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BRIEF COMMUNICATION

Metoclopramide Decreases Apomorphine-Induced Yawning and Penile Erection[1]

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HEATON, J. P. W. AND S. J. VARRIN. *Metoclopramide decreases apomorphine-induced yawning and penile erection.* PHARMACOL BIOCHEM BEHAV **38**(4) 917–920, 1991.—Acute administration of metoclopramide, a dopamine (D2) antagonist, reduced both apomorphine-induced yawning and penile erections. Metoclopramide, prominent in clinical use as an effective antiemetic, has been shown to be associated with decreased erectile function in humans. Experimentally naive rats were given a standardized dose of apomorphine and one of a range of doses of metoclopramide. The study shows that metoclopramide decreases the erectile response to apomorphine and suggests that the erectile difficulties experienced in humans after metoclopramide treatment may be a result of interference with a central dopaminergic mechanism(s).

Impotence Metoclopramide Apomorphine Yawning Dopamine

APOMORPHINE (APO) is a dopamine receptor agonist that has been shown to produce a syndrome of yawning and penile erection (14–16) in rats. The increase in both yawning and erection seen after APO administration is in direct contrast to the low spontaneous rates of these behaviors seen after administration of saline (14,16). This phenomenon has been harnessed to form an effective bioassay for the testing of the erectolytic (erection-diminishing) effects of various pharmaceutical agents.

The specific mechanisms by which APO acts to produce an erectile response are not yet completely understood, however, several hypotheses have been put forth on the basis of the properties of the response to explain the phenomenon. APO has been documented to have a biphasic effect on yawning behavior. Yawning behavior is initiated at approximately 20–25 μg/kg and is inhibited by doses exceeding 400–500 μg/kg (5, 10, 20, 34). It has been shown that a decrease in yawning frequency at higher doses of APO parallels the decrease in the number of erections (14). It has been postulated that low doses of APO cause yawning by preferential stimulation of dopaminergic presynaptic receptors or autoreceptors (32,34), while higher doses have been shown to exert a stimulatory effect on postsynaptic neurons. This view, however, has been challenged recently by Stahle and Ungerstedt (30). They showed that, if basal levels of DA are increased by approximately 200% by the administration of amphetamine, it is still possible to induce yawning behavior using low doses of APO. Yet, according to the autoreceptor hypothesis, it is a reduction in basal levels of DA via autoreceptor stimulation that is responsible for PE/SYS.

Other studies are also felt to provide evidence counter to the autoreceptor hypothesis (4,20). These studies provide evidence that high doses of APO elicit an erectile/yawning response and are thus felt by some to be counter to the hypothesis explaining the behavior through the action of low doses activating dopaminergic autoreceptors. Although the ability of high doses of APO to stimulate an erectile response could probably be taken as evidence against the autoreceptor hypothesis a fundamental aspect becomes evident when reviewing these studies. For example, a study where the erectile response is stimulated by high doses of APO given by oral intubation cannot be compared, in terms of dosing, with those studies using APO administered by the subcutaneous or intraperitoneal route as APO has been shown to have very poor oral bioavailability (3,28). Again, the study by Hull et al. (20) used the direct infusion of high doses of APO to study the effects on sexual behavior. High doses of APO administered to the lateral ventricle or medial preoptic area increased sexual behavior as defined by an increased ejaculation frequency or a decreased intermission interval. However, can this be taken as evidence against the autoreceptor hypothesis? With high doses of

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directly infused APO the risk of spreading of drug into adjacent areas that are more directly involved in the PE/SYS phenomenon, but require low doses, must be considered. In fact, it has been shown that low doses of APO infused into the paraventricular nucleus (PVN) are effective in stimulating a yawning and erectile response (27), while lesioning of this nucleus abolished the ability of systemic APO to induce the response (2). Thus high doses of APO infused in areas in close proximity to the PVN may indeed elicit a response. In light of the above, caution must be exercised when evaluating studies that examine APO and its ability to produce PE/SYS or confusion may be added to the already complicated picture of the mechanism of this response.

