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Review

Serotonin and the neurobiology of the ejaculatory threshold

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Abstract

Disorders of the ejaculatory threshold, such as lifelong premature ejaculation, are fairly common in humans and can have a great impact on the quality of life.

Research in humans and rats have indicated that increased serotonin levels in the central nervous system elevate the ejaculatory threshold, probably via 5-HT_{1B} and 5-HT_{2C} receptors, whereas depletion of serotonin decreases the ejaculatory threshold. 5-HT_{1A} receptor activation strongly lowers the ejaculatory threshold, probably mediated by both the reduction of serotonin levels via presynaptic 5-HT_{1A} receptors and yet unknown effects of postsynaptic 5-HT_{1A} receptors.

The present review attempts to integrate psychopharmacological data on serotonergic control over ejaculation with the knowledge of the neuroanatomical substrate of ejaculation, indicating the importance of the lumbosacral spinal cord, the nucleus paragigantocellularis, the lateral hypothalamic area and several other supraspinal areas. In addition, the gaps in our understanding of the role of serotonin in the ejaculatory threshold are discussed. Filling in those gaps might help to design specific drugs that alter the ejaculatory threshold, thereby alleviating ejaculatory disorders.

Keywords: Ejaculation; 5-HT; SSRIs; Spinal cord; Nucleus paragigantocellularis; Lateral hypothalamic area

Contents

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1. Introduction

Male sexual behaviour differs widely between mammalian species, but it has two common factors: the stimulation of the genitals by insertion of the penis into the vagina (intromission) and the expulsion of semen in the female genital tract (ejaculation) (Meisel and Sachs, 1994). The ejaculatory threshold, which can be defined as the number of intromissions preceding ejaculation (intromission frequency) and/or the latency time from the start of copulation to ejaculation (ejaculation latency), can therefore be determined for all male mammals including rats and humans (Bitran and Hull, 1987; Waldinger, 2003).

Investigating the ejaculatory threshold is of great importance, since disorders of this threshold, such as lifelong premature and retarded ejaculation, are fairly common in human males and can have a great impact on the quality of life (Hartmann and Waldinger, 2005; Waldinger, 2005; Waldinger and Schweitzer, 2005; Waldinger et al., 2005b). Premature ejaculation is now often successfully treated with antidepressant drugs that alter serotonergic neurotransmission (Waldinger, 2005), but drugs designed specifically to treat ejaculatory disorders are called for. In order to find such drugs, the neural substrate of the ejaculatory threshold needs to be determined, including all neuroanatomical, physiological and pharmacological aspects.

Although some research on ejaculation has been performed in men (Waldinger et al., 1998b, 2001), the practical and ethical limitations to conduct neuroanatomical and psychopharmacological experiments in humans require the use of animal models. The vast majority of sexual behaviour research has been performed in rats. Therefore, all experiments discussed in this review were conducted in rats unless stated otherwise. The reasons to use rats in sexual behaviour research are various (Pfaus, 1996), and include the fact that their intromissions and ejaculations are clearly discernable (Bitran and Hull, 1987). In addition, both rats and humans have an average ejaculation latency of about five minutes, although large individual differences exist within both human and rat populations (Olivier et al., 2005; Pattij et al., 2005; Waldinger et al., 2005a). Other aspects of sexual behaviour obviously differ between rat and human males. Rats are much more influenced by olfactory cues than humans, the male rat has little physical contact with the female in the seconds between each mount and intromission, and male rats have multiple ejaculations during copulation. A schematic overview of male rat sexual behaviour is given in Fig. 1, which is an adaptation of the figure in the review of Larsson and Ahlenius (Larsson and Ahlenius, 1999).

The neurotransmitter serotonin (5-HT) has been implicated in the central regulation of blood pressure, body fluid homeostasis, locomotion, food intake, nociception, cognition, arousal, stress responses, mood and many other autonomic and behavioural functions. The ubiquitous presence of 5-HT fibres throughout the central nervous system (Steinbusch, 1981), the many different 5-HT receptor subtypes (Barnes and Sharp, 1999), the variety of signal transduction mechanisms activated by each 5-HT receptor subtype (Raymond et al., 2001) and the diversity in autoregulatory mechanisms in the 5-HT system (Pineyro and Blier, 1999) make it highly complicated to unravel the precise role of serotonin in behaviour. The specific role of 5-HT in the ejaculatory threshold has been investigated since the early 1970s, and it was soon established that 5-HT, in contrast to dopamine, inhibits ejaculation. Since then, increasingly sophisticated neuroanatomical and psychopharmacological tools have revealed more specific roles of 5-HT and its receptor subtypes in the ejaculatory threshold.

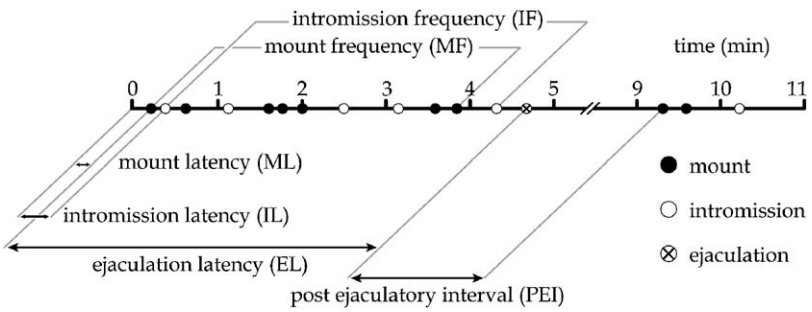

Fig. 1. The temporal pattern of male rat sexual behavior. Adapted from Larsson and Ahlenius (1999).

