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Pharmacology Of Sexuality

Michel Bourin*

Neurobiology of anxiety and mood disorders, University of Nantes, France

Abstract

This paper is a review of the effects in mammals of drug induced behaviors or other pharmacological tools that modify the dopaminergic, cholinergic and GABAergic systems, i.e. those that most often participate in the activity psychotropic drugs used in therapeutics. Moreover, we will consider the pharmacology of erection, as well as the side effects of drugs on sexual performance and the effects of drugs on spermatogenesis.

Introduction

Mammalian reproductive pathways are controlled by sex steroids acting in the central nervous system (CNS). These behaviors have multiple determinants because hormonal control varies with species. In the human species, they can be modified by thought, the environment and culture. The animal is therefore the reference to understand the role of biological substrates of such functions [1].

In the brain, steroid hormones have two types of action:

- They act on the membrane receptors to increase the excitability of the neurons.

- They act at the genome level in the cell nucleus to increase the synthesis of the neurotransmitter either directly for the neuropeptides or indirectly by increasing the production of the enzymes responsible for the synthesis of the non-peptide neurotransmitters.

Thus, in adult mammals, steroids produced by the gonads, directly control reproductive tract; however, the behaviors are also elaborated by experience.

We have chosen to review effects in mammals, drug induced behaviors or other pharmacological tools that modify the dopaminergic, cholinergic and GABAergic systems, i.e. those that most often participate in the activity psychotropic drugs used in therapeutics. Moreover, we will consider the pharmacology of erection, as well as the side effects of drugs on sexual performance and the effects of drugs on spermatogenesis.

Description and quantification of sexual behaviors in rats

We will discuss the rapid quantification of sexual and maternal conduct in rats, because most studies with drugs or neurotransmitters have been done in these species.

Sexual behavior in male [2]

Males who have not undergone castration have copulation after a short delay in the discovery of a sexually receptive female. The males repeatedly cover the female; during mating, males grab the females' flanks with their forelegs and perform rapid pelvic movements. The male, as soon as he finishes the intromission, jumps back rapidly and rises quickly. It ejaculates only after a certain number of intromissions (8 to 12 in a sexually active rat). Substances that facilitate this increase the number of rats engaging in copulatory conduct increase the number of rats ejaculating increase the number of climbs and intromissions necessary to achieve ejaculation. As in other mammals, one can thus identify in the male rat 3 components: excitation, copulatory conduct and penile reflexes [3].

Sexual behavior in female [2]

Sexual behavior in the female rat can be divided into three components:

- Attraction, which is induced by the production of pheromones and changes in vascularization of the perineum (usually dilation),

- Prospective behaviors that stimulate the sexual advances of males which consist of a jumping and abrupt movement of approach towards the male with a rapid vibration of the ears,

- Receptive behavior in female rat is due to the fact that to be copulated by rats, females must adopt a lordosis posture which facilitates access to the vagina.

- Most studies of the effects of drugs and neurotransmitters involved in female sexual behavior in the female rat have been focused on lordosis [3, 4, 5].

Maternal behaviors [6]

Maternal behavior is composed of a number of components that coordinate the behaviors that result from cleaning, reheating, feeding and protecting young animals until they are able to take care of themselves, same. Detailed descriptions of maternal behaviors in different mammalian species have been developed [7]. Most researchers determine the presence or absence of one or more components to determine if maternal conduct is present, thus asserting that the components of the maternal tubing tend to be in fact united into a single unit that is sufficient if one of the components is present to say that it exists. Some researchers,

however, have measured the presence or absence of different components of maternal behavior.

A rapid onset of maternal behavior may occur after postpartum. They depend in the female rat of the increase in estrogen and the fall in progesterone concentrations that appear during the last days of gestation. Treatment of nulliparous according to a pattern that mimics the changes in ovarian steroids that appear at the end of gestation may actually decrease the latency of the onset of maternal conduct. Shortly after parturition, maintenance of maternal behavior becomes independent of ovarian steroids. Once postpartum the rats can acquire some maternal experiences. These maternal responses to the newborn emerge after long periods of separation from the newborn. The role of ovarian steroids and their expression in maternal behaviors have been well described.

