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Inhibitory and disinhibitory effects of psychomotor stimulants and depressants on the sexual behavior of male and female rats

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ABSTRACT

Drugs of abuse comprise several pharmacological classes, including psychomotor stimulants, such as amphetamine and cocaine, and CNS depressants, such as morphine and alcohol. Few studies have examined the effects of those drugs systematically on human sexual behavior, although substantial clinical and epidemiological literatures suggest that drugs in both classes either inhibit sexual responding or can be "prosexual" in certain situations, thereby increasing the potential of risky sexual activity and the spread of sexually transmitted diseases. This paper reviews original data in rats showing that both classes of drug inhibit or disinhibit sexual behavior depending on the animal's baseline level of sexual responding, hormonal status, whether the drug is given acutely or chronically, and whether the animal has learned to inhibit sexual responding toward nonreceptive partners or in the presence of conditioned olfactory cues that predict sexual nonreward.

"Sex and drugs and rock and roll
is all my brain and body need
Sex and drugs and rock and roll
are very good indeed!"
—Ian Dury and the Blockheads, 1977

Introduction

Drugs have been taken throughout human history to relieve pain and distress, to induce euphoria or enhance the perception of normative experiences, or to stimulate behavior in conditions of psychological or physiological inhibition. However, medical and recreational uses have been differentiated along "moral" lines in Western culture. Medical use is viewed as necessary, whereas recreational use has been idolized or marginalized, and habitual users, addicted or dependent, have been glorified or vilified as criminals, degenerates, or mentally ill. Efforts to understand drug addiction as a medical condition have helped remove some of the stigma associated with it, but regular recreational use of illegal–or even legal–substances remains immoral in the eyes of many. One current battleground in the debate concerns the use of drugs to treat "lifestyle problems", such as obesity or sexual dysfunction. If such problems have a physiological basis and can be shown to be beyond an affected individual's ability to treat using changes in lifestyle, then pharmacotherapies are more likely to be approved by regulatory agencies and viewed as acceptable by the public.

The debate over lifestyle drugs has been particularly visible around the quest for, and use of, "aphrodisiacs" (Crenshaw and Goldberg, 1996; Miller 1993; Sandroni, 2001). Putative aphrodisiacs can be classified into at least three categories: (1) compounds that increase sexual desire, (2) compounds that increase "potency" (usually referring to the stiffness of an erection, but that could refer generally to drugs that increase genital blood flow), and (3) compounds that increase sexual pleasure (Sandroni, 2001). A variety of plant, herbal, and insect-derived extracts possess psychomotor and autonomic stimulant properties (e.g., panax alkaloids in ginsing; methyl-xanthenes like caffeine; cathinone found in khat; harmine and harmaline found in Yagé, or kaempferol in *Ginko biloba*, that act as short-term monoamine oxidase inhibitors; asarone found in sweet flag that acts as a non-amine precursor to phenethylamine; cantharidin, a vesicant derived from blister beetles that stimulates β-adrenergic receptors; and yohimbine from the bark of the yohimbe or quebracho trees in Africa and South America, respectively, that acts as an α2-adrenergic autoreceptor antagonist). Some act as parasympathetic antagonists (e.g., scopolamine or atropine found in Mandrake root). Still others act to induce euphoria and relaxation that enhances

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the pleasure of orgasm (e.g., indoles like ibogaine from the Iboga root, opiate alkaloids like morphine found in opium and wild lettuce extracts). Other extracts may contain phytoandrogens, such as sarsaparilla root, or phytoestrogens, such as soy, licorice root, hop flowers, palmetto berries, dong kwai, and bee pollen (Miller, 1993). In those latter cases, effects on the brain may include stimulation of catecholamine, neuropeptide, and nitric oxide transmission (Balthazart et al., 1996; Blaustein et al., 1994; Fabré-Nys, 1998; Kow and Pfaff, 1998; Lee and Pfaff, 2008; Pfaus, 2009; Putnam et al., 2005; Sato et al., 2007) and thus may augment neural responses in hypothalamic or limbic structures to sexually arousing stimuli, in addition to the peripheral stimulation of appropriate sympathetic and parasympathetic responses that prepare the body for sexual interaction.

Distilled to core principles, putative aphrodisiacs can enhance sexual arousal, desire, or pleasure, by enhancing the activation of excitatory systems for sexual behavior (e.g., dopamine, norepinephrine, melanocortins, and oxytocin), or by blunting the activation of inhibitory systems that normally shut sexual responding down (e.g., opioids, endocannabinoids, and serotonin), as might occur during a refractory period or in the presence of stress, pain, or sexual nonreward (Pfaus, 2009). However, those effects depend critically on the baseline sexual functioning of the individual. People (or animals) that are sexually sluggish may well find their sexual arousal, desire, and propensity for pleasure increased with substances that act as stimulants, whereas individuals with too much arousal or stress may gain the ability to experience "normal" sexual activity with substances that inhibit arousal. Conversely, individuals with too much endogenous inhibition may find their sexual responses "released" with substances that act to blunt inhibitory systems. Thus, one person's aphrodisiac can be another's dysfunction (e.g., Bang-Ping, 2009).

