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Review

Sexual side effects of serotonergic antidepressants: Mediated by inhibition of serotonin on central dopamine release?☆

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ABSTRACT

Antidepressant-induced sexual dysfunction adversely affects the quality of life of antidepressant users and reduces compliance with treatment. Animal models provide an instructive approach for examining potential sexual side effects of novel drugs. This review discusses the stability and reproducibility of our standardized test procedure that assesses the acute, subchronic and chronic effects of psychoactive compounds in a 30 minute mating test. In addition, we present an overview of the effects of several different (putative) antidepressants on male rat sexual behavior, as tested in our standardized test procedure. By comparing the effects of these mechanistically distinct antidepressants (paroxetine, venlafaxine, bupropion, buspirone, DOV 216,303 and S32006), this review discusses the putative mechanism underlying sexual side effects of antidepressants and their normalization.

This review shows that sexual behavior is mainly inhibited by antidepressants that increase serotonin neurotransmission via blockade of serotonin transporters, while those that mainly increase the levels of dopamine and noradrenaline are devoid of sexual side effects. Those sexual disturbances cannot be normalized by simultaneously increasing noradrenaline neurotransmission, but are normalized by increasing both noradrenaline and dopamine neurotransmission. Therefore, it is hypothesized that the sexual side effects of selective serotonin reuptake inhibitors may be mediated by their inhibitory effects on dopamine signaling in sex brain circuits. Clinical development of novel antidepressants should therefore focus on compounds that simultaneously increase both serotonin and dopamine signaling.

Contents

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1. Introduction

Pharmacological treatment of CNS diseases often affects sexual functioning and are often a reason to stop treatment prematurely (Millan, 2006; Serretti and Chiesa, 2009). Antidepressants in general, and particularly selective serotonin reuptake inhibitors (SSRIs, e.g. paroxetine, fluoxetine, (es)citalopram, fluvoxamine, sertraline), are notorious for their sexual side effects, which is often concomitant to the already lowered libido of depressed patients (Dorevitch and Davis, 1994; Hsu and Shen, 1995; Montejo-Gonzalez et al., 1997; Waldinger et al., 1998b). It is clear that new antidepressants should have no inhibitory action on sexual behavior or, preferentially, should even stimulate an often lower sexual drive or libido in depressed patients.

Although the serotonin–noradrenaline reuptake inhibitor (SNRI) venlafaxine has been promoted as having less sexual side effects, emerging data indicate no substantial difference from the SSRIs (Kennedy et al., 2000; Lee et al., 2010). On the other hand, antidepressants with a non-serotonergic mechanism of action, like the dopamine-noradrenaline reuptake inhibitor bupropion, have few sexual side effects, and may favor sexual function (Clayton et al., 2002; Kennedy et al., 2002; Nieuwstraten and Dolovich, 2001). In addition, novel antidepressants that selectively target specific serotonin receptors (e.g. the 5-HT1A agonist buspirone) or combine SSRI activity with selective serotonin receptor activity (e.g. the SSRI-5HT1A partial agonist vilazodone) seem to have less, or are devoid of, sexual side effects (Clayton et al., 2013; Landen et al., 1999, 2005). Thus, a multi-target strategy, additionally targeting dopamine neurotransmission or regulating selective serotonin receptor activity, may prevent sexual side effects of antidepressants and thereby improve both tolerability and compliance, and consequently therapeutic efficacy.

This review discusses the stability and reproducibility of our standardized test procedure that assesses the acute, subchronic and chronic effects of psychoactive compounds on male sexual performance in a 30 minute mating test. In addition, we present an overview of the effects of several different (putative) antidepressants on male rat sexual behavior, as tested in our standardized test procedure. Moreover, by comparing the effects of these mechanistically distinct antidepressants (paroxetine, venlafaxine, bupropion, buspirone, DOV 216,303 and S32006) on sexual performance, this review discusses the putative mechanism underlying sexual side effects of antidepressants and their normalization.

2. Assessing sexual side effects in male rats

As we are still dependent on animal models to figure out whether a new innovative molecule with antidepressant properties exerts modulating effects on sexual behavior, it is of paramount importance to use and develop animal models that have predictive validity for sexual (side) effects in human (depressed) patients. An ideal animal model predicting sexual side effects should follow such a time course: acutely no or marginal effects, with an inhibitory effect on sexual behavior occurring after subchronic (one week) or chronic (two weeks) treatment. If the model is also able to detect pro-sexual activities of psychotropics, this would further support its use in predicting their putative influence on sexual behavior in humans.

