the vasa deferentia [18].

During emission the sphincter urethrae internus muscle (bladder neck) contracts by sympathetic influence, preventing the semen to enter the bladder (retrograde ejaculation). The second phase is initiated by pressure on the wall of the ampulla urethrae by the semen, giving rise to afferent impulses which reach the S2–S4 sacral cord segments via the pudendal and pelvic nerves [40]. The expulsion is mediated by motoneurons in the nucleus of Onuf, which, by way of the pudendal nerve [45] produce co-ordinated contractions of the bulbocavernous muscles of the pelvic floor. How the afferent impulses of the urethral wall are relayed to the motoneurons of Onuf’s nucleus is not known.

The ejaculatory response is triggered by genital and cortical stimulation. In genital stimulation the afferent sensory impulses are mediated via touch receptors on the glans penis, which are connected with sensory fibers that travel in the dorsal penile and pudendal nerves and enter the sacral spinal cord. How cortical activation, such as visual and auditory impulses, reach the ejaculation related systems is not known.

3. Peripheral serotonin and the central nervous system

The first indication of the presence of serotonin dates from more than 100 years ago, when a vasoconstrictive agent in blood was accidentally discovered, which later appeared to be present in serum. In the 1930s, an agent (enteramine) was discovered in the gut [20], but it was not clear whether this agent was the same as that found in serum. By the end of the 1940s this endogenous factor was identified. After purification it was called ‘serotonin’ because of its ‘serum tonic’ properties. In 1952, it became clear that serotonin or 5-hydroxytryptamine (5-HT; [39]) and enteramine were identical [19].

4. Peripheral serotonin

The majority of 5-HT is found in the enterochromaffin cells in the gastrointestinal tract, where it accounts for approximately 80% of total body 5-HT content [14,21]. In the periphery 5-HT acts as a vasoconstrictor and pro-aggregator when released from aggregating platelets, as a neurotransmitter in the enteric plexuses of the gut and as an autocrine hormone when released from enterochromaffin cells from the gut, pancreas and elsewhere [25,21]. Circulating 5-HT does not enter the brain because it cannot cross the blood–brain barrier.

5. Serotonin in the central nervous system

After the discovery that 5-HT occurred in the central nervous system also [51], Woolley and Shaw [57] postulated in 1954, a central role for 5-HT in psychiatric disorders, in particular because the 5-HT agonist D-LSD exerted such a potent psychomimetic action. Reserpine, a drug given in serious hypertension, was found to induce a depressive mood. As reserpine induces an initial release of 5-HT from presynaptic terminals followed by the ceasing of 5-HT release, a relation was suggested between low 5-HT levels and depression. Further research has led to the hypothesis that a deficit in monoamines (including 5-HT) could lead to depression. This theory has led to the development of the selective serotonin re-uptake inhibitors (SSRIs) which proved to be effective antidepressants. The serotonin system in the brain was visualized using histochemical techniques (Falck–Hillarp techniques) in the 1960s. This relatively primitive localization method was strongly improved by the development of antibodies against 5-HT [48] and later still, by autoradiographic techniques, which made it possible to reveal detailed 5-HT receptor locations.
Fig. 1. A schematic representation of a serotonergic neuron and a post-synaptic neuron. All known 5-HT receptors and their putative localization are depicted (hypothetical).

In 1979, using radioligand binding technology, two classes of 5-HT receptors in the CNS were shown [38]. This was the start of an era in which a continuous stream of new 5-HT receptors has been detected. Presently, at least sixteen different 5-HT receptors have been found, cloned and the structure described (5-HT_1A, 5-HT_1B, 5-HT_1D_α, 5-HT_1D_β, 5-HT_1E, 5-HT_1F, 5-HT_2A, 5-HT_2B, 5-HT_2C, 5-HT_3, 5-HT_4, 5-HT_5A, 5-HT_5B, 5-HT_6, 5-HT_7). A schematic representation of these different 5-HT receptors and their putative locations are depicted on a cartoon of a 5-HT presynaptic neuron and a post-synaptic neuron (Fig. 1).