Many drugs of abuse are associated with changes in sexual function. In particular, use of psychomotor stimulants like amphetamine, caffeine, cocaine, methylenedioxy methamphetamine (MDMA, or "Ecstasy"), or depressants such as alcohol or heroin, have been considered "prosexual" and are often used in sexual situations where they are believed to increase sexual arousal or desire, or to enhance the intensity of sexual stimulation during intercourse (Abel, 1984; Buffum and Moser, 1986; Kall, 1992; Miller, 1993; Pfaus and Gorzalka, 1987; Semple et al., 2009). Some of those effects may be direct, such as the facilitation of erection or an increased sensory awareness that can amplify sexual stimulation and the intensity of orgasm. Other effects may be indirect, and stem from a general cognitive disinhibition that prompts individuals to engage in highly arousing ("naughty"), promiscuous, unsafe, "marathon," or even violent sexual activity, without regard to its consequences. It is also important to consider those effects in light of cultural belief in the power of the drugs to disinhibit sexual activity and thus provide an "excuse" for otherwise unacceptable behavior (Leigh, 1990). How can we distinguish among those effects and study their etiology? Although human drug use and sexual behavior are best studied in humans, it is almost impossible to do so using anything other than retrospective analyses. It is therefore necessary to use animal models to examine etiological and neurobiological factors.

Animal models

Both acute and chronic effects of psychomotor stimulants and CNS depressants on the sexual behavior of sexually experienced male and female rats have been examined using both traditional measures of copulation, or paradigms in which copulatory behavior is suppressed, either by hormonal manipulations or inhibitory conditioning, in order to reveal potential disinhibitory effects. Typically we assess drug effects in bilevel chambers (Pfaus et al., 1990, 1999), in which females control the copulatory contact by running from level to level, and in which we can evaluate anticipatory level changes as a measure of sexual motivation during a 5-min period prior to copulation. We also assess drug effects in unilevel pacing chambers bisected by a Plexiglas divider with small holes at the base that allow the female to regulate sexual contact by crossing to and from the "male's side." These chambers allow us to assess appetitive sexual behaviors that animals engage in before copulatory contact, such as conditioned psychomotor stimulation in anticipation of the arrival of a sex partner, and consummatory sexual behaviors that animals engage in once contact is made, including chases, mounts, intromissions, and ejaculations in males, and solicitations, hops and darts, pacing behavior, and lordosis in females. We have also examined the ability of drugs to disrupt both primary and second-order conditioned inhibition in male rats. In the former paradigm, sexually experienced males learn not to attempt copulation with sexually nonreceptive females. In the latter paradigm, males learn not to copulate with sexually nonreceptive females bearing a neutral odor (e.g., almond) that acquires conditioned inhibitory properties. Subsequently, males are placed into an open field and presented with two sexually receptive females, one scented with the inhibitory odor and one unscented for a 30-min test. In this paradigm, males typically copulate and ejaculate preferentially with the unscented female on the final open-field test (Kippin et al. 1998).

Dose–response effects are assessed acutely during the first administration, and chronically at 4-day or weekly intervals. A total of between 4 to 20 drug tests are conducted, depending on the drug and the dose, after which the animals receive a final saline withdrawal test to examine whether the changes in sexual responding induced by the drug are long-lasting. Such tests also reveal whether tolerance or sensitization to particular drug effects on sexual behavior have occurred. Subsequent studies employ a "before and after" paradigm (e.g., Carlton and Wolgin, 1971; Pinel et al. 1991) to assess whether tolerance or sensitization effects are contingent on the animal attempting to engage in sexual responding under the influence of the drug, or are simply due to drug exposure per se. Animals are administered a dose of the drug before or after sex behavior tests, with a control group receiving saline before the sex behavior tests. On the final test, all animals receive the drug before the test. Typically, animals that have become tolerant to the effect of a drug during training continue to display tolerance, whereas animals in both the control and drug-after groups have not developed tolerance, and thus display a similar disruption of sexual behavior as observed in the drug-before group during their first trial. Those paradigms together provide strong evidence of a drug's ability to disrupt or enhance different aspects of sexual responding, and whether the drug effect will diminish or become more potent with continued use.

Psychomotor stimulants

Psychomotor stimulants include amphetamine and its derivatives methamphetamine and MDMA, cocaine, caffeine, ephedrine, and many natural ingredients in plant extracts (e.g., the α_2 adrenergic antagonist yohimbine) that act as sympathomimetics. Those compounds increase behavioral and motor activation and mental "alertness" by interacting with monoamine transporter proteins in the presynaptic terminals of dopamine, noradrenaline, and serotonin neurons, thus blocking monoamine reuptake (Everitt and Wolf, 2002). In some cases, drugs like amphetamine also stimulate dopamine and noradrenaline release independently of changes in neuronal membrane potentials (Berridge, 2006). Drugs in this class also increase arousal (largely sympathetic), either by stimulating sympathetic outflow directly (e.g., ephedrine) or by antagonizing systems that normally blunt arousal (e.g., caffeine). The acute and chronic effects of several psychomotor stimulants have been examined in sexually experienced and naïve male and female rats. Those include amphetamine and its derivatives methamphetamine and MDMA, cocaine, caffeine, and yohimbine.