2. Neuroanatomical substrate

The autonomic and somatic motor neurons that execute the different phases of ejaculation are located in the thoracolumbar and lumbosacral spinal cord. These motor neurons are activated in a coordinated manner when sufficient sensory input to reach the ejaculatory threshold has entered the central nervous system. Interneurons in the lumbar spinal cord as well as neurons originating from various supraspinal areas are thought to modulate the ejaculatory threshold, possibly using serotonin as neurotransmitter.

2.1. Spinal cord

Ejaculation occurs in two stages, referred to as emission and expulsion (ejection), which are executed via noradrenergic sympathetic, cholinergic parasympathetic and cholinergic somatic motor neurons originating in the spinal cord. Emission of spermatozoa from the testes and seminal fluids from the seminal vesicles and prostate is induced by sympathetic motor neurons in the thoracolumbar intermediolateral cell column (IML) and parasympathetic motor neurons in the sacral parasympathetic nucleus (SPN). Somatic motor neurons in the dorsolateral and dorsomedial ventral horn of the lumbosacral spinal cord cause rhythmic contractions of the striated ischiocavernosus and bulbospongiosus muscles in the pelvic floor that lead to the forceful expulsion of semen from the urethra (Coolen et al., 2004b; Marson and McKenna, 1996; McKenna, 2000; Steers, 2000; Waldinger et al., 1998a). A schematic overview of the relevant spinal cord areas is given in Fig. 2, which is an adaptation from the figures in Paxinos and Watson (Paxinos and Watson, 1998).

The motor neurons involved in ejaculation are triggered, amongst others, by sensory input from the genitals. This genitosensory input is predominantly generated by intromissions and reaches the dorsal horns and dorsal grey commissure of the lumbosacral spinal cord via the dorsal penile nerve, a branch of the pudendal nerve (McKenna and Nadelhaft, 1986; Ueyama et al., 1987). Urethral distension, which stimulates the dorsal penile nerve, elicits an 'urethrogenital reflex' in anesthetized rats with a transection of the spinal cord at the T6 level. This reflex includes rhythmic contractions of the striated muscles and expulsion of the urethral contents, and is therefore used as a model for ejaculation (Carro-Juarez and Rodriguez-Manzo, 2000; Chung et al., 1988; Duran et al., 1997; McKenna et al., 1991).

Apparently, the relay of genitosensory input to ejaculatory motor output takes place at the level of the spinal cord in the form of a reflex arc. A group of galaninergic interneurons in the border area of laminae 7 and 10 at the lumbar 3 and 4 levels of the spinal cord, called the lumbar spinothalamic cells (LSt cells), is the most likely candidate for such a relay centre (Truitt and Coolen, 2002). Galaninergic fibres originating from the LSt cells project

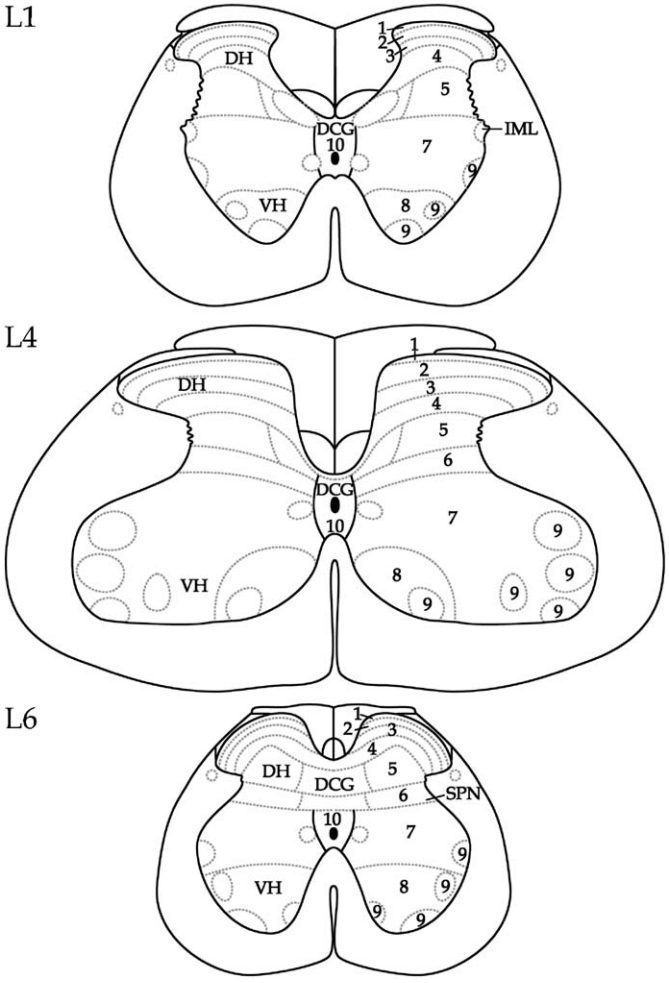

Fig. 2. Schematic representation of coronal spinal cord sections at the lumbar 1, 4 and 6 levels. Numbers represent the laminae; DH: dorsal horn; VH: ventral horn; DCG: dorsal commissural grey; IML: intermediate lateral cell column; SPN: sacral parasympathetic nucleus. Adapted from Paxinos and Watson (2005).

to all areas in the spinal cord containing motor neurons involved in ejaculation, and selective lesion of the LSt cells eliminates ejaculation without affecting other parameters of sexual behaviour (Truitt and Coolen, 2002; Xu et al., 2005). The activation of LSt cells probably plays an important role in the ejaculatory threshold.