The effects of some drugs or neuropeptides on maternal behavior have been studied in parturient or lactating females and other treatments have been tested in nulliparous animals treated with steroids [8]. Some treatments have been carried out to study changes in the delay of onset of maternal behaviors and others have been carried out to establish the nature of the maternal conduits, their maintenance or emergence, few treatments have been made for both types of conduct. Because these mechanisms of appearance differ in various ways from the mechanisms of maintenance or re-emergence of maternal behaviors; the effects of drugs and neuropeptides may differ between these phases of maternal responses

Effect of substances on sexual behaviors and maternal behaviors

Substances affecting serotonergic transmission

Action on sexual behavior

Serotonin (5-HT) has an inhibitory effect on most aspects of male sexual activity, particularly copulatory behavior [9].

The peripheral injection of the serotonin precursor 5-HTP, serotonin agonists and fenfluramine which increase serotonin release and / or serotonin reuptake inhibitors (SRI) inhibit sexual conduct both in The male than in the female (this is the case in human clinical IRS). Depletion of serotonin by administration of a tryptophan hydroxylase inhibitor, which is parachlorophenylalanine (PCPA), increases the coupling rate.

Direct injection of 5-HT in the preoptic area and nucleus accumbens inhibit sexual activity while it stimulates it if it is injected into the dorsal or median raphe, where it probably exerts an effect on the auto-receptor 5-HT on the cell bodies and thus inhibits its release. 8-OH-DPAT which is a 5-HT1A agonist may act at the level of the self-receptors in these two brain regions [10]. More recent work has shown that 5-HT1B agonists, such as RU 24964 and 1- (m-chlorophenyl) piperazine (mCPP) have inhibitory action [11].

Peripheral administration of 5-HT antagonists increases both the lordosis of the female and the cover line in the male. Serotonin antagonist implants such as methysergide or mianserin in the anterior preoptic hypothalamic area or in the posterior hypothalamus or in the amygdala or in the dorsal hippocampus or injections of methysergide in the preoptic area or In the ventral-medial hypothalamus increase lordosis while 5 HT injection in the pre-optic medial area or ventral-medial arc of the hypothalamus suppresses lordosis. The destruction of ascending axons, serotonergic neurons in the middle brain with local involvement of a neurotoxin, 5, 7-dihydroxytryptamine (5, 7-DHT) or moderates prospective or receptive behaviors or has no effect on the sexual conduct of the female. Intra hypothalamic injections of this neurotoxin, 5, 7-DHT increase lordosis. Thus, in the rat there is much evidence that treatments that increase central neurotransmission of serotonin are inhibitors whereas treatments that decrease central neurotransmission of 5 HT facilitate sexual conduct. This is the case in the human species for behavior other than sexual.

The role of 5 HT in the sexual behavior of other species is less clear. While fenfluramine inhibits lordosis, administration of PCPA and methysergide has no inhibitory effect on lordosis in guinea pigs [12]. Intraventricular injections of a 5 HT agonist, quipazine, inhibit the lordosis of guinea pigs when injected before, but not after the onset of sexual receptivity. Parachlorophenylalanine (PCPA), in monkeys, restores susceptibility after adrenalectomy or decreases 5 HT, sexual receptivity. Administration of 5 HTP, i.e. the precursor of 5 HT, decreases prospective behavior and treatment with clomipramine that decreases serotonin reuptake decreases prospective and receptive behavior in rhesus monkeys [13].

