

Development of a rat model of sexual performance anxiety: effect of behavioural and pharmacological hyperadrenergic stimulation on APO-induced erections

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As part of the multifactorial nature of erectile dysfunction, anxiety associated with sexual performance (SPA) remains a major contributing factor to its progression. In fact, the heightened sympathetic activity associated with sexual performance anxiety may be a key early component of this disruption of normal erectile responses. We are not aware that any animal models have been developed to assess this phenomenon. Using apomorphine (APO, 80 µg/kg s.c.)-induced erections in rats we characterised the effects of behavioural or pharmacological hyperadrenergic stimulation (that is, anxiety) on erections and hemodynamics. We developed an experimental SPA paradigm by exposing male rats to the stress of being observed by a larger, older male rat placed in close proximity to test rats during APO testing. In a separate group, adrenergic stress was simulated using a sympathomimetic, methoxamine (MXA) given prior to APO testing. In a third group, the changes in circulatory parameters (mean arterial pressure, heart rate) were determined following instrumentation with radiotelemetric transducers for each scenario. APO-induced erections were significantly lower in both the behavioural (1.25 ± 0.8) and pharmacological (0.33 ± 0.5) stressor paradigms compared to controls (2.81 ± 0.9). Further, erections in MXA-treated rats were significantly lower than in the observed scenario. Despite the differences in erections hemodynamic assessments showed no differences in MAP or HR changes between the different experimental conditions. Thus, both the behavioural and pharmacological paradigms of SPA decreased erections, but did not affect the circulation. This suggests that the level of hyperadrenergic input required to induce erectile dysfunction can be subtle, and target only erectogenic pathways.

International Journal of Impotence Research (2002) 14, 107–115. DOI: 10.1038/sj/ijir/3900836

Keywords: erectile dysfunction; apomorphine; anxiety

Introduction

The declaration of Masters and Johnson in 1970¹ that the fear of inadequacy is the greatest known deterrent to effective sexual functioning occurred during a time when it was thought that impotence was a psychologically based problem caused by anxiety.² It is now believed that impotence, or more correctly erectile dysfunction, is a multifactorial disease where sexual performance anxiety may constitute one of the many factors contributing to erectile dysfunction.

Erectile dysfunction is the most common sexual dysfunction in men, affecting approximately 33 million North Americans,³ and is clinically described as the inability to achieve or maintain an erection of sufficient rigidity for sexual intercourse. The ability to generate an erection involves the combined and overlapping activity of neural, hemodynamic and hormonal inputs.^{4–6} This multifaceted nature of the erectile response is beneficial such that in the presence of a dysfunctional input, a redundant or overlapping input can compensate for the insufficiency and a penile erection can still occur. However, if multiple dysfunctional inputs exist, it is more likely that erectile dysfunction will occur. For example, episodic erectile failure due to mild-to-moderate organic disease such as cardiovascular disease when combined with progressive sexual performance anxiety (ie fear of failure) that develops following the initial erectile failure may, over time, develop into chronic erectile dysfunction. This multifactorial and integrative basis of erectile

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Received 27 July 2001; revised 30 November 2001; accepted 18 December 2001

dysfunction is more comprehensive than previous concepts that suggest that the inability to achieve an erection be strictly due to psychological interference or anxiety.⁷

Despite the multifactorial nature of erectile dysfunction, it is probable that anxiety associated with sexual performance is a major contributing factor to the development of chronic dysfunction. Indeed, aberrant central nervous system (CNS) activity can interfere with the neural pathways involved in generating penile erections. For example, general anxiety, and more often anxiety associated with sexual performance can contribute in whole or in part to erectile failure in men.⁸ Anxiety disorders involve both a cognitive component (originates in CNS) and a physiological component (peripheral outcome).⁹ The cognitive component of anxiety is associated with feelings of concern, fear of failure and frustration, resulting in distraction from tasks relevant to a situation.¹⁰ Therefore, in the sexual setting, the cognitive component is characterised by feelings of sexual inadequacy, fear of failure during sexual performance and the resulting distraction from sensation and sexual pleasure.^{7,11} The cognitive component of anxiety contributes to the physiological component, which is associated with increased sympathetic activity.⁸ Therefore, the heightened sympathetic activity associated with sexual performance anxiety may disrupt the balance of factors involved in normal penile erections. Thus, the parasympathetic activity and production of local dilators with sexual arousal may be overwhelmed by hyperadrenergic input, decreasing or eliminating erectile function.