Serotonergic fibres have been found in all the areas of the spinal cord containing sensory fibres and motor neurons involved in ejaculation, in particular the lumbosacral dorsal and ventral horns, dorsal commissural grey and IML and SPN (Maxwell et al., 1996; Ranson et al., 2003; Tang et al., 1998). Serotonergic fibres were found in close association with cell bodies in the IML showing Fos-expression in response to the urethrogenital reflex (Marson and Gravitt, 2004), and they make synaptic contact with SPN neurons labelled by retrograde tracers injected in the pelvic nerve as well as lumbosacral somatic motor neurons labelled by retrograde tracers injected in the striated pelvic floor muscles (Tang et al., 1998). In addition, serotonergic

fibres have been found in close apposition to the LSt cells (Coolen et al., 2004a). Serotonin might affect ejaculation via any of these possible connections.

2.2. Supraspinal areas

A modulating role for supraspinal areas in the ejaculatory threshold was indicated by the finding that the urethrogenital reflex cannot be elicited in intact rats, but usually requires either thoracic spinal transection or lesion of the nucleus paragigantocellularis (nPGi), an area in the ventrolateral medulla in the brainstem (Marson and McKenna, 1990). Lesioning of the nPGi also facilitates ejaculation in copulating rats (Yells et al., 1992). Since neurons in the nPGi are consistently labelled when retrograde transneuronal tracers are injected into the penis, bulbospongiosus muscle, epididymis or prostate (Gerendai et al., 2001; Marson et al., 1993; Orr and Marson, 1998; Tang et al., 1999), the nPGi is thought to exert a tonic inhibition over ejaculation via relays in the spinal cord. Serotonin probably mediates this inhibition, since a large portion of neurons in the nPGi that project to the motor neurons innervating the bulbospongiosus muscle contain serotonin (Marson and McKenna, 1992). The medial preoptic area (MPOA), a hypothalamic brain area that integrates the sensory information induced by female pheromones and genital stimulation (Bressler and Baum, 1996; Coolen et al., 1998, 2003b) and is a crucial structure for the performance of sexual behaviour (Hansen et al., 1982; Liu et al., 1997b; Meisel and Sachs, 1994; Paredes et al., 1993), projects heavily to the nPGi via relays in the periaqueductal grey and might lower the ejaculatory threshold by removing the tonic serotonergic inhibition exerted by the nPGi (Marson, 2004; Marson and McKenna, 1994b; Murphy and Hoffman, 2001; Murphy et al., 1999). Stimulation of the MPOA can elicit the urethrogenital reflex, even without spinal transection or lesion of the nPGi (Marson and McKenna, 1994b).

Besides the MPOA-PAG-nPGi-spinal cord pathway, there is at least one other serotonergic pathway that influences sexual behaviour. Serotonin release in the anterior lateral hypothalamic area, most likely from axons originating from the dorsal and median raphe nuclei and travelling through the medial forebrain bundle (van de Kar and Lorens, 1979), increases sharply in response to an ejaculation (Lorrain et al., 1997). This is thought to induce the suppression of copulation during the post-ejaculatory interval, and could be partly mediated by an inhibition of dopaminergic neurotransmission in the nucleus accumbens (Lorrain et al., 1999). Indeed, electrolytic lesions of the median raphe nucleus and, less consistently, the dorsal raphe nucleus lowered the ejaculatory threshold by reducing intromission frequency and ejaculation latency (Albinsson et al., 1996; McIntosh and Barfield, 1984). Selective degeneration of serotonergic fibres in the medial forebrain bundle by local injection of the serotonergic toxin 5,7-dihydroxytryptamine (5,7-DHT) led to an increased percentage of rats ejaculating and a decreased intromission frequency compared to sham-lesioned rats (Rodriguez et al., 1984).

In these two pathways, the link between serotonergic neurotransmission and ejaculation is evident. In many other brain areas that are known to influence ejaculation, a mediating role of serotonin is possible but not yet demonstrated. Experiments using lesions (Kondo and Yamanouchi, 1995; Liu et al., 1997b) or the staining of Fos (Baum and Everitt, 1992; Coolen et al., 1997a, 1996; Greco et al., 1996) in rats, gerbils and hamsters have implicated the medial amygdala, the posterior medial bed nucleus of the stria terminalis and the medial parvocellular subparafascicular thalamic nucleus in ejaculation and the post-ejaculatory interval, possibly via their reciprocal connections with the MPOA (Coolen et al., 1998, 2003a; Heeb and Yahr, 2001; Parfitt and Newman, 1998). These areas contain some serotonergic fibres (Steinbusch, 1981) that might play a role in the effects on ejaculation.

Furthermore, the nucleus accumbens, paraventricular hypothalamic nucleus and arcuate hypothalamic nucleus all receive serotonergic input (Casu et al., 2004; Larsen et al., 1996; Steinbusch, 1981; Steinbusch and Nieuwenhuys, 1981). The nucleus accumbens is thought to play a role in sexual motivation and reward (Balfour et al., 2004), and lesion of this nucleus disrupts ejaculation (Kippin et al., 2004). The paraventricular hypothalamic nucleus contains oxytocin that lowers the ejaculatory threshold (Stoneham et al., 1985), and lesion of this nucleus increases the ejaculatory threshold (Liu et al., 1997a). The arcuate hypothalamic nucleus is connected with the MPOA, the medial amygdala, the bed nucleus of the stria terminalis and the paraventricular nucleus, and is thought to integrate information about metabolism with reproductive activity (Gottsch et al., 2004; Magoul et al., 1994). In conclusion, the current understanding of the neuroanatomical association between serotonin and the ejaculatory threshold is far from complete and needs to be further investigated.

3. Serotonin levels

In the last four decades, many researchers have demonstrated that pharmacological manipulations of serotonergic neurotransmission markedly changed parameters of sexual behaviour, in particular the intromission frequency and ejaculation latency.