Although the specific mechanism of APO-induced PE/SYS remains unidentified, most investigators agree that the response is the result of central stimulation rather than the direct peripheral stimulation of the penile vasculature (causing erection) or facial vasculature (to cause yawning). Sulpiride and haloperidol, central dopamine receptor blockers, antagonize the ability of apomorphine to elicit PE/SYS (14). The dopamine (D2) antagonist domperidone, which unlike sulpiride and haloperidol is a peripherally acting agent (22), has been shown to have no effect on APO-induced penile erections (29). Thus yawning and probably the accompanying erectile behavior, is felt to be centrally mediated (14,34).

Regardless of the specific mechanism of APO-induced PE/SYS the establishment of a rat bioassay for erectile function allows for the testing of various pharmaceutical agents with properties known or thought to have an impact on the erectile pathway(s). Metoclopramide (MET) is such an agent. The antagonistic actions of metoclopramide are said to be four to five times greater on the presynaptic receptors than on the corresponding postsynaptic receptors (1). The ability of MET to inhibit APO-induced yawning in rats (18) has suggested the present study that examines the effect of MET on APO-induced erections. These pathways and responses may play an important physiological role in the central control of some erectile responses and in some erectile dysfunction.

METHOD

Forty experimentally naive male Wistar rats (230–260 g) were obtained from Charles River Laboratories Canada Inc. (St. Constant, Quebec). Animals were housed in individual stainless steel wire cages with a twelve-hour light/dark cycle, the dark (waking) cycle commencing at 1850 hours. The ambient room temperature was maintained at 24°C and the relative humidity at 50%. Free access to standard laboratory food and water was provided for all rats.

After two weeks of handling and acclimatization, the rats were randomly divided into four groups of ten. Each group received only one of four doses of MET (vehicle, 0.7, 1.0, 2.0 mg/kg). Each MET dose was followed 10 minutes later by a standard dose of APO and then the rat was video monitored. In this way, rats in each MET dose group were challenged with a known stimulant to erection.

Rats were transported from the housing facility to the experimental room after weighing. MET (A.H. Robins, Montreal, Quebec) dissolved in phosphate-buffered normal saline (pH 7.4) was injected in a constant volume of 2 ml/kg of body weight. MET doses were administered by intraperitoneal injection. After injection with MET the study animals were placed one at a time in the test cage (26 × 18 × 18 cm). The room lights were dimmed leaving sufficient light for video-monitoring. After a ten-minute habituation period, the rat was injected with APO (Sigma Chemical Co., St. Louis, MO) dissolved in phosphate-buffered normal saline and ascorbic acid (0.5 mg/kg) (Sigma Chemical Co., St. Louis, MO). APO was given subcutaneously (SC) in the loose skin of the back of the neck. A dose of 80 μg/kg (5.0 ml/kg) was used, this dose is known to produce erections in ≥95% of normal rats (16). Each rat was used only once. A solid state Hitachi videocamera (VK-C 1500, Hitachi Ltd., Tokyo, Japan) connected to a Hitachi monitor (MT-2860, Hitachi Ltd., Tokyo, Japan) in an adjacent room was used to observe the animal. The videocamera was placed underneath and to the side of the test cage to obtain the best view of the animals' behavior. Each animal was observed for a thirty-minute period in which time the number of yawns and erections were counted and tabulated by the experimenter. A yawn was identified as an apparently involuntary opening of the mouth accompanied by an apparent respiratory movement but not associated with functional mastication. An erection was counted when pelvic thrusts were followed by an upright stance, the emergence of the glans penis and distal penile shaft. Experimentation began at 1900 hours and each rat was tested at the same time of day to minimize variation due to circadian rhythm.

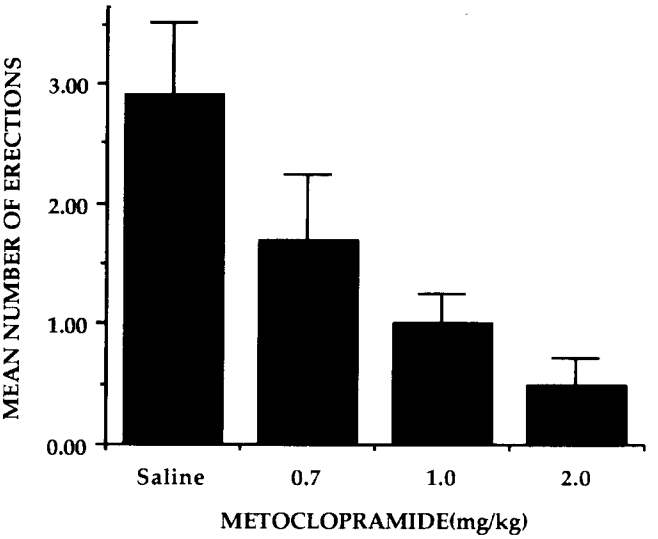

FIG. 1. A comparison of the mean number of penile erections (standard error of mean) after pretreatment with metoclopramide.