Experimentally, erectile function can be assessed using the apomorphine-induced erection model established by Heaton *et al*.¹² Apomorphine (APO), a non-selective dopamine (D₁/D₂) receptor agonist when administered in low doses to rats, induces a characteristic erectile and yawning response via D₂ receptor stimulation in the brain.^{13,14} These pharmacologically-induced, centrally-initiated penile erections have been shown to follow similar neural pathways as psychogenic erections.¹⁵ The rat model of APO-induced erections involves an integrated response of the total CNS–peripheral neural pathway–erectile system. This approach thereby provides a means of experimentally assessing the effects of sympathetically-mediated sexual performance anxiety on erectile function in rats. The problem of characterising a specific setting of sexual performance anxiety (SPA) in experimental animals is that the level of anxiety cannot be verified. However, several studies have overcome this difficulty by creating general anxiety in a sexual setting, thus capitalising on the principle that general anxiety and SPA both involve cognitive disruption causing distraction from specific tasks.^{16,17}

In the current investigation, we hypothesise that SPA involves increased sympathetic nervous system

activity, which contributes to the development of erectile dysfunction. To assess this hypothesis, an animal model of SPA was characterised using the APO-model of inducing erections in rats in conjunction with the principles of general anxiety as described above. This was subsequently compared to a model of pharmacologically-induced ‘stress’ using low-doses of the selective α_1 -adrenoceptor agonist methoxamine (MXA) to mimic the increased sympathetic input to the vasculature generated by the anxiety paradigm. In addition, in a separate group of rats we also determined the hemodynamic (that is mean arterial pressure and heart rate) effects of these scenarios to assess whether generalised alterations in the circulation are either a sole cause or a contributing factor to the erectile dysfunction.

Materials and methods

Study 1: Determination of the effects of anxiety on apomorphine (APO)-induced erections

Animals. Twenty-eight male Wistar rats from Charles River Laboratories (Montreal, Quebec) weighing 325–350 g were used in the investigation. Animals were individually housed in a climate controlled room under a 12-h light/dark cycle and allowed access to food and water *ad libitum*. All procedures were performed in accordance with the guidelines set out by the Canadian Council on Animal Care. The animals were allowed to acclimate 7 days prior to testing and were handled daily by the investigator over the acclimation period.

Experimental procedure. The rat model of APO-induced erections used to assess the effects of performance anxiety on physiological erectile function was based on the model developed by Heaton and Varrin.¹² Briefly, animals were placed separately in hanging wire test cages in an isolated, dark and soundproof room and allowed to acclimate to the surroundings for 10 min. Animals in the test cages were visually unaware of other rats unless otherwise noted. Each rat received 80 μ g/kg APO (Sigma Chemical Co., St. Louis, MO) prepared with 100 μ g/kg ascorbic acid dissolved in physiological saline via subcutaneous (s.c.) injection volume of 1 ml/kg in the back of the neck. Erectile and yawning responses to APO were recorded at intervals of 5 min for a total of 30 min in an adjacent room via a video monitoring system.

An erection was counted when an engorged glans penis and distal shaft were fully exposed. A yawn was identified by an opening of the mouth associated with appropriate respiratory movement.

Each rat was subjected to a control APO administration prior to performance anxiety test scenarios to determine initial erectile response. Rats displaying unsatisfactory erectile responses (ie less than 2 erections per 30 min) were removed from further study. After sexual performance anxiety testing, rats were subject to another control APO test to determine recovery of normal erectile response.

Sexual performance anxiety scenario. A total of 16 rats were used to assess SPA. Each rat was subjected to a control APO administration prior to performance anxiety test scenarios to determine baseline erectile response values ('control' APO response). To assess the effects of sexual performance anxiety on erectile function in rats, the paradigm of general anxiety in a sexual setting was used. Under normal testing conditions, rats are visually unaware of other rats. In order to create general anxiety, a hanging wire cage was set up in front of the testing cages such that it was visible to all rats being tested (Figure 1B). SPA tests involved a 10-min acclimation period as described in the Experimental Procedure. A large adult observer rat, not administered with APO and weighing 500–600 g (that is 200–300 g more than the rats being tested) was placed in the facing hanging wire cage *after* APO administration to test rats, marking the commencement of the 30 min erectile and yawning response monitoring.

