

Pharmacological manipulation of sexual behaviour in stallions

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Summary. Series of experiments and clinical trials were conducted to evaluate the effects of psychoneurotropic agents on sexual behaviour of stallions. The benzodiazepine derivative, diazepam (Valium), effectively reversed experimentally suppressed pre-copulatory arousal and response. Diazepam treatment also blocked the negative effect of novel environment on sexual response. The dibenzazepines imipramine and clomipramine induced erection, masturbation, and ejaculation in the absence of a sexual stimulus.

Introduction

Sexual behaviour dysfunction remains one of the most difficult problems in equine reproduction. About one fourth of the stallions evaluated each year by the University of Pennsylvania Hofmann Center Reproduction Clinic involves a fertility-limiting behaviour problem. Although there is no reliable way to translate these figures to the stallion population at large, the costs represented are enormous.

Advances in the neurophysiology and neuropharmacology of sexual behaviour have brought a multitude of potential approaches to the control of male sexual arousal and response. This paper briefly reviews our recent experimental and clinical studies of the effects of psychopharmacological agents on sexual behaviour of stallions. Sexual response includes at least two principal interdependent neural processes. The first is the more cerebrally mediated process of goal-directed interest and arousal. The second is the more peripherally mediated ability to achieve and maintain erection, copulate and ejaculate. Accordingly, our work towards understanding and manipulating sexual behaviour of stallions has had two areas of focus corresponding to these processes.

Sexual Interest and Arousal

Following work done in other species suggesting effects of various CNS-active agents on general sexual interest and arousal, we are systematically evaluating the effects of several drugs on sexual response in experimental horse and pony stallions and geldings, as well as in clinical case stallions.

GnRH

A number of studies in mammals suggests that the hypothalamic decapeptide, known as gonadotrophin-releasing hormone (GnRH) for its role in regulating the pituitary-testicular axis-mediated endocrine events, may have a direct CNS-mediated role in the regulation of sexual behaviour (Moss, 1978). When GnRH challenge tests (500 µg i.v.; Cystorelin: CEVA Laboratories, Overlook Park, KS) were administered to clinical case stallions with low-normal androgen levels in order to evaluate the integrity of the pituitary-gonadal axis, we observed Flehmen response as well as sudden

improvement (subjectively assessed) in sexual interest and arousal. We conducted an experiment to evaluate the effects of synthetic GnRH (25 µg s.c. every 3 h for 3 weeks; Cystorelin: CEVA Laboratories) on sexual behaviour of long-term pony geldings (N = 12) with or without androgen replacement (testosterone propionate, 200 µg/kg every 48 h for 3 weeks; Sigma Chemical Company, St Louis, MO). Preliminary evaluation of performance in a series of sexual behaviour trials (4-min teasing exposure to an ovariectomized oestrogen-primed stimulus mare, 3 times per week, 2 weeks of baseline, 3 weeks of treatment, 3 weeks post-treatment) indicated a significant effect of GnRH treatment on olfactory investigation responses in geldings with androgen replacement. There were no significant effects of GnRH treatment on aggression, erection, or mounting responses.

Yohimbine

Yohimbine, an indolealkylamine alkaloid similar to reserpine, is a centuries-old purported aphrodisiac which is currently under renewed scientific scrutiny for its effects on sexual behaviour. Work in rats has shown that this alpha-2 adrenergic receptor antagonist enhances sexual interest and arousal (Clark *et al.*, 1984). However, similar effects have been difficult to demonstrate in other animal species or in man. In a preliminary experiment, we administered yohimbine (0.15 mg/kg s.c. or i.v. 1 S-20 min before sexual exposure; Sigma) or vehicle to long-term pony geldings (N = 12) with and without low level androgen replacement (testosterone propionate, 50 µg/kg s.c. 3 times/week at 16 h before a sexual behaviour test; Sigma). After intravenous yohimbine administration the animals exhibited moderately heightened general activity and excitability. Several bucked and frolicked on their way to and while in the sexual behaviour test pen. However, treatment had no apparent effects on precopulatory investigatory behaviour, aggressive responses, erection, mounting, or thrusting measured during standardized sexual behaviour trials (4-min teasing exposure to an ovariectomized oestrogen-primed stimulus mare, 3 times weekly for 2 weeks).