RESULTS

Results are analyzed using a one-way analysis of variance (ANOVA). The results show that MET alters APO-induced erections (see Fig. 1), as well as yawning behavior (see Fig. 2). Overall ANOVA revealed that MET significantly reduced the number of APO-induced erections, $F(1,36) = 12.70$, $p<0.01$ and yawns, $F(1,36) = 10.51$, $p<0.01$, as compared to saline controls. More specifically, ANOVA showed that 0.7 mg/kg MET failed to reduce yawning and erections. However, both yawning, $F(1,18) = 9.77$, $p<0.01$, and penile erections, $F(1,18) = 7.94$, $p<0.01$, were significantly reduced when 1.0 mg/kg was injected prior to APO administration. Similarly, yawning, $F(1,18) = 10.82$, $p<0.01$ and erectile behavior, $F(1,18) = 13.16$, $p<0.01$ were also reduced after the administration of 2.0 mg/kg MET.

DISCUSSION

The results of the present study show that one known stimulant of erections in the rat, apomorphine, may be antagonized by metoclopramide a D2 blocker. The decrease in the erectile response is paralleled by a decrease in yawning behavior. This probably indicates that the suppression of APO-induced erectile

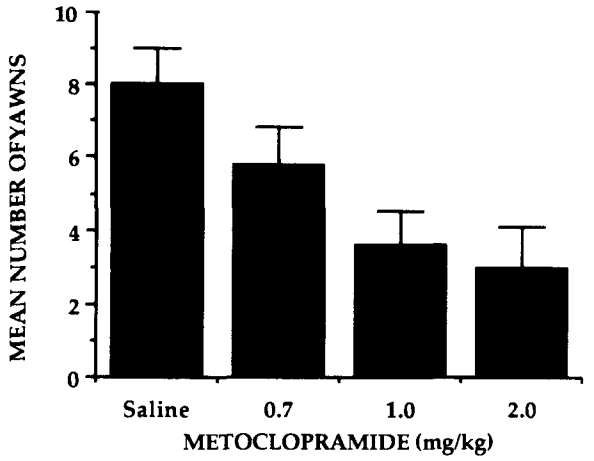

FIG. 2. A comparison of the mean number of yawns (standard error of mean) after pretreatment with metoclopramide.

activity is a result of central antagonism as is the suppression of the yawning. It is not yet known whether MET interferes with the normal sexual response of the rat or whether MET interferes with nocturnal erectile responses in the rat, if indeed these responses are different.

In humans, MET is an effective antiemetic with selective affinity for D2 receptors. MET has been reported to be associated with impotence (6, 31, 33). The mechanism by which MET reduces erectile potential in man is unknown, although the data presented here may point to an alteration in dopaminergic mechanisms. However, the bioassay of potency such as is described here, may be used to examine the specific mechanisms of these alterations in an animal model in detail.

We have discussed one possible mechanism for the interference of MET with APO-induced erections and yawning, one that lies at the level of D2 receptor blockade. There are other potential sources of interaction. For instance, MET has been shown to interfere with both androgen (25) and prolactin homeostasis (12,26). We have recently shown that manipulation of the androgen milieu degrades the erectile function of the rat (17). Similarly, elevated serum prolactin is associated with erectile dysfunction in animals (9,21) and man (11,13).

The validity of extrapolating the results of the rat bioassay for potency and erectile function to man is suggested by the reports that man responds to APO with erection (7, 8, 23, 24) and it is not unreasonable to speculate that MET may cause erectile dysfunction in man by a similar mechanism as that seen in the rat.

In summary, the above data illustrates how the erectolytic effects of a drug may be modeled and tested using APO induced erections as a standard. The APO bioassay may be applied to assess the impact of any physical or pharmacological manipulation with a possible effect on erectile function.

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