3.1. Increased 5-HT levels

Since 5-HT does not cross the blood brain barrier, the net effects of serotonin on the ejaculatory threshold have been investigated using systemic injection of the 5-HT precursor 5-hydroxytryptophan (5-HTP), which does cross the blood brain barrier. 5-HTP has been found to increase 5-HT release from serotonergic neurons in the lateral hypothalamic area and the lumbar spinal cord for as long as three hours (Gartside et al., 1992; Kimura et al., 1983;

Samathanam et al., 1989; Shimizu et al., 1992). Systemic injection of 5-HTP increased the intromission frequency and ejaculation latency in rats (Ahlenius and Larsson, 1984, 1985, 1991, 1998; Ahlenius et al., 1980; Fernandez-Guasti and Rodriguez-Manzo, 1992), and mongrel dogs treated with 5-HTP failed to ejaculate upon genital stimulation (Kimura et al., 1977). Serotonin levels can also be elevated throughout the central nervous system by acute systemic administration of the 5-HT releasers para-chloroamphetamine (*p*-CA) or fenfluramine (Gardier et al., 1994; Schwartz et al., 1989; Series et al., 1994). This leads to an increased ejaculation latency as well (Foreman et al., 1992).

To avoid the blood brain barrier, 5-HT can be injected directly into the brain or the cerebrospinal fluid. Local injection of 5-HT into the nucleus accumbens, MPOA and amygdala, as well as intracerebroventricular or intrathecal injections, increased the intromission frequency and ejaculation latency (Drago et al., 1999; Fernandez-Guasti et al., 1992b; Hillegaart et al., 1991) or decreased the percentage of rats that reached an ejaculation (Svensson and Hansen, 1984; Verma et al., 1989). Thus, the elevation of serotonin levels in many brain areas and the spinal cord increases the ejaculatory threshold.

Conversely, local injection of 5-HT in low doses into the dorsal or median raphe nuclei lowered the ejaculatory threshold (Hillegaart et al., 1989), interpreted by assuming that feedback systems, which inhibit cell firing and decrease 5-HT levels in projection areas, were activated (Pineyro and Blier, 1999). However, injection of higher doses of 5-HT into the dorsal and median raphe nuclei had no effect on ejaculation (Fernandez-Guasti et al., 1992a; Hillegaart et al., 1989).

3.2. SSRIs

The selective serotonin reuptake inhibitors (SSRIs) fluoxetine, paroxetine, fluvoxamine, citalopram and sertraline are widely used and effective antidepressants. They all act similarly by blocking 5-HT transporters, thereby preventing the reuptake of 5-HT from the synaptic cleft into the presynaptic serotonergic neuron. This leads to elevated extracellular 5-HT levels, as shown by microdialysis studies following acute systemic administration of fluoxetine (Bymaster et al., 2002; Felton et al., 2003; Hervas and Artigas, 1998; Malagie et al., 1995), paroxetine (Hajos-Korcsok et al., 2000; Malagie et al., 2000; Nakayama, 2002), fluvoxamine (Ago et al., 2005; Bosker et al., 1995; Denys et al., 2004), citalopram (Invernizzi et al., 1995; Moret and Briley, 1996; Wegener et al., 2003; Yoshitake et al., 2003) and sertraline (Sprouse et al., 1996; Zhang et al., 2000).

Besides an increased activation of postsynaptic 5-HT receptors, elevated 5-HT levels also turn on negative feedback systems via serotonin autoreceptors, leading to a reduced release of serotonin from nerve terminals. This probably attenuates acute effects of SSRI treatment on mood disorders. During chronic SSRI-treatment (3–4 weeks) 5-HT autoreceptors, especially 5-HT_{1A} receptors, become desensitized, and this has been proposed as one means to enable the antidepressant effects to occur (Blier et al., 1998; Elena Castro et al., 2003; Hensler, 2003; Invernizzi et al., 1996; Le Poul et al., 2000; Newman et al., 2004; Pineyro and Blier, 1999).

Treatment with SSRIs often causes sexual problems, of which delayed ejaculation and the inability to ejaculate are the most commonly reported (Gregorian et al., 2002; Montgomery et al., 2002; Rosen et al., 1999). These side effects are generally perceived as negative, but SSRI-induced delayed ejaculation has turned out to be very useful in the treatment of lifelong premature ejaculation (Chia, 2002; Kara et al., 1996; Kim and Seo, 1998; McMahon et al., 2004; Moreland and Makela, 2005; Waldinger et al., 2004).

The use of the so-called intravaginal ejaculation latency time (IELT), as measured with a stopwatch (Waldinger, 2003), has greatly increased the amount of objective data on the effects of SSRIs on the ejaculatory threshold. Interestingly, this method revealed marked differences between SSRIs in their ability to delay ejaculation in patients suffering from premature ejaculation: paroxetine delayed ejaculation more strongly than the other SSRIs, whereas citalopram and fluvoxamine affected ejaculation much less (Waldinger et al., 1998b, 2001, 2004). In addition, the effects of paroxetine and fluoxetine became clinically relevant only after a few weeks of chronic treatment and increased over time (Waldinger et al., 1998b, 2001).

There have been some studies dealing with the effects of SSRIs on sexual behaviour in rats. These studies often failed to find a significant effect of acute systemic injection of several SSRIs on the ejaculatory threshold (Ahlenius et al., 1979; Ahlenius and Larsson, 1999; Cantor et al., 1999; de Jong et al., 2005a, b; Mos et al., 1999), although acutely administered fluoxetine or paroxetine sometimes delayed ejaculation (Waldinger et al., 2002; Yells et al., 1994), and acute local injection of the SSRI alaproclate into the lateral hypothalamic area increased both local serotonin levels and ejaculation latency (Lorrain et al., 1997). Apparently, the ejaculatory threshold is somewhat less sensitive to acute systemic injection of an SSRI compared to acute systemic injection of 5-HTP, despite their shared ability to elevate serotonin levels. This might be explained by the difference in pharmacology between the two drugs: 5-HTP increases 5-HT release, whereas SSRIs prevent 5-HT reuptake. However, a direct comparison between the two compounds on 5-HT levels in brain areas relevant for ejaculation has not yet been performed.

