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The effect of methamphetamine on an animal model of erectile function

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Abstract

In the U.S. methamphetamine is considered a first-line treatment for attention-deficit hyperactivity disorder. It is also a common drug of abuse. Reports in patients and abusers suggest its use results in impotence. The efficacy of phosphodiesterase-5 inhibitors (PDE5i) to restore erectile function in these patient groups also has not been determined. In these studies we determined if the rat is a suitable animal model for the physiological effects of methamphetamine on erectile function, and if a PDE5i (tadalafil) has an effect on erectile function following methamphetamine treatment.

In acute phase studies, erectile function was measured in male Sprague-Dawley rats, before and after administration of 10 mg/kg methamphetamine i.p. Chronically treated animals received escalating doses of methamphetamine (2.5 mg/kg (1st week), 5 mg/kg (2nd week), and 10 mg/kg (3rd week)) i.p. daily for three weeks and erectile function compared to untreated controls. The effect of co-administration of tadalafil was also investigated in rats acutely and chronically treated with methamphetamine. Erectile function was determined by measuring the intracorporal pressure/blood pressure ratio (ICP/BP) following cavernous nerve stimulation.

In both acute and chronic phase studies we observed a significant increase in the rates of spontaneous erections after methamphetamine administration. In addition, following stimulation of the cavernous nerve at 4 and 6mA, there was a significant decrease in the ICP/BP ratio (approximately 50%), indicative of impaired erectile function. Tadalafil treatment reversed this effect. In chronically treated animals the ICP/BP ratio following 4 and 6mA stimulation decreased by approximately 50% compared to untreated animals and erectile dysfunction was also reversed by tadalafil.

Overall our data suggests that the rat is a suitable animal model to study the physiological effect of methamphetamine on erectile function. Our work also provides a rationale for treating patients

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Conflict of Interest
None declared.

that report erectile dysfunction associated with therapeutics containing methamphetamine or amphetamine with PDE5i.

Introduction

Oral methamphetamine (Desoxyn, Ovation Pharmaceuticals) and its primary metabolic product, amphetamine, (the active ingredient in medications such as Adderall, Shire BioChem Inc. and Dexedrine, GlaxoSmithKline) are considered first-line treatments in the U.S. for attention-deficit hyperactivity disorder (ADHD) in children, adolescents and adults (Heal, et al., 2013). Methamphetamine is also a commonly abused recreational drug, with surveys showing that over 10 million U.S. citizens over the age of 12 have tried methamphetamine, which represents more than 4 percent of the population (see reference (Gonzales, et al.) and results from the 2005 and 2008 National Survey on Drug Use and Health). The use of these drugs in adult patient groups has been associated with a low but significant increase in vascular disorders, which includes impotence (Bang-Ping, 2009, Broadley, 2010).

Methamphetamine and amphetamine primarily act on the sympathetic nervous system, causing increased release of the neurotransmitter norepinephrine and allowing norepinephrine to remain active by decreasing its uptake (Rothman, et al., 2001, Sulzer, et al., 2005). In the acute phase following methamphetamine administration this increase in norepinephrine accelerates the heart rate, constricts blood vessels, and raises blood pressure (Thompson, 2008). Constriction of blood vessels in the corpora cavernosum of the penis would be expected to result in erectile dysfunction (ED). At present there are no peer-reviewed studies on the effects of methamphetamine on erectile function from animal models or clinical studies. However, the negative effect of methamphetamine on erectile function is supported in the literature by the observation that men taking methamphetamine recreationally often combine its use with the oral erectogenic phosphodiesterase-5 inhibitors (PDE5i) (such as Viagra®, Levitra® or Cialis®) (Mansergh, et al., 2006, Prestage, et al., 2009). However, the ability of PDE5i to restore erectile function following methamphetamine use has not been scientifically investigated. The PDE5i and methamphetamine affect different signaling pathways that are involved in erectile physiology. PDE5i target the nitric system, whereas methamphetamine targets the adrenergic system. However, there is no evidence suggesting that PDE5i mediated activation of the NO-cGMP pathway will overcome the effects of methamphetamine.

In animal studies, several of the effects of chronic methamphetamine administration on the vascular system were reversed when methamphetamine was withdrawn (Islam, et al., 1995). However, there have been no scientifically peer-reviewed studies determining if the effects of long-term methamphetamine use results in irreversible ED, and whether ED in chronic users is treatable using PDE5i.

Scientific knowledge concerning the deleterious effect of methamphetamine could guide medical intervention in patients prescribed methamphetamine, and in current and former methamphetamine abusers. In addition knowledge that methamphetamine can result in ED may also act as a deterrent for its abuse. In the current paper we investigated if the rat might

serve as an animal model for the association of methamphetamine with ED, and determined if a PDE5i (tadalafil) was effective in treating ED following one hour (acute) and three weeks (chronic) methamphetamine administration.

Materials and Methods

Animals

Male Sprague-Dawley rats (Taconic Farms, Germantown, NY) aged 8–10 wk (200–240 g) were used in these studies. The number of replicates in each experiment is given in the figure legends. Rats were fed Purina laboratory rodent chow ad libitum and housed individually with a 07:00–19:00 light cycle. All animal experiments were approved by the Institute of Animal Studies of the Albert Einstein College of Medicine.