Several years ago we noticed that upon testing of young adult male rats on their sexual activity against a female in estrus (spontaneous or hormone-induced), males exhibit variable levels of sexual performance. Some animals were sexually very active, some not at all and all the intermediates between them (Pattij et al., 2005). We standardly tested all males subsequently for four weekly sex tests of 30 min, establishing for each individual male a stable sexual performance level, expressed as the number of ejaculations reached during the 30-min test, leading to the hypothesis that male rats display sexual endophenotypes (Olivier et al., 2006). Over the last decade we tested (trained) more than 2000 males in this way and from these data we established that sexually trained rats fall unto sexual endophenotypic distribution of slow, normal and fast ejaculators. Our combined training data reveals that on average 20 to 30% are slow (0–1 ejaculation/30 min) and 10% are fast (4–5 ejaculations/30 min) (Fig. 1). The rats with 2–3 ejaculations/30 min are considered to show 'normal' sexual performance. We argued that rats notoriously low in their sexual behavior might model delayed or retarded ejaculation in men, and those with 4 or more ejaculations per test as fast ejaculators, putatively reflecting premature ejaculation in men (Olivier et al., 2006). In this review we focus on the 'normal' ejaculating males for psychopharmacological studies. We reason that 'normal' ejaculating males are ideally suited to test the effects of psychotropic drugs, because both inhibitory and stimulatory effects can be detected. So, to assess sexual side effects of psychotropic drugs we designed an experimental drug test that consists of 14 days of daily treatment with a drug followed by a wash out test one week after stopping the last treatment. We measure the sexual performance of all rats after acute, 8 days (subchronic), 15 days (chronic) and 22 days (wash-out) of treatment (Chan et al., 2010). This set-up allows the assessment of sexual behavior of individual rats both after acute as well as (sub) chronic administration, paralleling the putative onset of action of the drugs tested. Using this experimental design, we tested various drugs which are either clinically used as antidepressants, viz. paroxetine (selective serotonin reuptake inhibitor; SSRI), venlafaxine (serotonin and noradrenalin reuptake inhibitor; SNRI), bupropion (dopamine and noradrenaline reuptake inhibitor; DNRI) and buspirone (5-HT_{1A} receptor agonist), or in development for clinical use as putative antidepressants (DOV-216,303, a triple reuptake inhibitor; TRI) and S32006 (5-HT_{2C} receptor antagonist (Dekeyne et al., 2008)). Their effects on sexual performance and the relationship between these effects and their mechanism of action will be reviewed in the next section.

2.1. Stability of sexual behavior and inhibiting effects of paroxetine across experiments

Reliable comparison between drug effects across experiments can only be made if vehicle treated animals show stable behavior across time and between experiments and if the reference compound, the SSRI paroxetine (10 mg/kg) in our set-up, shows stable effects across experiments. Therefore we analyzed the stability and reproducibility of the level of male sexual behavior and its inhibition by paroxetine within and across experiments. All 7 experiments were performed according to the protocol described in Box 1 (Chan et al., 2010). Fig. 2 shows all the individual data for our main outcome measure, ejaculation

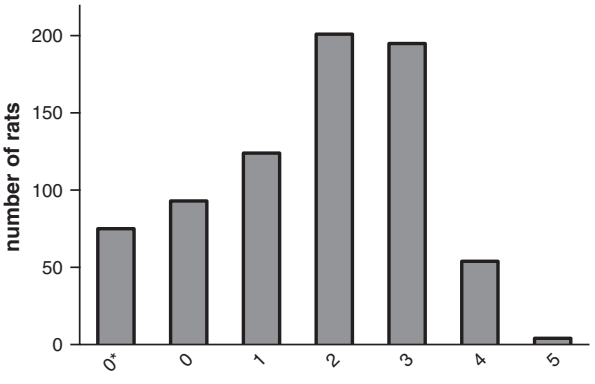

Fig. 1. Distribution of ejaculation frequencies of sexually trained male Wistar rats in the 4th training (total n = 766, obtained from 7 experiments, gathered from the years 2004 to 2009). Based on the fourth mating test, these male rats can be classified with the stable copulatory behaviors of "normal" (2 to 3 ejaculations/30 min), "sluggish" (0 to 1 ejaculation/30 min) and "fast" (4 to 5 ejaculations/30 min) ejaculating. The 0* represents "real zero's", i.e. never reached an ejaculation during any of the training sessions.