

The Mechanisms of Post-SSRI Sexual Dysfunction (PSSD)

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Abstract

SSRI antidepressants are among the most widely prescribed prescription medications in the United States. They are most commonly prescribed for Major Depressive Disorder (MDD), Panic Disorder, and Anxiety. SSRIs are widely deemed to be the safest and most effective chemical treatments for these prevalent disorders. While SSRIs have a much lower side effect profile than most traditional antidepressants, they still have many side effects that drive patients to end treatment prematurely. In a vast majority of cases, these side effects recede within days or weeks of the end of treatment. For a few very unlucky people, they persist for months or years after the last pill. This has been largely undocumented in medical literature. Recently there have been a few studies that back up what the people with these lasting side effects already know: Things that go wrong while on SSRIs don't always go away.

Introduction

In the Raphe Nuclei (RN), the 5HT1A receptor acts as a presynaptic somatodendritic autoreceptor. At the ends of its projections in the hippocampus, frontal cortex, and hypothalamus, it functions as a presynaptic autoreceptor and a postsynaptic heteroreceptor (Sotelo et al., 1990; Burnet et al., 1995; Riad et al., 2000). When more Serotonin (5-HT) is found in the synapses in the RN, binding of autoreceptors inhibits the release of 5-HT in the projections of RN neurons (Koek et al., 1998; Gobbi et al., 2001). In this manner, 5-HT1A autoreceptors work as an effective regulator of 5-HT levels in the brain (Bang et al., 2012). Decreased 5-HT transmission has long been associated with MDD (Van Praag et al. 1970) and it is thought that the RN is where SSRI antidepressants exhibit their therapeutic effects. It then comes as little surprise that the 5-HT1A has been heavily implicated in effective clinical treatment of depression and anxiety. SSRIs are believed to block 5-HT reuptake by binding to SERT (5-HTT) and reducing its reuptake abilities (Murphy et al., 2004). If this was the only result, increased somatodendritic and terminal autoreceptor binding would inhibit release of 5-HT into the synapse: Resulting in no increased 5-HT levels. Through a process that is still unknown, serotonin transmission is eventually enhanced by "desensitization" of both the somatodendritic and terminal autoreceptors (Chaput et al., 1985), allowing synaptic 5-HT to accumulate in the synapse. This accounts for the characteristic 4-8 week delay between treatment origins and therapeutic relief (Gartside et al., 1995; Blier, 2010; Richardson-Jones et al., 2010). 5-HT and 5-HT1A agonist binding on the presynaptic autoreceptor inhibits 5-HT activity by hyperpolarizing the neuronal membrane (Penington and Fox, 1994). Presynaptic 5-HT1A receptors are preferentially desensitized by chronic SSRI treatment while postsynaptic receptors are not

(Pineyro and Blier, 1999). This preferential presynaptic desensitization is also seen after chronic administration of 5-HT1A agonists (Blier and de Montigny, 1994). 5-HT1B/1D autoreceptor agonists have shown less inhibitory action in cells treated chronically with low dose Fluvoxamine (Blier and de Montigny, 1983).

This model explains the widespread negative sexual and emotional changes that many people with PSSD report. Increased synaptic levels of Serotonin at RN projections would lead to more post-synaptic 5-HT receptor binding. Activation of post-synaptic 5-HT receptors inhibits the release of dopamine (DA) (Montgomery et al., 1991). Synaptic DA levels have been shown to have their activity and firing rate reduced after the administration of Escitalopram (a common SSRI antidepressant) for as little as two days (Dremencov et al., 2009). This suggests that there are several 5-HT receptors and autoreceptors that play a role in PSSD. With each SSRI likely affecting specific receptors differently. Dr. Dremencov observed that administration of a 5-HT2C antagonist completely reversed this DA inhibition in the VTA (Fig. 1). It is well known that Dopamine plays a critical role in pleasure and reward: Especially in the sexual response. A decrease in DA activity and firing rate could explain many of the symptoms associated with PSSD. Further, DA D2 binding has been shown to inhibit the secretion of Prolactin by the pituitary gland (Ben-Jonathan et al., 2001). Increased Prolactin levels are shown to negatively impact male sexual drive and ability, and play a role in the refractory period (Haake et al., 2003) (This can be seen as Hyperprolactinemia in some patients on D2 antagonists for the treatment of Schizophrenia). Because of these downstream implications of desensitization of the 5-HT1A Autoreceptor, it is very common to see sexual dysfunction in SSRI patients.