Delayed ejaculation reliably occurs in rats in response to chronic treatment with paroxetine or fluoxetine (de Jong et al., 2005b; Vega et al., 1998; Waldinger et al., 2002), but less so or not at all in response to citalopram or fluvoxamine (de Jong et al., 2005a, b; Waldinger et al., 2002), which resembles the situation in humans (Waldinger

et al., 1998b, 2001). The difference between acute and chronic treatment suggests that desensitization mechanisms may play a role in the effects of paroxetine and fluoxetine on ejaculation. In addition, the lack of effects of fluvoxamine and citalopram indicate that these desensitization mechanisms vary from one SSRI to another. More evidence in that direction is discussed in the paragraph about 5-HT_{1A} receptors.

3.3. 5-HT depletion

Multiple systemic injections of para-chlorophenylalanine (*p*-CPA), which strongly depletes 5-HT in the central nervous system (Kimura et al., 1977; Qureshi et al., 1989), decreased the ejaculation latency (Ahlenius et al., 1971; Dahlof and Larsson, 1979; Gessa and Tagliamonte, 1974; Qureshi et al., 1989; Salis and Dewsbury, 1971; Yamanouchi and Kakeyama, 1992) and intromission frequency (Fernandez-Guasti and Escalante, 1991) and increased the ejaculation frequency (Tsutsui et al., 1994; Yamanouchi and Kakeyama, 1992). Intracerebroventricular injection of 5,7-DHT, which decreased serotonin levels in the hypothalamus, brainstem and spinal cord, enabled the urethrogenital reflex to occur upon urethral distension in intact rats. A similar result was found when 5,7-DHT was injected intrathecally, which decreased serotonin levels only in the spinal cord (Marson and McKenna, 1994a). Taken together, a decrease in serotonin levels in the spinal cord and supraspinal areas lowers the ejaculatory threshold.

3.4. Serotonin receptors

The abundant evidence that serotonin is involved in the mechanisms mediating the ejaculatory threshold encouraged researchers to determine which serotonin receptors contribute to this process. The increasing availability of selective serotonin receptor agonists and antagonists greatly advanced the knowledge about the roles of specific receptor subtypes. So far, 5-HT_{1A}, 5-HT_{1B} and 5-HT_{2C} receptors are the only serotonin receptor subtypes that have been shown to affect the ejaculatory threshold. All three receptor subtypes are located in the thoracolumbar IML, the lumbar dorsal commissural grey and laminae 7 and 10, the lumbosacral dorsal and ventral horns and the SPN (Bancila et al., 1999; Fonseca et al., 2001; Thor et al., 1993), indicating that serotonin may modulate the ejaculatory threshold directly via these receptors in the spinal cord. In addition, the presence of these 5-HT receptor subtypes in supraspinal areas involved in ejaculation may play a role as well.

3.5. 5-HT_{1A} receptors

5-HT_{1A} receptors are positioned presynaptically on the soma and dendrites of serotonergic neurons as well as postsynaptically on neurons containing a wide variety of neurotransmitters (Barnes and Sharp, 1999). Activation of somatodendritic 5-HT_{1A} autoreceptors leads to a potent inhibition of the firing frequency of serotonergic neurons (Hajos et al., 1999), constituting a negative feedback system through inhibition of 5-HT release in projection areas (Hjorth and Sharp, 1991; Pineyro and Blier, 1999). Activation of postsynaptic 5-HT_{1A} heteroreceptors can lead to a wide variety of actions, depending on the electrophysiological properties, projection areas and neurotransmitters used by the postsynaptic neuron.

The staining of 5-HT_{1A} receptor proteins or mRNA has shown that these receptors are located in the raphe nuclei (Kia et al., 1996; Li et al., 1997a; Pompeiano et al., 1992; Wright et al., 1995) and the nucleus paragigantocellularis (Helke et al., 1997; Kia et al., 1996; Pompeiano et al., 1992), where they probably act as autoreceptors on serotonergic neurons. Postsynaptic 5-HT_{1A} receptors are distributed throughout the brain, including nuclei implicated in ejaculation such as the MPOA (Aznar et al., 2003; Pompeiano et al., 1992), lateral hypothalamic area (Collin et al., 2002; Kia et al., 1996; Li et al., 1997a), medial amygdala (Aznar et al., 2003; Li et al., 1997a; Pompeiano et al., 1992), bed nucleus of the stria terminalis (Kia et al., 1996; Pompeiano et al., 1992), nucleus accumbens (Aznar et al., 2003; Wright et al., 1995), paraventricular hypothalamic nucleus (Collin et al., 2002; Li et al., 1997a; Zhang et al., 2004) and arcuate hypothalamic nucleus (Aznar et al., 2003; Collin et al., 2002).

Selective activation of 5-HT_{1A} receptors has a remarkably strong effect on the ejaculatory threshold. The first report that systemic administration of the 5-HT_{1A} receptor agonist 8-OH-DPAT reduced the intromission frequency and ejaculation latency was published in 1981 (Ahlenius et al., 1981), and this finding has been reproduced many times (Ahlenius and Larsson, 1984; Coolen et al., 1997b; Fernandez-Guasti and Rodriguez-Manzo, 1997; Mendelson and Gorzalka, 1986; Morali and Larsson, 1984; Rehman et al., 1999; Schnur et al., 1989; Sura et al., 2001). Although 8-OH-DPAT has considerable affinity for the 5-HT7 receptor (Bard et al., 1993; Neumaier et al., 2001), the findings that systemic injection of other 5-HT_{1A} receptor agonists had similar effects on ejaculation (Ahlenius and Larsson, 1991; Andersson and Larsson, 1994; Haensel and Slob, 1997; Mathes et al., 1990) and that these effects could be reversed completely by systemic injection of selective 5-HT_{1A} receptor antagonists (Ahlenius and Larsson, 1998; Hillegaart and Ahlenius, 1998) indicate that 5-HT_{1A} receptor activation is responsible for the lowering of the ejaculatory threshold.