Pharmacological model of anxiety—hyperadrenergic stimulation with methoxamine. A separate group of six rats were used in the pharmacological model of a 'stress' scenario. Prior to treatment with the α -adrenergic agonist methoxamine (MXA), rats were subjected to a control APO test. The following

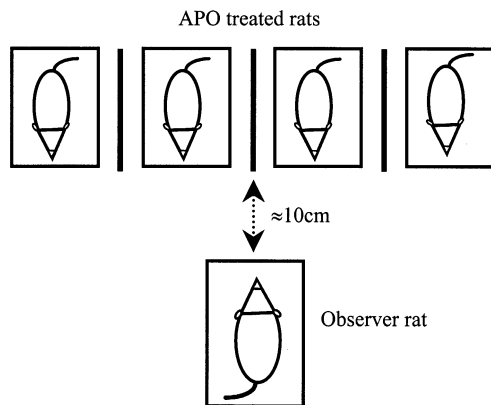


Figure 1 Schematic diagram of the SPA paradigm used in the APO erectile monitoring protocol and the radiotelemetry hemodynamic protocol. Observer rat (not given APO) was introduced to APO treated rats only after administration of APO.

day, rats were administered MXA (0.5 mg/kg s.c.) 30 min prior to APO. Ten minutes preceding APO administration rats were placed in the test cages, and APO was administered.

Study 2: Radiotelemetric monitoring of MAP and HR in response to anxiety surgical procedure

Due to the invasiveness of surgically instrumenting rats for direct measurement of MAP (ie cannulation of abdominal aorta), a separate group of rats ($n=4$; male Wistars; Charles River) were used for the determination of the effects of the sexual performance anxiety model and hyperadrenergic stimulation on MAP and HR. Rats were anaesthetised using isoflurane (dosed to effect, via inhalation) and ketamine/xylazine (70/5 mg/kg, i.p.) and radio-telemetric pressure transducers (model TA11PA-C40; Data Sciences Inc., St Paul NM, USA) were implanted abdominally. Through a midline incision, the abdominal aorta was exposed and the tip of the catheter, attached to the transducer, was introduced via a small puncture into the vessel and was held in place with cyanoacrylate glue and a cellulose patch. The transducer body was then sutured to the midline abdominal musculature. Animals were allowed to fully recover from surgery for 2 weeks prior to experimentation.

Monitoring of mean arterial pressure (MAP) and heart rate (HR). All procedures were performed in an attempt to mimic the procedures followed for Study 1, however erectile responses were not monitored in this group of rats (that is we had implanted the catheters in the lower abdominal aorta thus potentially altering distal blood flow). Rats were subjected to the following tests: (i) control; (ii) saline injection; (iii) APO injection; (iv) APO injection in the presence of an observer rat (Observed); and (v) APO injection 30 min after injection of the sympathomimetic, methoxamine (MXA). All experiments occurred in a dimly lit, quiet room.

For each scenario, rats were placed in individual, clear test cages, and each cage was placed on a separate biotelemetry receiver (model RA1010 and RPC-1, Data Sciences, St Paul MN) which received radio signals from the transducer within the rat. The cages were arranged such that rats were visually unaware of the proximity of other rats except during the SPA scenario. The digital signals from each receiver were transferred via a consolidation matrix (BCM100, Data Sciences), to a computer-based data acquisition system (Dataquest IV, Version 2, Data Sciences) located in an adjacent room. The arterial pressure of each animal was then collected online at 150 Hz for 15 s every minute during the

experimental time period, and the Dataquest software program calculated the mean arterial pressure (MAP) over each 15 s interval. Heart rates of each rat were collected at the same interval for 15 s and the software calculated the average heart rate over the sampling period.

Experimental scenarios. Rats were housed as per the APO protocol, and monitoring of MAP and HR occurred only during the experimental protocol. For each scenario, once rats were placed in test cages, the cages were placed on the biotelemetry receivers and monitoring of MAP and HR began. The control experiment involved rats being placed in test cages for a total of 40 min to determine the baseline MAP and HR of rats in the test cages without further manipulation. For the saline injection, rats were placed in test cages, and after 10 min of acclimation to the cage during which baseline MAP and HR were determined for this scenario, saline (1 ml/kg, s.c.) was injected. MAP and HR were sampled for 30 min following the saline injection, for a total of 40 min. The APO injection mimicked the timing of procedures used to determine the control erectile response to APO where rats were placed in test cages, and following the 10 min acclimation period (baseline MAP and HR determination), APO (80 µg/kg, s.c.) was injected. MAP and HR were sampled every minute for an additional 30 min following the APO administration. For the 'Observed' scenario, rats underwent the 10 min acclimation/baseline MAP and HR period, after which, APO (80 µg/kg, s.c.) was given and an observer rat (one per four test rats) was placed directly in front and in view of the test cages. MAP and HR were sampled for an additional 30 min following APO and introduction of observer rat. Finally, for the hyperadrenergic stimulation scenario, rats were placed in test cages and after 10 min acclimation/baseline MAP and HR determination, given MXA (0.5 mg/kg s.c.). Rats remained in test cages after MXA to determine the effects of the sympathomimetic on MAP and HR. Thirty minutes following MXA, APO was administered and MAP and HR were sampled for an additional 30 min following APO administration.