5.1. Serotonergic neurons

Serotonergic cell bodies are present in the brainstem in the raphe nuclei and adjacent reticular formation (Fig. 2). There is a clear dichotomy in the 5-HT system neuronal cell groups. Firstly, a rostral part with cell bodies in the midbrain and rostral pons projecting to the forebrain. Secondly, a caudal part with cell bodies predominantly in the medulla oblongata with important projections to the spinal cord. Both parts also project to areas in the brainstem and the cerebellum [31].

5.2. Rostral and caudal serotonergic cell groups

The rostral part of the 5-HT system consists of the caudal linear nucleus and the dorsal and median raphe nuclei. The number of 5-HT cells in the dorsal raphe is the largest among all raphe nuclei and contains approximately 24,000 in the cat and 165,000 in man [50]. Besides the raphe nuclei, a number of 5-HT neurons are present in the adjoining reticular formation of pons and midbrain. The caudal system contains the nuclei raphe magnus, pallidus and obscurus and some in the adjoining medullary reticular formation, solitary nucleus and the area of the nucleus (sub)coeruleus.

5.3. Projections of the serotonergic cell groups

5.3.1. Ascending projections

The ascending 5-HT system consists of two more or less parallel projection pathways, presumably with different functions [50]. The first system is called ‘Basket-axon’ system and originates in the median raphe nucleus. It has thick fibers (M-fibers) that branch into short, thin fibers and form large, round boutons (varicosities) with extensive synaptic contacts. These beaded axons often intensively embanch certain cortical cells (baskets) and form classical synaptic contacts.

The second system originates in the dorsal raphe nucleus. It has thin fibers (D-fibers) with many spindle-sized varicosities. These fibers branch extensively and diffusely and contain small fusiform boutons. However, these boutons do not seem to contain real synaptic structures.

Both systems (M- and D-fibers) can be found together in most brain areas, but to a different extent. The cerebral cortex is the area where both systems co-exist extensively, whereas the striatum almost exclusively receives fine varicose D-fibers and the gyrus...
dentatus primarily thick M-fibers. The functional role of these two 5-HT systems is rather unclear, although they display a differential sensitivity for certain substituted amphetamines like MDMA [37]. Such drugs destroy the fine varicose system but leave the thick, beaded system intact.

5.3.2. Descending projections
The caudal raphe nuclei project to the caudal brain stem and spinal cord. The raphe magnus nucleus predominantly projects to the dorsal horn and the nuclei raphe pallidus and obscurus to the ventral horn, intermediate zone and the intermediolateral cell column (IML) of the thoracolumbar and sacral spinal cord. The latter areas contain preganglionic sympathetic and parasympathetic motoneurons, respectively.

5.3.3. Afferents of the caudal serotonergic raphe nuclei
The afferents of the caudal raphe nuclei originate largely from medial structures in the so called limbic system. The most important are the mesencephalic periaqueductal grey and medial cell groups in hypothalamus and pre-optic area [28].

5.3.4. Regulation
Serotonergic neurons have various mechanisms to regulate their own activity, viz. somatodendritic autoreceptors (5-HT1A receptors), presynaptic autoreceptors (5-HT1B/1D receptors) and the 5-HT re-uptake process (5-HT transporter).

5.3.4.1. Somatodendritic (5-HT1A) autoreceptors. The 5-HT1A autoreceptors are present in high densities on the cell bodies and dendrites of serotonergic neurons in the raphe nuclei (Fig. 3). Upon activation of these receptors, the firing rate of the 5-HT neuron decreases. Under normal physiological conditions endogenous 5-HT activates this 5-HT1A autoreceptor. It is as yet not clear from where this endogenous 5-HT originates, but it is assumed that it derives from somatodendritic release, which differs from synaptic release. Application of the selective 5-HT1A receptor agonists (i.e. 8-OH-DPAT or flesinoxan) either systemically or locally in the raphe nuclei, inhibits the release of 5-HT in the synaptic cleft.

