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Review

Serotonergic polymorphisms in the control of ejaculation

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ABSTRACT

Serotonin has long been implicated in the regulation of the processes that trigger the ejaculatory reflex. Most evidence of serotonergic involvement is, however, indirect, stemming either from studies on rodents or clinical trials investigating effects of serotonergic drugs. In the past decade, emerging evidence for heritability (i.e., genetic effects) of premature ejaculation (PE) symptoms has spawned a number of scholarly attempts to identify genes that regulate ejaculation, most of which have focused on candidate genes related to the serotonergic system. The aim of the present review article was to summarize the literature concerning genetic association studies of PE, with focus on serotonergic genes. However, methodological obstacles relating to the candidate gene approach predict that *a priori* hypotheses regarding candidate genes are likely to generate ambiguous and spurious results if samples (e.g., if samples are underpowered and/or stratified). Attempts to replicate reported novel associations between PE symptoms and serotonergic candidate genes have largely failed (thereby adding to the growing body of evidence casting doubt on the reliability of the candidate gene approach), and at present, it is not possible to determine with acceptable certainty which serotonergic genes, if any, are involved in ejaculatory function.

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1. Introduction

A genetic component in the etiology of premature ejaculation (PE) was suggested already in 1943 by Schapiro, who in a review of 1130 cases noted that male family members of PE patients seemed to be at an increased risk of having PE themselves (Schapiro, 1943). Similarly, Waldinger et al. noted that primary PE was common among interviewed first-degree relatives of PE-patients (Waldinger et al., 1998a). The first quantitative heritability studies using population-based twin samples were conducted by Jern et al., in 2007 (Jern et al., 2007, 2009, 2010), showing that 28% of the variance in PE was explained by genetic factors, as measured by a composite variable of self-reported symptoms (latency time, ejaculatory control, and satisfaction with ejaculatory function). However, it is possible that the genetic effect is underestimated in population-based samples, as the prevalence of clinical cases of PE (intra-vaginal latency times [IELTs] of 1 min or less) is low in the general population.

A number of different etiological hypotheses for PE have been proposed and empirically tested in the past decades. For example, various hormones have been implicated in PE etiology: Corona et al. (2011). reported that PE symptoms are positively correlated with testosterone levels and negatively correlated with levels of prolactin. Jern et al. (2014), on the other hand, found no association

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between free testosterone levels and PE symptoms. There is strong evidence to implicate thyroid hormones in PE etiology, for example in that normalization of thyroid function in men with hyperthyroidism reduces the likelihood of the patient exhibiting comorbid PE symptoms (Carani et al., 2005).

Indirect evidence from studies in both humans and animals implicate that central serotonin (or 5- hydroxytryptamine; 5-HT) transmission plays a major role in PE. In humans, selective serotonin re-uptake inhibitors have been shown to exert a strong ejaculation delaying effect (Buvat et al., 2009; McMahon and Touma, 1999; Waldinger et al., 1994, 2004; Pryor et al., 2006), and are currently considered first-line treatments for PE (Althof et al., 2014). It has been hypothesized that this is because a man suffering from PE needs an increased concentration of 5-HT in the synaptic cleft (i.e., between pre- and post-synaptic cell membranes, Fig. 1) compared to unaffected men, which can be pharmacologically induced (Jannini et al., 2015a). In rats, it has been shown that administration of a serotonin receptor 1A (5-HTR_{1A}) agonist drastically facilitates ejaculation (Camacho et al., 2007), while 5-HTR_{1A} antagonists delay ejaculation (De Jong et al., 1006). Further, an inhibitory role has been suggested for 5-HTR_{1B} receptors in rats (Ahlenius and Larsson, 1998). It has been postulated that short ejaculatory latency is associated with diminished serotonin neurotransmission, hyperfunction of $5HTR_{1A}$ receptors and/or hypofunction of 5-HTR_{2C} receptors (Waldinger et al., 1998b). Given the established genetic component in the etiology of PE by means of quantitative genetic studies (Jern et al., 2007, 2009, 2010), a number of studies have attempted to identify effects of specific serotonergic polymorphisms on PE in humans. Thus far, all attempts to identify the actual genetic loci that contribute to variation in ejaculatory function have been pursued by means of candidate gene studies (i.e., an approach in which loci in *a priori* hypothesized genes are tested for statistical associations with the phenotype; in this case PE). The aim of the present paper is to review this literature.

2. Literature search

A literature search was conducted in the PubMed database. Search queries included queries for premature ejaculation and relevant genetic terms, see Table 1. The search resulted in 395 potentially relevant articles. Titles and abstracts were screened, and full texts of 13 original articles on serotonergic polymorphisms related to PE were retrieved. One additional article that was not found in the database search was identified from a previous review (Jannini et al., 2015b). In total, 14 studies were included in the review.

3. Review of the literature

An overview of articles included in the review is found in Table 2. The most extensively studied serotonergic polymorphism

Table 1
Queries and search strings used in the literature search.

Search	Query	Items found
#1	premature ejaculation	1477
#2	early ejaculation	357
#3	rapid ejaculation	246
#4	#1 OR #2 OR #3	1958
#5	polymorphism	278064
#6	serotonin	135785
#7	5-HT*	50758
#8	#5 OR #6 OR #7	415078
#9	#4 AND #10	395

Note. Search conducted in PubMed on March 30th, 2017.

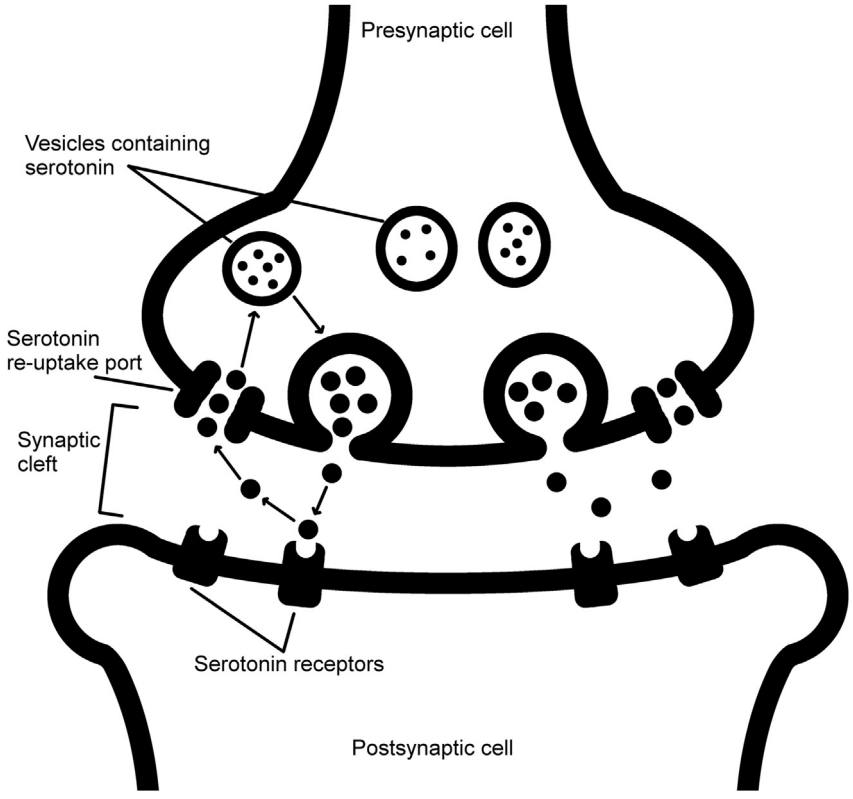

Fig. 1. The physiology of serotonin action.