Statistical analysis

The average erectile and yawning responses were determined for each 30 min testing scenario: Control, Observed and MXA treated. The average erections or yawns in each scenario were compared using a one-way analysis of variance with a Newman-Keuls *post-hoc* analysis ($*P < 0.05$). The per cent of control erectile or yawning responses were recorded for the Observed and MXA scenarios. The APO responses were then examined according to the

distribution of responses over the three 10 min time segments in the 30 min monitoring period. Average number of erections or yawns in each 10 min segment for each testing scenario (control, observed, MXA) were compared using a one-way ANOVA with Newman-Keuls *post hoc* analysis. Per cent of total erectile responses or yawning were also calculated for each testing scenario.

MAP and HR were determined using the Data Sciences software. Per cent change in baseline MAP (that is average MAP over 10 minute acclimation period) were determined for all scenarios, and area under the curves (AUC) were performed for each rat to determine the effects of the manipulations on MAP. AUC were compared using repeated-measures ANOVA with Newman-Keuls *post hoc* analyses. Similar analysis was performed with the HR data. In order to compare the distribution of erections or yawns according to the MAP and HR during the same time period, AUC of absolute MAP or HR were determined for each 10 min segment in the 30 min monitoring period for each scenario. Differences in the AUC were compared using repeated measures ANOVA with Newman-Keuls *post hoc* for MAP and HR.

Results

Study 1: Determination of the effects of anxiety on APO-induced erections

In comparison to the average control erections (2.81 ± 0.9 ; Figure 2A) the presence of the observer rat significantly decreased the erectile response to APO (1.25 ± 0.8 ; $*P \leq 0.05$ vs control). Hyperadrenergic stimulation induced pharmacologically with MXA further decreased the erectile response (0.33 ± 0.5) compared to that in the Observed rats as well as versus controls. In contrast, there was no significant alterations of APO-induced yawning responses during either experimental scenario (APO control yawns, 6.9 ± 3.7 , Observed 5.7 ± 4 , MXA 3.0 ± 3).

Study 2: Radiotelemetric monitoring of MAP and HR in response to anxiety

Subcutaneous injection of any agent (such as saline, APO or MXA prior to APO administration) increased MAP and HR by approximately 25% above each scenario baseline value (Figure 3A and B). This increase in hemodynamic parameters regardless of agent injected is most likely due to a behavioural response of the animals to being handled during the injection process. Administration of MXA caused an

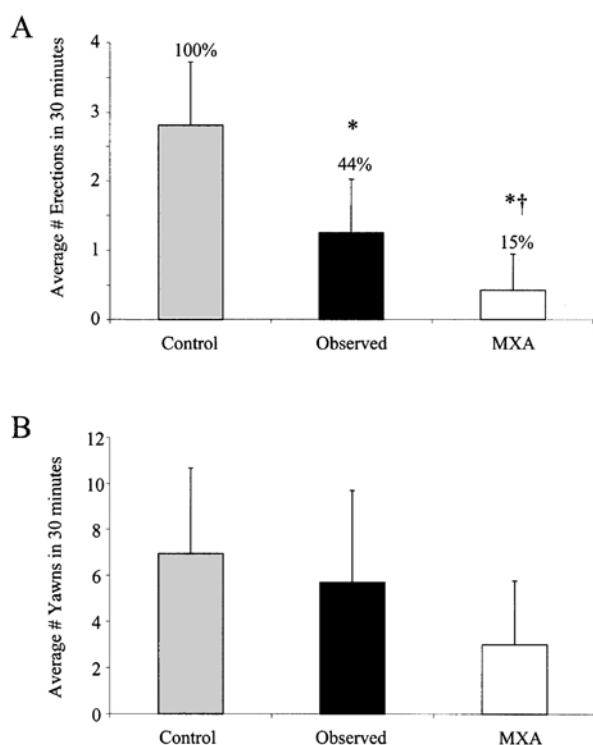


Figure 2 (A) APO-induced erections in the Control ($n=22$), Observed (SPA paradigm; $n=16$) and MXA ($n=6$) scenarios. Erections were significantly decreased compared to Control in the Observed and MXA scenarios ($*P < 0.05$). Erections following MXA were also significantly decreased compared to the Observed scenario ($†P < 0.05$). (B) Yawning responses to APO in the Control, Observed and MXA scenarios. There were no significant differences in the yawning responses in all test scenarios.