The effect on the sexual conduct of the rat of peripheral administration of 5 HT agonists such as lysergic acid amide (LSD) varies with dose [14]. High doses decrease, while low doses increase, both the conduct of copulation in the male and in the female. It is believed that low doses preferentially stimulate the auto-receptors and thus decrease the synaptic transmission of the 5 HT whereas the high doses mimic the high doses of neurotransmission by preferentially stimulating the postsynaptic receptors. The effects of 5 HT on lordosis appear to be progesterone dependent. High doses of 5 HTP or other agonists are more effective in inhibiting lordosis in estrogen and progesterone treated rats than in estrogen-treated rates alone. However, the effects of low doses of LSD that increase lordosis are increased by treatment with progesterone. It was thus hypothesized that progesterone increases sexual conduct by increasing the presynaptic activity of 5-HT.

Action on maternal conduct

Clomipramine that blocks serotonin reuptake has no effect on the maternal behavior of treated rats during gestation or lactation. Administration of 5-HT inhibits the latency of murder of neonates but does not decrease the high incidence of infanticide in mice from which the olfactory bulb has been removed. Yet serotonin-specific lesions of the dorsal raphe disrupt maternal aggression and caregiving in postpartum rats [15].

Substances acting on dopaminergic transmission

Action on sexual conduct

1) In male Dopamine is involved in the three components of male sexual behavior.

- Excitation (awakening): It seems that the stimulating effect of the dopamine (DA) on the copulatory duct is an indirect effect linked to its action on the stimulation of the excitation.

- Testosterone acts on the preoptic area by sending impulses to the diencephalon by stimulating the centers of reward located at that level [16]. This hormone appears to be important in maintaining the dopaminergic activity in the nucleus accumbens because concentrations of DA and DOPAC (dihydroxyphenylacetic acid, major metabolite of DA) fall after castration and rise after testosterone replacement [17].

- Copulatory activity: Taking as a parameter the frequency of cover and intromission as a measure of copulatory activity, most studies show that the stimulating effect is exerted via D2 receptors [18]. This has been widely demonstrated both in rodents and in humans after administration of numerous agonists whose action has been antagonized by D2 antagonists. The ratio of D2 / D1 activity may be important in controlling sexual activity; in particular an increase in D2 / D1 can reduce ejaculation latency but also decrease the erectile reflex [19].

- The erectile reflex: The stimulating effect on the erection requires the presence of testosterone and is probably exerted in the telencephalon at the level of the dopaminergic receptors post-synaptic [20].

2) In female Peripheral injection of agonists or dopaminergic precursors at high doses inhibits lordosis, but on the contrary facilitates it at low doses. D1 receptors do not appear to be involved at all, suggesting that the action of low doses of agonists or AD would be presynaptic and would decrease dopaminergic transmission. In rats, dopaminergic receptor antagonists facilitate lordosis but inhibit prospective behavior. Furthermore, the injection of dopaminergic receptor agonists into the median preoptic area or the ventromedial arched zone of the arched nucleus of the hypothalamus facilitates lordosis, whereas the action of dopaminergic antagonists inhibits it [21].

The administration of dopaminergic agonists does not produce any deficit in the initiation or maintenance of maternal behaviors in the Spleen but decreases the maternal aggressiveness or other components of maternal behavior in the Hamsters. Dopamine antagonists often inhibit maternal conduct [22]. Treatment with chlorpromazine in lactating rats reduces contact with the newborn and the nest production line. Haloperidol inhibits in a dose-dependent manner both the onset and re-emergence of several components of maternal conduct in ovariectomized rats or in postpartum rats. Haloperidol inhibits more caring for newborns than lactation management itself suggesting a specific effect on maternal motivations apomorphine is able to reset maternal neonatal ducts in haloperidol-treated female rats.

The administration of amphetamine in lactating rats inhibits maternal conduct at a much higher dose than increases in locomotor ducts. Low doses of amphetamine in Velvet monkeys eliminate the initiation of physical and visual contact with their children. The chronic administration of imipramine decreases the reuptake of norepinephrine decreases in the maternal behavior of the rats during lactation.

Substances affecting noradrenergic transmission

The effects on sexual behavior of drugs that alter noradrenergic transmission are difficult to understand according to a clear mechanistic pattern [23]. Peripheral administration of alpha-adrenergic agonists appears to inhibit sexual behavior in the rat, whereas beta-adrenergic agonists appear to facilitate it in sexually inactive rats. Clonidine, which is an alpha 2 agonist, inhibits lordosis in the spleen, decreases coverage latency but increases the frequency of coverage in the male.