5.3.4.2. 5-HT1B/1D autoreceptors. This pre-synaptic receptor inhibits, after activation, the 5-HT release into the synaptic cleft. The 5-HT1B/1D receptor is coupled to an inhibitory (GI-protein) transaction mechanism that apparently blocks the release of 5-HT from the synaptic vesicles in an as yet not understood manner. This feedback mechanism of the cell, where the released 5-HT inhibits its own release, is a frequently occurring principle in neurotransmitter regulation and provides the system with the possibility to prevent overstimulation of (post)synaptic receptors.

5.3.4.3. 5-HT re-uptake. If 5-HT is released into the synaptic cleft it should be removed again as fast as possible to prevent overstimulation of the (post)synaptic receptors (desensitization). The 5-HT neuron, therefore, possesses large quantities of 5-HT transporters (5-HTT), not only on the synaptic endings but also on the cell bodies and dendrites of serotonergic neurons. Apart from this 5-HT cell system, glial cells have also a transport system which presumably contributes to the remove of released 5-HT. After blockade of the 5-HT transporters via selective serotonin re-uptake inhibitors (SSRIs), the synaptic 5-HT increases,
although this process is counteracted by activation of 5-HT$_{1A}$ autoreceptors, which are stimulated by enhanced 5-HT and inhibit the 5-HT release.

5.3.4.4. Acute and chronic administration of SSRIs. After acute administration of an SSRI all 5-HT transporters are blocked. This leads to high 5-HT levels in the extracellular space around the 5-HT cell bodies in the raphe nuclei, leading to activation of 5-HT$_{1A}$ autoreceptors and thus to a decrease in the firing frequency of the cell and a decreased release of 5-HT in the synaptic cleft. This decreased release is (completely or partially) compensated by blockade of the 5-HT re-uptake in the synaptic cleft. The net effect in the synaptic cleft is difficult to predict, both an increase in or lack of effect have been observed. If a post-synaptic increase occurs, activation of the pre-synaptic 5-HT$_{1B/1D}$ autoreceptor will further dampen the release process. In general, acute administration of SSRIs will presumably lead to a mild increase of 5-HT neurotransmission leading to some stimulation of all post-synaptic 5-HT receptors.

After chronic administration a number of adaptive processes may play a role, although much is still quite speculative. Because the 5-HTTs are chronically blocked, a chronically enhanced level of 5-HT is present at somatodendritic level. This leads to desensitization of the 5-HT$_{1A}$ receptors and consequently to lesser (or no) inhibition of the cell firing of the 5-HT neuron, leading to higher 5-HT release. Simultaneously, also the synaptic 5-HTTs are chronically blocked which means, together with the enhanced release of 5-HT, to strongly enhanced synaptic levels of 5-HT. It is possible, although not fully elucidated yet, that the 5-HT$_{1B/1D}$ autoreceptors also desensitize, which might contribute to the process of enhanced 5-HT neurotransmission. The net effect of chronic SSRI administration is thus a strongly enhanced 5-HT neurotransmission. Apparently, activation of one (or more) of the post-synaptic 5-HT receptors, contributes to the antidepressant and anxiolytic effects of the SSRIs.

6. Premature ejaculation and 5-HT

Some of the SSRIs appear effective in inhibiting the premature ejaculation both after acute and chronic administration [55,52,54,53] whereas their antidepressant and anxiolytic effects only gradually emerge over time. This remarkably rapid onset is not well understood. It is suggested that acute blockade of 5-HT re-uptake enhances 5-HT transmission into the synapse. These acute synaptic effects occur within hours of administering antidepressant SSRIs. Since the rapid onset of postponement of ejaculation by SSRIs has a similar time course as the synaptic effects it is suggested that the postponement of ejaculation is mediated by the acutely enhanced 5-HT neurotransmission.