initial 13% increase in MAP within the first 10 min following administration (99.6 ± 13 mmHg baseline to 113.2 ± 10 mmHg after MXA), and a 10% increase in HR (379.6 ± 34 baseline to 416.8 ± 19). These increases in hemodynamic parameters are not significantly different from the changes in MAP and HR associated with injection (s.c.) of saline or APO, therefore although this dose of MXA (0.5 mg/kg s.c.) was erectolytic, it did not have a global effect on the circulation. Interestingly, it should be noted that although there was a characteristic increase in MAP following s.c. injection of APO in the MXA pre-treated rats, the corresponding characteristic rise in HR was not present in this group (Figure 3B). The AUCs for the MAP profiles with the Saline, APO, Observed and MXA scenarios were all significantly greater than that of the Control (i.e. no injection; $*P \leq 0.05$) scenario, but did not differ from each other. In contrast, the AUC of the HR profiles for Saline, APO and Observed scenarios were all significantly greater than the Control scenario ($*P \leq 0.05$) and the MXA scenario ($†P \leq 0.05$). The lack of change in HR from baseline

in the MXA pretreated animals following APO administration is most likely due to conditioning of the animals to the handling and injection procedure. APO was administered 30 min following MXA administration, with a similar pattern of animal handling and injection, therefore by the second subcutaneous injection (that being of MXA), the rats may have become accustomed to the procedure.

A comparison of the distribution of erections over the 30 min monitoring period with the change in MAP and HR in response to subcutaneous injection of APO was performed (Figure 4). The greatest proportion of erections (Figure 4A) in all three scenarios occurs during the first 10 min of the monitoring period, where the increase in MAP (Figure 4A) and HR (Figure 4C) occurs in response to handling and subcutaneous injection. There was no significant difference in the proportion of erections occurring across the three 10 min segments of the monitoring period. Changes in MAP with the MXA scenario were significantly less than Control in the last 20 min monitoring period ($*P < 0.05$). Changes in HR were significantly less than Control in the first 10 min segment of the Observed scenario, significantly less during the entire monitoring period of MXA scenario ($*P < 0.05$).

Discussion

The major finding is that a decrease in erectile function occurs following exposure to relatively mild conditions of stress. In particular, the successful application of a negative behavioural distracter (such as the observer rat) to the APO-testing environment induced a condition of stress or 'anxiety' which models, at least in part, sexual performance anxiety. Specifically, in the presence of an observer rat, erectile responses were significantly lower than during the control period. In addition, simulation of this stress using low doses of the α -adrenoceptor sympathomimetic, methoxamine produced a similar reduction in erections. The subtlety of these erectolytic effects on vascular control mechanisms was demonstrated by the lack of significant alteration in MAP and HR in both the pharmacological and behavioural scenarios. These results suggest that even minimally increasing sympathetic nervous system input, by either behavioural means or pharmacological manipulation, is sufficient to substantially impact on erectile function, without necessarily inducing global circulatory changes.

During APO-testing with the observer rat present, the general activity of the rats in the test cages was increased compared to animal responses during either the control or recovery testing periods. For example, the heightened rat locomotor activity was