Yohimbine is particularly active in stimulating "arousal" (anxiety?) and copulative behavior because it removes the inhibition of norepinephrine via autoreceptors on the activity of noradrenergic neurons that originate in the locus coeruleus [24].

Substances acting on cholinergic transmission

Action on Sexual Conduct

Lordosis is decreased 30 minutes later, but increased 3 hours after the peripheral injection of muscarinic agonists. Because the inhibitory effects of muscarinic agonists are increased by MAOIs and decrease with chlorophenylanaline (PCPA) but with alphamethyl-paratyrosine; it was concluded that 5 HT but not catecholamine's, mediated muscarinic inhibition of lordosis. Hypophysectomy is capable of preventing the effects of muscarine agonists suggesting that facilitation of lordosis may result from the release of substances from the adrenal medulla [25].

The peripheral injection of muscarinic antagonists such as atropine inhibits the coupling pathways in the male. Peripheral nicotine injection appears to increase lordosis or to facilitate or inhibit sexual behavior of the male [26]. The implantation or injection of carbachol or atropine in the hypothalamus or in the limbic area increases the lordosis [27].

Action on maternal behaviors

Intracerebral injection of atropine inhibits in a dose-dependent manner the appearance of maternal conduct in nulliparous patients who have been treated with ovarian steroids [28]. A nicotinic receptor antagonist, hexamethonium was ineffective. Drugs acting on alpha-amino-butyric acid (GABA).

Substances acting on GABAergic transmission [29]

Action on sexual conduct

Injection into the black substance of a substance that inhibits GABA receptors such as picrotoxin inhibits the lordosis frequencies that occur with bilateral lesions of the septum. Intranigral injections of hydrazinopropionic acid which inhibits the transamination of GABA or the GABA agonist such as muscimol

in rats on which lesions have been performed facilitate lordosis.

In the human species benzodiazepines which facilitate GABAergic activity, and are often disinhibitory facilitate libido [30].

Action on maternal conduct

Drugs that decrease GABAergic neurotransmission, i.e. caffeine, pentyleneteazole, significantly decrease food intake and aggression in newly born female rats.

Effects of substances acting on opioid transmission [31]

The chronic administration of opioids decreases the sexual interest of women. In rats, systemic administration of morphine reduces both prospective and receptive behavior at non-sedative doses. This action is antagonized by naloxone. Experimental results in the spleen show that mu and delta opioids have opposite effects on sexual activity. Thus, a delta peptide agonist (D-Tyr-Sera-Glyn-PH-Leu-Th) stimulates lordosis and the stimulatory effects of beta-endorphin at high concentration (intracerebroventricular) are reduced by a selective antagonist Delta (ICI 154129) but not by a selective antagonist mu (naloxone) [32].

On the other hand, it has been suggested that endogenous opioid peptides have a dual action on female sexual behavior, facilitating initially perhaps receptivity because of their analgesic action helping intromission. However, after ejaculation, the opioid system in the spinal cord exerts an inhibitory effect and is responsible for decreasing female sexual behavior in parallel with the depression period in the male after ejaculation.

Pharmacology of erection

It is necessary to obtain an erection that a large amount of blood arrives at the level of the corpora cavernosa and the spongy body of the urethra. It is therefore necessary to have a good arterial vascularization and an adequate penile perfusion pressure [33]. The extrinsic innervation of the chemical mediators involved in these phenomena consists of nerve fibers originating from the parasympathetic nuclei of the sacral marrow and thoracolumbar sympathetic nuclei [34]. The stimulation of the parasympathetic fibers causes a vasodilation of the corpus cavernosum, but the mediator involved is not acetylcholine since atropine does not agonize the phenomenon and acetylcholine itself is inactive. In the sympathetic domain, norepinephrine and adrenaline cause vasoconstriction of the erectile tissue which is found to be very rich in alpha-adrenergic receptors (100 times more than in beta-adrenergic receptors) [35].