PCPA

Parachlorophenylalanine, a CNS-active selective serotonin synthesis inhibitor has been shown to influence sexual behaviour in rats (Sachs & Dewsbury, 1971), cats (Ferguson *et al.*, 1970), monkeys (Redmond *et al.*, 1971), and men (Sicuteri *et al.*, 1975). In a preliminary experimental trial, we administered PCPA (4 mg/kg i.m., twice/day for 1 week; Pfizer, Groton, CT) to a single pony stallion. This animal became extremely depressed and anorexic, and treatment was terminated. In spite of this adverse effect similar to that reported in cats and primates, sexual response (attention time, erection latency, erection time, mount frequency and olfactory investigation in weekly 4-min exposures to an ovariectomized oestrogen-primed stimulus mare) was greater than before treatment.

Naloxone

Endogenous opiate peptides have been implicated in an inhibitory role in regulation of sexual motivation. Several opiate antagonists have had facilitatory effects on male sexual arousal and response in some species (Sachs *et al.*, 1981). In preliminary evaluation of two pony stallions, we have seen no effect of the opiate antagonist naloxone hydrochloride (4 mg i.v. 2 min before sexual exposure: Narcan, Dupont Pharmaceuticals, Manati, Puerto Rico) on sexual arousal or response in standardized 4-min teasing trials as above.

Benzodiazepines

In the domestic stallion, considerable clinical evidence suggests that dysfunction may result from man-made experiences which inadvertently or by design inhibit sexual interest or arousal. Recent experimental findings confirm that inadequate sexual behaviour can result from negative experiences

similar to those encountered by domestic stallions (McDonnell *et al.*, 1985, 1986; McDonnell, 1985). Therefore, a considerable portion of our work towards pharmacological manipulation of sexual behaviour in stallions has focussed on agents known to reverse or block the effects of negative experience on goal-directed behaviour. The benzodiazepines, or minor tranquilizers, have distinct anxiolytic or antidepressant effects at dose levels which do not impair ongoing motor or goal-directed behaviour. They reverse or block negative experience suppression of goal-directed behaviour. Among the benzodiazepine derivatives, diazepam (Valium) remains the most intensively studied for its ability to attenuate effects of negative experience. We have studied the effects of diazepam on several types of experimentally-induced sexual suppression in stallions, as well as on a small number of spontaneously 'inhibited' clinical case stallions.

One type of experience-related sexual suppression that we have successfully modelled in the stallion is 'response-contingent aversive conditioning'. This paradigm involves direct punishment alone or in combination with negative reinforcement of sexual interest, arousal, or response. This results in a rapid, nearly complete suppression of sexual response. Using the appropriate contingencies it is possible to model specific variations of this type of suppression, including mare- or situation-specific suppression similar to that reported in clinical cases with spontaneous dysfunction. Conditioned as well as direct aversive stimuli are effective in suppressing response. In all variations of response-contingent aversive suppression that we have modelled, diazepam (0.05 mg/kg slow i.v., 5-7 min before sexual exposure; Valium, Hoffmann-LaRoche, Nutley, NJ) has effectively reversed or blocked the suppression. For example, stallions that showed no interest in the stimulus after aversive conditioning returned to normal sexual behaviour when given diazepam, while saline-treated controls remained suppressed. In addition, the administration of diazepam during the aversive conditioning procedures appeared to delay the ensuing suppression. In several clinical case stallions with spontaneous dysfunction that may have been related to negative experience, diazepam treatment has been judged by clinicians to be one of the key factors in the successful retraining. These clinical cases have included shy, novice breeding stallions, experienced natural service breeding stallions with apparent aversion to collection by artificial vagina, and stallions that exhibit normal arousal and mounting but suddenly dismount before ejaculation.

Erection and Ejaculation

Several vasoactive or neuromyotropic agents have been used to facilitate erection and ejaculation, principally to enhance smooth muscle activity in the reproductive tract. Several beta-antagonists, prostaglandins and oxytocin have been administered to stallions, with inconsistent results. We have completed preliminary studies of agents with both central and peripheral effects on neurotransmission.