The somewhat puzzling opposite effects of 5-HT itself, which is the natural ligand of 5-HT_{1A} receptors, versus 5-HT_{1A} receptor agonists on the ejaculatory threshold might be explained by their activation of somatodendritic 5-HT_{1A} autoreceptors, which causes a reduction of 5-HT levels in projection areas and thus mimics the effects of serotonin depletion (Hjorth and Sharp, 1991; Hughes et al., 2005; Invernizzi et al., 1995, 1996). Indeed, micro-injection of 8-OH-DPAT into the median raphe nucleus reduced the

ejaculation latency and intromission frequency (Hillegaart et al., 1991), although a similar injection into the dorsal raphe nucleus failed to affect sexual behaviour (Fernandez-Guasti et al., 1992b; Hillegaart et al., 1991).

On the other hand, the reduction of intromission frequency and ejaculation latency following depletion of 5-HT levels by systemic injection of *p*-CPA or intracerebroventricular injection of 5,7 DHT was further decreased by systemic administration of 8-OH-DPAT (Fernandez-Guasti and Escalante, 1991), suggesting that both pre- and postsynaptic 5-HT_{1A} receptors are involved in the lowering of the ejaculatory threshold. In addition, intrathecal injection of 5-HT_{1A} receptor agonists strongly reduced the intromission frequency and ejaculation latency (Lee et al., 1990; Mathes et al., 1990; Svensson and Hansen, 1984). Since the spinal cord contains neither serotonergic cell bodies nor 5-HT_{1A} autoreceptors, spinal postsynaptic 5-HT_{1A} receptors probably mediated these effects. Moreover, micro-injection of 5-HT_{1A} receptor agonists in the nucleus accumbens and MPOA lowered the ejaculatory threshold as well (Fernandez-Guasti et al., 1992b; Hillegaart et al., 1991; Matuszewich et al., 1999), suggesting an additional role for supraspinal 5-HT_{1A} receptors. However, the ability of 8-OH-DPAT to increase dopamine levels (Gobert et al., 1998) and bind to D2 receptors (Rinken et al., 1999) might mediate some of the effects on ejaculation in these areas. Indeed, local injection of 8-OH-DPAT in the MPOA led to increased dopamine levels in that area (Lorrain et al., 1998) and a lowering of the ejaculatory threshold that could be reversed by a D2 receptor antagonist, but not a 5-HT_{1A} receptor antagonist (Matuszewich et al., 1999). It should be noted here that, in contrast to systemic injection, local injection with 8-OH-DPAT increased serotonin levels in the MPOA (Lorrain et al., 1998). This finding indicates that elevated serotonin levels in the MPOA do not always coincide with an increased ejaculatory threshold. Possibly, the simultaneously elevated dopamine levels and increased D2 receptor activation acted as compensatory mechanisms in this particular situation.

The effects of 5-HT_{1A} receptor agonists on the ejaculatory threshold are not universal. Systemic injection of 8-OH-DPAT inhibits ejaculation in mice (Rodriguez-Manzo et al., 2002), rabbits (Paredes et al., 2000), dogs (Yonezawa et al., 2004) and ferrets (Paredes et al., 1994), and either lowers or elevates the ejaculatory threshold in rhesus monkeys, depending on dose (Pomerantz et al., 1993b). Since 5-HT_{1A} autoreceptors probably have the same location and function in different mammalian species (Price et al., 1996), a difference in distribution of postsynaptic 5-HT_{1A} receptors in brain and spinal cord areas might explain this 8-OH-DPAT induced elevation of the ejaculatory threshold.

Interestingly, systemic injection of the selective 5-HT_{1A} receptor antagonist WAY-100635 does not increase the ejaculatory threshold by itself, indicating that activation of 5-HT_{1A} receptors is not necessary to reach ejaculation during normal copulation (Ahlenius and Larsson, 1998; de Jong et al., 2005a). However, WAY-100635 strongly enhances the increased ejaculatory threshold induced by 5-HTP (Ahlenius and Larsson, 1998) or acute SSRI-treatment (Ahlenius and Larsson, 1999; de Jong et al., 2005a; Looney et al., 2005). This could be mediated by the blockade of 5-HT_{1A} autoreceptors that normally limit the increase in 5-HT levels induced by 5-HTP or SSRIs, or blockade of postsynaptic 5-HT_{1A} receptors that lower the ejaculatory threshold via the activation, disinhibition or perhaps inhibition of neurons in brain and spinal cord areas involved in ejaculation.

These findings imply that 5-HT_{1A} receptor activation becomes increasingly important to reach the ejaculatory threshold when serotonin levels are elevated, and that a combination of elevated serotonin levels and impaired 5-HT_{1A} receptor functioning strongly inhibits ejaculation. This might underlie SSRI-induced delayed ejaculation, since chronic treatment with the SSRI paroxetine, which delays ejaculation, reduced the facilitation of ejaculation induced by 8-OH-DPAT in rats (de Jong et al., 2005b), probably through 5-HT_{1A} receptor desensitization (Le Poul et al., 1995; Li et al., 1997b). Chronic treatment with fluvoxamine, an SSRI that has no sexual side effects in humans, failed to delay ejaculation and to reduce the effects of 8-OH-DPAT on ejaculation in rats (de Jong et al., 2005b). Further research might elucidate whether desensitization of pre- or postsynaptic 5-HT_{1A} receptors plays a role in SSRI-induced delayed ejaculation.