Since acetylcholine and noradrenaline are not the mediators responsible for the vasodilatation of penile arteries and erectile tissues, many studies have sought to determine the nature of this mediator. It is essentially towards the neuropeptides that research is oriented, in particular on the P substance side, bradykinin, and VIP (vaso active intestinal peptide). However, whatever the mediators involved, it appears that the erectile tissue receives at least three types of innervation [36]:

A) Parasympathetic (but not cholinergic which is relaxing)

B) Sympathetic (constrictive)

C) An indeterminate but relaxing nature

The first and third play a role in vasodilation and erection, the second in detumescence [37].

Many works have sought to correct, with drugs, impotence by direct injection into the corpus cavernosum of various substances. These injections are always performed slowly, in about 1 min, on the lateral face of the penis and most often without local anesthesia. The first substance studied is currently still the most used, papaverine [38]. Its intracavernous injection at doses ranging from 10 to 120 mg rapidly leads to (after 2 to 10 min) local vasodilation, increased penile arterial flow, transient interruption of venous drainage, increased intracavernous pressure and erectile dysfunction, a time varying according to the individuals and the doses. Apart from papaverine, numerous other vasodilators have been studied in healthy volunteers or in patients, in particular:

Alpha-adrenergic inhibitors

Phenoxybenzamine is undoubtedly the most potent substance. After its administration which is sometimes painful, its action begins after 5 to 8 min and the erection can last between 5 and 15 hours depending on the dose administered which varies from 2 to 4 mg [39].

Phentolamine at 1-10 mg gives short-lived erections in healthy volunteers and appears to be ineffective in the organic impotent [40].

Thymoxamine at 1-10 mg is not very effective in healthy volunteers but has shown good results especially in a standing position at a dose of 34 mg in impotent patients [41].

Idazoxan (0.10 to 2 mg), on the other hand, was found to be inactive in healthy volunteers.

Finally, yohimbine, which has long been shown to have aphrodisiac properties after oral administration, does not appear to be effective locally [42].

Phosphodiesterase 5 inhibitors [43]

Sildenafil citrate is a specific inhibitor of cyclic GMP type 5 (PDE5) phosphodiesterases in smooth muscle, where PDE5 is responsible for cGMP degradation. Sildenafil citrate increases cGMP concentrations in smooth muscle cells, resulting in relaxation and vasodilatation. In patients with pulmonary hypertension, this leads to vasodilatation of the pulmonary vascular bed and, to a lesser degree, vasodilation in the systemic circulation. In patients with erectile dysfunction, sildenafil citrate increases the effect of nitric oxide (NO) by inhibiting PDE5 in the corpus cavernosum. When sexual stimulation causes local NO release, inhibition of PDE5 by sildenafil citrate causes an increase in cGMP levels resulting in smooth muscle relaxation and an increase in blood flow in the corpus cavernosum [44].

Tadalafil [45] and vardenafil [46] are two other selective and reversible phosphodiesterase type 5 (PDE5) inhibitors, specific for cyclic guanosine monophosphate (cGMP). It is metabolized by the CYP 3A4 isoenzyme of cytochrome P450, which is at the origin of many drug interactions.

In conclusion, what can be said based on these results of the mechanism (s) involved in pharmacologically induced erections?

Local vasodilatation appears fundamental but any vasodilator is not active. The ineffectiveness of salbutamol appears to be related to the very small number of beta-adrenergic receptors in the corpus cavernosum. That of hydralazine is more difficult to explain because its mechanism of action is not well known, but there may not be adequate receptors in the corpus cavernosum. Finally, the ineffectiveness of neostigmine confirms that although there is a parasympathetic innervation in the corpus cavernosum, its mediator is not cholinergic in nature.