Apart from their rapid onset of action, the question remains why SSRIs, such as paroxetine [55,52,54], fluoxetine [55], sertraline [34,55] and to a lesser extent also fluvoxamine [55] delay ejaculation time. Human ejaculation is peripherally activated by $\alpha_{1}$-noradrena-
The involvement of the central serotonergic neurotransmission in human ejaculation has been investigated in animal studies. Induction of penile erections in rats and rhesus monkeys showed that responses due to SSRI treatment are identical to those seen after selective activation of 5-HT2C receptors [49,8,12] and are different from the responses seen after 5-HT1A and 5-HT2A receptor stimulation [58,11,36,30]. Moreover, a cross familiarization study showed that the drug stimuli of the SSRI’s fluoxetine and paroxetine most resemble those of a 5-HT2C-receptor agonist [10]. Apparently, it seems that the responses from SSRI treatment in these animals are due to 5-HT2C receptor activation [12,49]. Since paroxetine treatment results in ejaculation retardation, it is suggested that in humans premature ejaculation is caused by hyposensitivity of 5-HT2C receptors. Such a concept would correspond with the results of rat studies in which the 5-HT receptor agonists D-LSD (D-lysergic acid diethylamide) and quipazine increase the ejaculation latency [2]. Furthermore, DOI (2,5-dimethoxy-4-iodophenyl-2-aminopropane) which equally stimulates 5-HT2A and 5-HT2C receptors, also increases the ejaculation latency [22], while the selective 5-HT2A receptor agonist DOM (2,5-dimethoxy-4-methylamphetamine) does not have this effect [2].

In male rats also another 5-HT subtype receptor seems to be involved in the ejaculation process. Activation of 5-HT1A receptors by the selective 5-HT1A receptor agonist 8-OH-DPAT (8-hydroxy-2-(di-n-propylaminotetralin) shortens the ejaculation latency time and reduces the number of intermissions preceding ejaculation in animals [2]. The behavioral response to activation of 5-HT1A receptors is attenuated or completely blocked by co-activation of 5-HT2C receptors indicating that functional interactions between these receptors exists [9]. Extrapolating these findings from animal research to human premature ejaculation one might speculate that premature ejaculation may be caused by the hypersensitive 5-HT1A receptor. Treatment of premature ejaculation by an SSRI will then induce activation of the 5-HT2C receptor and consequently decrease the function of the 5-HT1A receptor or restore the balance between 5-HT1A and 5-HT2C receptor function, resulting in an overall delay of ejaculation.

However, the identification of which specific 5-HT receptor subtypes are involved in the human ejaculation process is only possible by administration of subtype selective 5-HT ligands in patients with premature ejaculation. Unfortunately, these agents are not yet available for human use.

7. SSRIs and their neurophysiological substrates of sexual side effects

Although it is well known that SSRIs have sexual side effects in humans, such as retardation of ejaculation and anorgasmia [35], the neural substrates involved in these effects are unknown. The bulk of psychopharmacological studies using SSRIs for depression, anxiety disorders or the obsessive-compulsive disorder have investigated their effects on serotonergic neurons and their projections to cortical and subcortical structures. However, studying sexual effects of SSRIs, such as their effect on ejaculation, necessitates studies not only on cortical and subcortical functions, but also on brainstem functions, spinal cord mechanisms and the peripheral nervous system.

The recent description of the emotional motor system (EMS) by Holstege [28,29] might represent a neuroanatomical substrate for the emotional influences on basic neurogenital pathways. Further research into the relationship between the central serotonergic system and the EMS might illuminate the speculative idea that a threshold for ejaculation is set and modulated somewhere in the central nervous system and can be changed by SSRI treatment.

References