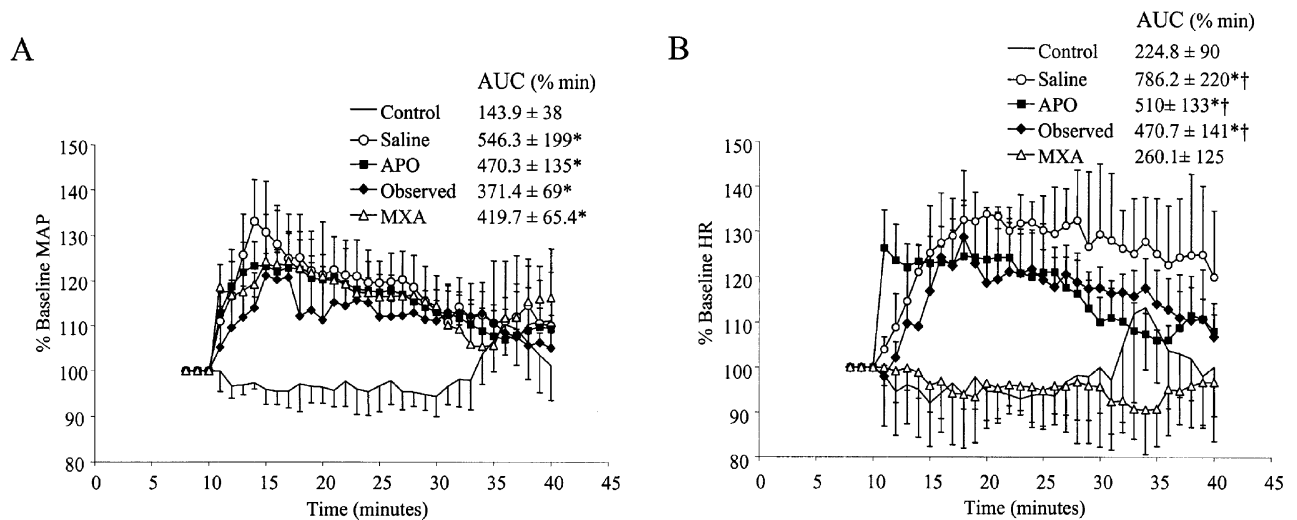


Figure 3 (A) The changes in MAP are expressed as percent baseline (that is before administration of subcutaneous, s.c., injection) for each scenario. Administration of s.c. injection increased MAP compared to each baseline, as indicated by the significantly greater AUC of scenarios with s.c. injection compared to the Control scenario ($*P < 0.05$) which did not involve any injections. There were no differences in the changes in MAP between Saline, APO, Observed and MXA scenarios. (B) Change in HR is expressed as per cent of baseline. The changes in HR were significantly greater than Control ($*P < 0.05$) or MXA ($†P < 0.05$) in the Saline, APO, and Observed scenarios, as per AUC analyses.

clearly revealed by the increased random movement throughout the cage, constant changing of positions, and more frequent grooming, all of which occurred while the animals faced the observer rat. These increases in activity are likely indicative of the degree of distraction from the specific tasks normally associated with the APO-induced erectile response. The integrated outcome, thus, constituted the cognitive component of anxiety. The primary physical component of anxiety that was of interest, sympathetic stimulation, would also have been incorporated into the increased activity profile of the observed rats. Stressor stimuli, increased peripheral sympathetic nervous system activity and elevated locomotor/physical activity have been previously linked.^{18–21} Interestingly, previous investigations have revealed that prolonged exposure to stressors attenuates catecholaminergic activity in the brain, in part, via depletion of catecholamine levels. Associated with the chronic stress state is impairment of sexual function.²² In addition, studies have shown that responses specific to apomorphine were diminished following exposure to prolonged anxiety-like stressors.²³ Thus, there is apparent discordance between the responses of the brain and peripheral components of the adrenergic system during initial and adaptational responses to stress. In the present study, the ‘general anxiety’ or stress-induced modulation of the central and peripheral sympathetic system, occurring in the presence of the observer rat, effectively diminished erectile responses, but was not sufficient to alter hemodynamic parameters.

The dose of MXA employed in this investigation (0.5 mg/kg, s.c. bolus) is relatively low compared to that used in combination hemodynamic/erectile function studies previously performed in our laboratory. Indeed, in a previous studies involving acute blood pressure and heart rate monitoring in conjunction with monitoring APO-induced responses, a higher dose of MXA (3.3 mg/kg per h; continuous intravenous infusion) increased MAP by 36%, as well as associated baroreflex-mediated 23% decrease in HR compared to controls (Figure 5). In this experimental scenario using a high dose of an α -agonist, APO-induced erections were decreased by 71% although this erectolytic activity was associated with marked pressor changes in the circulation, in contrast to the low dose methoxamine results. What was not established was whether the change in erectile function resulted from systemic effects of MXA on the circulation, or from direct effects on erectile mechanisms. In the current investigation, we clarified this issue by employing a lower dose of MXA to selectively decrease erections using an adrenergic stimulus that did not alter systemic hemodynamics.