3.6. 5-HT_{1B} receptors

5-HT_{1B} receptors are located on pre- and postsynaptic axon terminals, where they act as autoreceptors and inhibit serotonin release (Barnes and Sharp, 1999; Raymond et al., 2001; Sari, 2004) or as heteroreceptors by inhibiting the release of various neurotransmitters (Clark and Neumaier, 2001; Sari, 2004). 5-HT_{1B} receptors are found in the raphe nuclei, lateral hypothalamic area, bed nucleus of the stria terminalis, nucleus accumbens, paraventricular hypothalamic nucleus and arcuate hypothalamic area (Makarenko et al., 2002; Neumaier et al., 1996).

Systemic injection of the selective 5-HT_{1B} receptor agonist anpirtoline elevated the ejaculatory threshold by increasing the ejaculation latency and intromission frequency, which could be reversed by several 5-HT_{1B} receptor antagonists (Hillegaart and Ahlenius, 1998). In addition, systemic injection of the mixed 5-$HT_{1B/2C}$ receptor agonist *N*-[3-(trifluoromethyl)phenyl] piperazine (TFMPP) strongly reduced the percentage of rats ejaculating (Fernandez-Guasti et al., 1989), and local injection of TFMPP in the nucleus accumbens or MPOA increased the ejaculation latency (Fernandez-Guasti et al., 1992b). However, since 5-HT_{1B} receptors have not been found in the MPOA, these effects might have been mediated partly by 5-HT_{2C} receptors.

The elevation of the ejaculatory threshold by systemic injection of 5-HTP could be reversed by the 5-HT_{1B}

receptor antagonist isamoltane (Ahlenius and Larsson, 1998), indicating that 5-HT_{1B} receptors mediate the inhibition of ejaculation induced by serotonin. However, systemic injection of 5-HT_{1B} receptor antagonists did not affect or very weakly facilitated ejaculation (Ahlenius and Larsson, 1998; Hillegaart and Ahlenius, 1998), indicating that during normal copulation the ejaculatory threshold is not maintained solely by 5-HT_{1B} receptor activation. In addition, the ejaculatory threshold is increased in 5-HT_{1B} knockout mice compared to wild type mice, indicating that the absence of 5-HT_{1B} receptors does not facilitate ejaculation in mice.

Possible mechanisms by which 5-HT_{1B} receptors inhibit ejaculation have not yet been demonstrated. A role of 5-HT_{1B} autoreceptors seems unlikely, since these receptors cause a reduction of serotonin release that would be expected to lower the ejaculatory threshold. 5-HT_{1B} heteroreceptor activation possibly inhibits the release of neurotransmitters that facilitate ejaculation, such as acetylcholine (Duran et al., 2000; Sarhan and Fillion, 1999), glutamate (Chambille and Rampin, 2002; Powell et al., 2003; Sari, 2004) or perhaps galanin (Coolen et al., 2004a), in brain and spinal cord areas involved in the ejaculatory threshold.

3.7. 5-HT_{2C} receptors

5-HT_{2C} receptors are found on postsynaptic dendrites where they generally cause cell excitation. They have not been implicated in autoregulatory feedback mechanisms (Barnes and Sharp, 1999). 5-HT_{2C} receptors are widely distributed in the central nervous system, including the raphe nuclei, MPOA, medial amygdala, bed nucleus of the stria terminalis, nucleus accumbens and arcuate hypothalamic nucleus (Abramowski et al., 1995; Clemett et al., 2000).

Systemic injection of the non-selective 5-HT_2 receptor agonist [+/−]-2,5-dimethoxy-4-iodoamphetamine (DOI) strongly decreased the percentage of rats ejaculating and increased the ejaculation latency, which could be reversed by several 5-HT2 receptor antagonists (Foreman et al., 1989; Klint et al., 1992; Klint and Larsson, 1995; Watson and Gorzalka, 1991). Systemic administration of the 5-HT_{2C} agonist m-CPP produced a dose-dependent decline in the percent of rats and male rhesus monkeys achieving ejaculation (Mendelson and Gorzalka, 1990; Pomerantz et al., 1993a).

The elevation of the ejaculatory threshold induced by systemic injection of the serotonin-releasers *p*-CA and fenfluramine could be prevented by pre-treatment with the 5-HT_2 receptor antagonist LY53857 (Foreman et al., 1992), whereas the increased ejaculation latency induced by 5-HTP could not be reversed by the 5-HT_2 receptor antagonist ritanserin (Ahlenius and Larsson, 1998). Systemic injection of the 5-HT2 receptor antagonist LY53857 reduced the ejaculation latency (Foreman et al., 1989), whereas ritanserin had no such effect (Watson and Gorzalka, 1991). Possibly, yet unknown differences in the neuropharmacological properties of these antagonists could explain the differences in their effect on the ejaculatory threshold.

So far, there are no reports on the possible mechanisms by which 5-HT_{2C} receptor activation elevates the ejaculatory threshold. The presence of 5-HT_{2C} receptors in many spinal and supraspinal areas involved in ejaculation indicates numerous options that should be investigated extensively.