Dibenzazepines

The tricyclic antidepressants have been implicated in effecting changes in erection and ejaculation. Human patients taking tricyclic antidepressants for manic-depressive or obsessive-compulsive personality disorders have reported both disturbance and facilitation of libido, erection and ejaculation (Quirk & Einarson, 1982; McLean *et al.*, 1983; Beeley, 1984). Despite inconsistency of effects and poorly understood mechanism of action, these drugs have been used to treat retrograde ejaculation (Brookes *et al.*, 1980) and premature ejaculation (Mitchell & Popkin, 1983).

We have studied the effects of imipramine on sexual behaviour in horses. Imipramine was administered to 5 male horses (400-500 kg body wt): one was an inexperienced young stallion, two were mature normal breeding stallions, one was a 5-year-old stallion with erection and ejaculatory dysfunction, and one a long-term castrated male horse. Oral treatment (100-600 mg, twice/day; imipramine hydrochloride: Rugby Laboratories, Rockville Centre, Long Island, NY) led to frequent

erection and masturbation while at rest in the stall in a non-sexual context. Intravenous treatment, over a range of doses (50–1000 mg, imipramine hydrochloride in sterile water; Sigma), similarly induced erection and masturbation in all animals. Typically, erection occurred within 10 min after injection, and the erection and masturbation continued intermittently for 1–2 h. These erections proceeded as during sexual excitement to a normal firmness and eventual engorgement of the glans penis. Two stallions ejaculated while masturbating. Mild ataxia and drowsiness appeared at the higher doses, but the animals remained responsive to auditory, visual and tactile stimuli. Erection and masturbation were often interrupted by activities about the barn or the approach of the handler, suggesting cortical inhibitory control of the erection. When tested in a sexual context, the two mature breeding stallions mated normally immediately after *i.v.* treatment (500 mg). The 5-year-old stallion, which had not ejaculated over several months of breeding attempts, spontaneously ejaculated after *i.v.* imipramine treatment. Subsequently, this stallion has ejaculated during copulation while on low dose oral (100 mg twice/day) imipramine treatment. Plasma total androgens increased during treatment in these stallions. The long-term castrate showed erection and masturbation after *i.v.* imipramine treatment, suggesting that the effect of imipramine is not testosterone-dependent. Prolonged imipramine treatment (6 months, 100 mg orally twice/day and intermittent *i.v.* injection) had no adverse effects on thyroid and adrenal function or serum chemistry and haemogram.

Preliminary trials have been conducted using the closely related tricyclic compound, clomipramine. Oral clomipramine treatment (100–600 mg twice/day) resulted in frequent erection and masturbation in the stall, with no adverse effects on thyroid and adrenal function or serum chemistry and haemogram.

We observed consistently positive effects of imipramine and clomipramine on erection and ejaculation in the horses studied. These penis drop and erection responses were clearly not an automatic peripheral neurovascular response, as they were under cortically-mediated inhibitory control. The erection and masturbation responses seemed to occur within the context of a general sexual motivational state induced by the drug treatment.

Discussion

As we learn more about the physiology and pharmacology of sexual behaviour it is becoming increasingly apparent that a variety of agents will emerge as aids to therapy. Some of these drugs may generally enhance sexual arousal, but many may have rather specific effects on one or a cluster of sexual responses. To treat sexual behaviour dysfunction in stallions effectively we must continue to work towards diagnosis of the specific nature of the dysfunction and accordingly select an appropriate agent or combination of agents for therapy. In this process, traditional evaluation and behavioural retraining procedures will remain the most important part of the overall therapeutic strategy.

Although most of our recent work follows similar work in other species, we view the stallion as an excellent model for study of human sexual behaviour and dysfunction, including pharmacological manipulation. Stallions, like primates, are single-mount, multiple-thrust ejaculators, with the musculocavernous penis being similar to that of man. In addition, the effects of experience on stallion sexual response closely resemble purported effects of experience in men. For these reasons, we believe that work in the stallion may lead the way to better understanding of the control of male sexual behaviour in mammals in general.

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