Interpretation of the hemodynamic and erectile responses following the low dose MXA and SPA scenarios reveals that there very likely are a number similarities in the control systems involved. Previously, Adams *et al*²⁴ suggested that the control mechanisms involved in the maintenance of vascular smooth muscle tone are also relevant in the generation of penile erections. Indeed, these multiple and overlapping control systems within the penis and

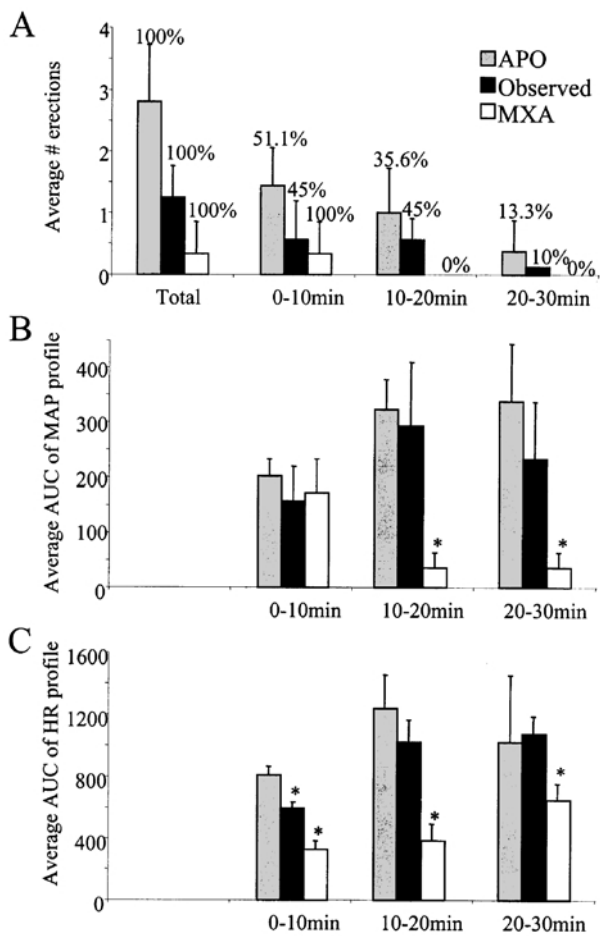


Figure 4 Distribution of erections (A), Change in MAP (B) and Change in HR (C) into 10 min segments during the 30 min monitoring period for the Control, Observed and MXA scenarios. There were no significant differences in the number of erections during each 10 min time segment during the 30 min monitoring period. Change in baseline MAP during the last 20 min of the monitoring period was significantly less compared to control in the MXA scenario (* $P < 0.05$). Change in baseline HR during the first 10 min segment of the Observed scenario was significantly less than Control (* $P < 0.05$). With the MXA scenario, the change in HR from baseline was significantly lower vs Control during the entire 30 min monitoring period (* $P < 0.05$).

the vasculature are redundant in order to maintain normal function.⁶ Herein, we demonstrate that a subcutaneous injection by itself increases MAP and HR for a period of approximately 15 min post-injection. This global hemodynamic response is indicative of increased sympathetic drive in response to the handling and injection stimulus (that is a mild form of ‘fight or flight response’).²⁵ It is important to note that despite the changes in hemodynamics in response to handling and injection, APO treatment produces the majority of erectile responses within this initial period of sympathetic hyperactivity. Clearly, under these circumstances, there is sufficient capacity in the

penile control mechanisms to allow normal erectile function to occur.

Although the hemodynamic alterations appear to be similar between the two SPA paradigms the mechanisms involved likely differ, at least in part. This is important to recognise since although the stressor inputs increased adrenergic stimulation above that induced by saline injection alone (MXA and observation testing), they did not further alter MAP and HR. This subtle increase in the basal sympathetic activity was mediated in one scenario by the systemic delivery of a sympathomimetic (MXA) whereas in the behavioural paradigm the output was centrally-mediated. Regardless of the mechanisms involved, in both cases there was insufficient compensation by penile control systems. This indicates that there may be more redundancy in the compensatory mechanisms involved in the control of the systemic circulation than that of penile vasculature. This is not surprising considering that blood flow to critical organ system such as the brain and heart are required for survival whereas penile blood flow is not.¹⁸ In fact, the activation of global compensatory mechanisms resulting in redistribution of blood flow may be a cause of the erectolytic effect. For example, we have demonstrated elsewhere that a rapid increase in MAP, with either NOS blockade, or infusion of angiotensin II, can acutely cause erectile dysfunction, whereas several hours following the increase in MAP, although MAP continues to be elevated, erectile function is restored.^{26–28} In addition, hypertensive males maintain the ability to have erections, at least in part, whereas initiation of antihypertensive therapy often results in erectile dysfunction. It is likely that the erectolytic action is due, in part, to the changes in hemodynamics. Thus, rather than the level of blood pressure dictating erectile function, often it is hemodynamic instability that is the cause of erectile dysfunction.