4. Ex copula ejaculation

Some studies on the effect of 5-HT on the ejaculatory threshold used the occurrence of spontaneous, ex copula ejaculations as a model. These seminal emissions are not dependent on genital stimulation and can be evoked by the injection of the 5-HT releaser *p*-CA (Humphries et al., 1981; Renyi, 1985; Yonezawa et al., 2000) or the non-selective 5-HT receptor agonist Me-ODMT (Mas et al., 1985), which respectively increase (Foreman et al., 1992) or decrease (Ahlenius and Larsson, 1991; Fernandez-Guasti et al., 1986) the ejaculatory threshold during copulation. Serotonin depletion induced by *p*-CPA, which by itself did not affect spontaneous ejaculation (Humphries et al., 1981), prevented the ex copula ejaculations caused by *p*-CA (Renyi, 1985; Yonezawa et al., 2000). The effects of *p*-CA and 5-MeODMT on spontaneous ejaculation could not be reversed by thoracic spinal transection (Mas et al., 1985; Yonezawa et al., 2000). These results suggest that activation of spinal serotonin receptors can directly activate the motor neurons involved in seminal emission. 5-HT_{1A} receptors seem likely candidates, but both systemic and intrathecal injection of 8-OH-DPAT (Lee et al., 1990; Rehman et al., 1999; Schnur et al., 1989) and buspirone (Mathes et al., 1990; Rehman et al., 1999), which strongly decrease the ejaculatory threshold in copula, inhibited spontaneous ex copula ejaculations. Although intracerebroventricular injection of 8-OH-DPAT induced rythmic contractions of the bulbospongiosus muscle, which is one aspect of ejaculation, this effect was probably mediated by D2 receptors (Clement et al., 2005). Taken together, these data indicate that the occurrence of spontaneous ex copula ejaculations is not representative of the situation during copulation, and should be used with great care as a model for the ejaculatory threshold.

5. Summary

Neuroanatomical studies have shown that there are at least two serotonergic pathways involved in the ejaculatory threshold. The tonic release of serotonin in the lumbosacral spinal cord originating from neurons in the nPGi inhibits ejaculation until sensory input overrules this tonic inhibition. Serotonin release in response to ejaculation in the anterior lateral hypothalamic area, and perhaps the medial amygdala and medial bed nucleus of the stria terminalis,

mediates the inhibition of copulation during the post-ejaculatory interval.

Psychopharmacological experiments revealed that injection of drugs that increase 5-HT levels in the central nervous system, including the lumbosacral spinal cord, lateral hypothalamic area, MPOA, amygdala and nucleus accumbens, elevates the ejaculatory threshold. 5-HT_{1B} and 5-HT_{2C} receptors possibly mediate this, because activation of these receptors inhibits ejaculation whereas their blockade prevents the inhibition of ejaculation by elevated serotonin levels.

Depletion of 5-HT in the central nervous system decreases the ejaculatory threshold. This might occur naturally during copulation, when pheromonal and genital stimulation are thought to trigger the MPOA to inhibit the serotonergic cell firing in the nPGi, which reduces serotonin release in the lumbosacral spinal cord. Reduced activation of inhibitory postsynaptic 5-HT_{1B} and/or 5-HT_{2C} receptors in the lumbosacral spinal cord might be responsible for the facilitation of ejaculation following 5-HT depletion, although systemic injection of 5-HT_{1B} or 5-HT_{2C} receptor antagonists alone do not consistently lower the ejaculatory threshold.

The role of 5-HT_{1A} receptors in the ejaculatory threshold is somewhat more complicated. Activation of 5-HT_{1A} receptors strongly lowers the ejaculatory threshold, and this is thought to be mediated by both reduction of 5-HT levels via 5-HT_{1A} autoreceptors and yet unknown effects of spinal or supraspinal postsynaptic 5-HT_{1A} receptors. Although 5-HT_{1A} receptors are not necessary for ejaculation during normal copulation, their activation becomes crucial for ejaculation when serotonin levels are elevated. Since serotonin levels can fluctuate under many circumstances, it is possible that this mechanism developed to favour successful copulation when serotonin levels are increased.

6. Further research

Although much information has been gathered by either neuroanatomical studies or psychopharmacological experiments, the constructive combination of both fields of science is needed to improve the knowledge of the effects of serotonin on the ejaculatory threshold.

For example, the neuropharmacology of serotonergic neurons in the nPGi involved in the ejaculatory threshold is barely known. It is unclear what triggers the firing of these neurons and what their electrophysiological properties are, and whether they contain 5-$HT_{1A/1B}$ autoreceptors on their soma or axon terminals. Moreover, it is unknown whether the serotonergic neurons in the nPGi make direct or indirect functional contact with the LSt cells. Interestingly, serotonergic neurons in the nPGi and serotonergic fibres in the lumbosacral spinal cord co-express substance P (Hokfelt et al., 2000; Maxwell et al., 1996), a neurotransmitter that binds to neurokinin-1 receptors, which are abundantly present on the LSt cells (Truitt and Coolen, 2002). Substance P has been found to lower the ejaculatory threshold when micro-injected in the medial preoptic/anterior hypothalamic area (Dornan and Malsbury, 1989). Further research to investigate the functional consequences of this co-expression is required.

It is not yet understood how serotonin influences the ejaculatory threshold in supraspinal areas. Inhibition of dopaminergic neurotransmission might play a role, since dopamine release in the MPOA mediated by the medial amygdala (Dominguez et al., 2001), and in the nucleus accumbens mediated by the lateral hypothalamic area (Lorrain et al., 1999), strongly facilitate ejaculation (Hull et al., 2004). Experiments investigating how serotonin decreases dopamine release in these areas are required.

There are surprisingly few data on the exact role of 5-HT_{1B} and 5-HT_{2C} receptors on the ejaculatory threshold. The existence of more selective receptor agonists and antagonists and the improved techniques to make local injections enable innovative experiments on this subject. In addition, the use of knockout mice or creation of knockout rats that lack the 5-HT_{1A}, 5-HT_{1B} or 5-HT_{2C} receptor could further elucidate the role of serotonin on the ejaculatory threshold.

Ultimately, new findings in all these directions might help to design drugs that elevate the ejaculatory threshold in men suffering from lifelong premature ejaculation, or perhaps relieve other ejaculatory disorders.

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