Alpha-adrenergic blockade is one of the mechanisms that can induce useful vasodilation. But it should be noted at the outset that idazoxan and yohimbine, an alpha2 adrenergic inhibitor, are inactive whereas all other substances studied that inhibit both alpha1 and alpha2 receptors induce erection.

The local administration of vasodilating agents thus makes it possible to provide a solution that is at least transient in a non-negligible percentage of impotent patients. The erections generated are generally of importance and duration dependent dose. They are generally more pronounced when standing [47].

Side effects of medicines on sexuality [48]

Antipsychotics are known to be inhibitors of ejaculation. It should be remembered that these drugs are blockers of dopaminergic receptors [49]. The imipraminic tricyclic antidepressants include impotence and delay to ejaculation or even non-ejaculation, difficulty of erection, decreased libido. These results are however controversial insofar as it is known that in the healthy volunteer imipramine is able, due to its alpha inhibitory properties to cause erection. It is difficult to distinguish between depressive illness and the use of antidepressants. Antidepressants have a bad reputation for leading to impotence but this remains to be proven [50]. Antiepileptic drugs, especially phenobarbital, lead to a decrease in libido; It is actually possible that it is only the sedative effect of these substances. Finally, valproic acid which is an antiepileptic widely used to treat bipolar disorder is capable of causing amenorrhea [51].

In another area, that of antihypertensive drugs, it seems to prove that clonidine leads to sexual impotence. As for alpha methyl dopa, the incidence on sexual impotence has been verified; it appears to be close to 15% in patients [52].

Spironolactones, which are diuretics with a steroidal molecular structure, cause disorders of the rules, impotence, and gynecomastia. Lipid-lowering agents, and especially statins, often result in loss of libido and / or impotence [53].

Finally, surprising findings have been made regarding the effects of heparin which would result in priapism. Twenty cases were recorded in France, mainly in young subjects under 20 years of age [54].

Pharmacology of sexual deviations [55]

One may think that drugs that decrease libido are effective in treating sexual deviations; the paraphilic behaviors sometimes appear to be attenuated by drugs decreasing serotonin [56].

Moreover, what is vulgarly called "chemical castration" is the fact of antitestosterones. In a study of the treatment of sexual deviations by low doses of medroxyprogesterone acetate (MPA), a decrease in testosterone levels and a decrease in sexual deviations were found [57]. The decrease was estimated by the clinician and the subject himself before testing for plasma concentrations of testosterone. Deviant subjects have comparable correlations between decreased nocturnal erections and decreased testosterone concentrations obtained by antiandrogen therapy. Still following antiandrogen treatment, correlations between testosterone concentrations and erection obtained under experimental conditions (laboratory stimulation) appear to be much less correlated.

Medicinal products and spermatogenesis [58]

The action of drugs on spermatogenesis can be classified into several categories.

1) *Those who act on endocrine control*

These are mainly androgens, estrogens, progestogens, reserpine but also diazepam and chlorpromazine which inhibit the secretion of gonadotrophin. These drugs all lead to a decrease in spermatogenesis. Conversely, substances that stimulate gonadotrophin, i.e. gonadotropin itself, clomiphene, tamoxifen (which are antiandrogens), and bromocriptine, increase the production of spermatogenesis [59]. Spironolactone also, inhibits the synthesis of androgens.

2) *Those that alter the cells of the germ line*, namely lead, cadmium, and cytotoxic substances. Some chemicals used in industry such as dibromochloropropane also cause this type of alteration, as well as gossypol. These are substances that alter the maturation of seminal cells. These are mainly anti-androgens (cyproterone, and alphachlorohydine, sulfasalazine) [60].

3) *Medicines that inhibit mobility* before ejaculation are nicotine and vaginal spermicides, notably nonéxynol-9-chlorhexidine, propranolol and glycerin. On the other hand, caffeine, calcium channel blockers and glycerin increase mobility after ejaculation

An American study showed that Coca-Cola decreased cell motility in vitro; this effect seems related to the acidic pH of this drink. However, it was noted that this decrease in motility was greater with "diet-coca" which does not contain sucrose but aspartame.

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