Alternatively, within the penis, a direct erectolytic effect of the increased adrenergic activity could have resulted from a selective increase in pudendal resistance resulting from proximal changes in erectile signalling pathways (for example, inability to compensate for extreme changes in the tone of penile tissue).²⁹ It is generally accepted that, in the flaccid state, characterised by low blood flow to penile tissue and high corporal smooth muscle tone, α_1 -adrenoceptor activation is the most important means by which corporal smooth muscle contraction is maintained.^{30,31} Furthermore, detumescence in the healthy penile erection is initiated and mediated by increased α -adrenergic tone which decreases arterial inflow, corporal smooth muscle relaxation and hence venous occlusion, thus allowing blood to drain from the penis.³² In contrast, in the case of priapism (that is prolonged erection) phenylephrine, an α -adrenoceptor agonist, is often administered intracavernosally to induce

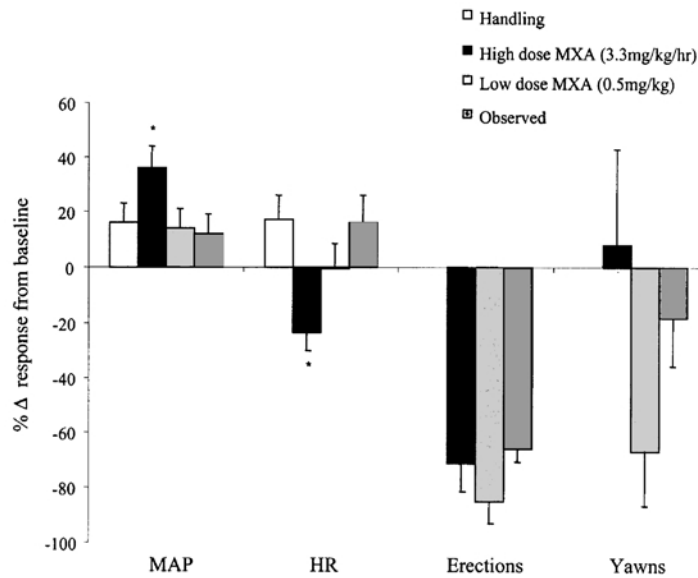


Figure 5 Change in baseline or control responses of MAP, HR, erections and yawns during handling, high dose MXA (3.3 mg/kg per h, i.v.) and low dose MXA (0.5 mg/kg s.c.) and Observed scenarios. High dose MXA had a significantly greater impact on MAP and HR compared to the other test scenarios ($*P < 0.05$), but did not alter APO-induced erections or yawns compared to the other scenarios.

detumescence.^{33,34} Anecdotally, another novel method has been proposed for initiating detumescence during priapism involving physical exercise. In this case, a user of intracavernosal injection therapy experiencing priapism found non-invasive relief with 15 min of rigorous bicycling.³⁵ Exercise increases sympathetic nervous system activity and circulating levels of catecholamines, without necessarily altering blood pressure.³⁴ Thus, it has been established that increased adrenergic activity, whether derived from intrapenile (local) or global signalling can be erectolytic. Taken together, in the present studies, the lack of further change in hemodynamics suggests that the decrease in erectile function observed is locally-mediated.

An additional consideration in defining the origin of the erectolytic signalling in both the pharmacological and behavioural SPA scenarios relates to whether or not any effects could have originated in the CNS.²⁶ This is unlikely for the pharmacological challenge since MXA works peripherally to mimic an increase in adrenergic activity, and does not cause central stimulation.³⁷ Finding that with both low and high doses of MXA there was no significant effect on the central initiated yawning response to APO further supports this. Thus, despite central mechanisms being involved with the behavioural scenario, the lack of a significant impact on the yawning response suggests that the APO-yawning pathway is distinct from the APO-erectogenic pathway.

In conclusion, we have developed an animal model involving a behavioural challenge that appears to mimic the actions of hyperadrenergic

stimulation similar to that caused by anxiety or stress. This model creates a behavioural paradigm similar to anxiety that selectively decreases erectile function while not causing hemodynamic changes. The development of an animal model of sexual performance anxiety provides another experimental tool for the investigation of the multifactorial nature of erectile dysfunction. By understanding the interactions of the many physiological and psychological aspects of erectile function in experimental animals, more effective multi-therapeutic treatment of erectile dysfunction can occur. Whether these treatments can involve selective action of peripheral α -adrenoceptor blockers or other selectively acting sympatholytic agents remains to be established.

Acknowledgements

The authors thank Shannon Parker for her technical support. The Kidney Foundation of Canada, and the Heart and Stroke Foundation of Ontario provided research funding for this investigation. SEB is a recipient of a Canadian Institutes of Health Research Doctoral Award.

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