However, this dysfunction is relieved in nearly all cases after the cessation of medication. Why then, do we see thousands of antidotal reports of sexual dysfunction after treatment has ceased? Even in the absence of residual mental illness? Male mice who had mothers on SSRIs showed a permanent decrease in sexual drive (Gouvêa et al., 2008) Recently there have been new studies that are reiterating what people suffering from PSSD already know (Sheetrit et al., 2015) (Farnsworth et al., 2009) (Stinson, 2009) (Waldinger et al., 2015) (Leiblum et al., 2008) (Bolton et al., 2006) (Csoka et al., 2006), sexual side effects can remain after treatment.

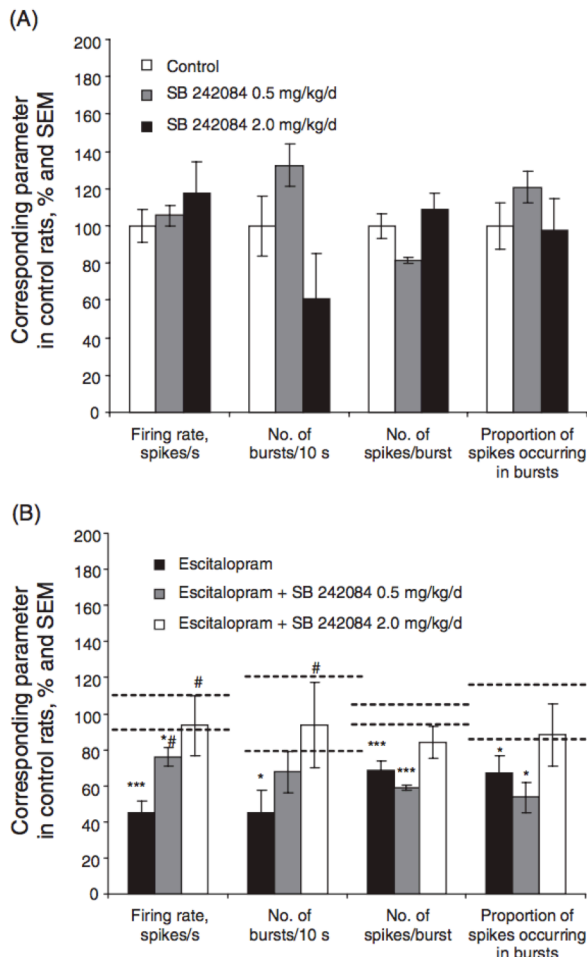


Fig. 1: 5-HT_{2C} antagonist SB-242084 completely reverses SSRI-induced DA inhibition in the rodent VTA (From Dremencov et al., 2009).

Discussion

Due to the stigma of sexual dysfunction, and doubt from physicians that persistent sexual dysfunction from SSRIs is possible, many PSSD sufferers remain silent (Stinson, 2013). Even more patients may have dysfunction that is mild or that they attribute to other factors such as aging. The emotional, social, and sexual implications of PSSD are widespread, and often lead to patients feeling alienated from their peers and loved ones (Stinson, 2013). There are several anecdotal

reports of spontaneous recovery but they are quite rare in the PSSD world. Many with PSSD therefore fear that their dysfunction is permanent. The terror of this realization adds to preexisting depressive, obsessive, or anxious behavior. Further research should focus on the methods of 5-HT autoreceptor downregulation in the DRN, and the downstream neural and hormonal effects of DRN disinhibition.

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