Metamphetamine treatment

For methamphetamine acute phase studies we first determined the “pretreatment” intracorporal pressure/blood pressure ratio (ICP/BP) following cavernous nerve stimulation. The cavernous nerve was stimulated at 0.75, 4 or 6 mA for one minute to determine ICP/BP (as described below). There were 5 minute intervals between subsequent cavernous nerve stimulation with measurement of ICP/BP. Pre-treatment determinations were completed within 40 minutes, at which time point rats were administered methamphetamine (Sigma) at 10 mg/kg i.p. while still under anesthesia. The rats remained under anesthesia for one hour following administration of methamphetamine after which the ICP/BP was determined again. The maximum duration of the experiments was 2.5 hours. Experiments in the control animals for the chronically methamphetamine treated animals showed that within this time frame repeated cavernous nerve stimulation following this protocol does not result in nerve fatigue (Figure 4A). The effect of a PDE5i (tadalafil) on erectile function was determined in a second set of animals which received 2.5mg/kg p.o. tadalafil in a saline solution using a rodent oral feeding tube at the same time as administering 10 mg/kg i.p. methamphetamine. This period of tadalafil treatment was based on pharmacokinetic studies which have shown that oral administration of tadalafil to rats results in peak plasma concentrations after approximately 45 minutes (Lee, et al., 2013). The effects of chronic i.p. injection of methamphetamine on erectile function was determined in animals injected i.p. daily with methamphetamine for three weeks with an escalating dose regimen 2.5 mg/kg (1st week), 5 mg/kg (2nd week), and 10 mg/kg (3rd week). Control animals received an injection of vehicle only. The effect of PDE5i was determined in methamphetamine treated animals by administering 2.5mg/kg p.o. tadalafil in a saline solution using a rodent oral feeding tube an hour prior to measurement of erectile function.

Determination of ICP/BP

The method for determining ICP/BP has been previously described (Davies, et al., 2007, Melman, et al., 2009). Briefly, rats were placed under general anesthesia (35 mg/kg of sodium pentobarbital, i.p.) and subsequent anesthesia maintained through injection with pentobarbital (10 mg/kg) given every 45–60 min, as required. Animals were kept warm using a heat lamp. In humans barbiturates do not greatly affect increased pulse rate caused by methamphetamine (Legge and Steinberg, 1962), suggesting pentobarbital would not

confound the effect of methamphetamine on the vascular system. The rats were placed supine, and the bladder and prostate exposed through a midline abdominal incision. The inferior hypogastric plexus (i.e. the pelvic plexus or major pelvic ganglia), pelvic nerves and the cavernous nerve were identified posterolateral to the prostate on both sides, and stainless-steel bipolar wire electrodes were placed around a cavernous nerve for electrical stimulation. The penis was then denuded of skin; both crura (corpus cavernosum) were exposed by removing part of the overlying ischiocavernosus muscle. To monitor the ICP, a 23 G PrecisionGlide® needle cannula was filled with 250 U/mL of heparin solution (1%), connected to polyethylene-60 tubing (Intramedic, Becton Dickinson, CA, USA) and inserted into the right corpus cavernosum. Systemic arterial BP was monitored via a 25 G cannula placed into the carotid artery. Both pressure lines were connected to a pressure transducer, and then via a transducer amplifier (ETH 400) to a data acquisition board which communicates real-time display and recording of ICP to a computer. The cavernous nerve was directly electrostimulated by a stainless-steel bipolar hook electrode attached to a multi-jointed clamp. Each probe was 0.2 mm in diameter; the two poles were separated by 1 mm. Monophasic rectangular pulses were delivered by a signal generator (custom-made and with integral constant-current amplifier). The stimulation parameters were 20 Hz, pulse width 0.22 ms, and duration 1 min; and an increasing current of 0.75, 4 or 6mA (as described in the figure legends). Changes in intracavernosal pressure (ICP) and systemic blood pressure (BP) were recorded at each level of neurostimulation. A one-way analysis of variance (ANOVA) was used to determine treatment effects. Results were expressed as the mean $\pm$ SEM.

Results

In the first series of experiments the effect of acute exposure of methamphetamine on the erectile function of rats was investigated. In this series of experiments we first determined the erectile function of animals prior to the administration of methamphetamine. The ICP/BP was determined following electrical stimulation of the cavernous nerve. Expressing results as ICP/BP normalized for the small increases in BP which follow methamphetamine administration. Increasing the level of stimulation increased the ICP/BP ratio, and resulted in an observable erection. In the same animals we then administered methamphetamine 10 mg/kg i.p. and after one hour we again determined erectile function by measuring the ICP/BP following stimulation of the cavernous nerve. A typical trace for stimulation at 4 and 6 mA is shown in Figure 1, and the results averaged in Figure 2. As shown in Figure 1, over the course of the experiment there was no significant change in systemic blood pressure. Following methamphetamine administration there was a significant decrease in the ICP/BP ratio following cavernous nerve stimulation at 4 and 6mA, indicating ED in these animals. Interestingly, animals treated with methamphetamine also exhibited spontaneous erections without stimulation (these spontaneous erections did not occur prior to methamphetamine administration). Spontaneous erections occurred approximately 5 minutes after the first cavernous nerve stimulation following administration of methamphetamine, and continued to occur throughout the remaining time of the experiment (approximately 45 minutes). These erections were approximately 1 min in duration, and generally had an ICP/BP >0.6 , corresponding to a visible erection.

In another group of animals PDE5i, tadalafil, was co-administered with methamphetamine. After one hour the ICP/BP was measured after cavernous nerve stimulation and compared with the response in animal receiving methamphetamine alone. As shown in Figure 3 tadalafil led to a significant improvement in the erectile response at the 4mA and 6mA stimulation level, with visible erections being observed in the tadalafil treated animals at the higher stimulation.

In a second series of experiments to look at the possible effects of chronic methamphetamine administration on erectile function animals were injected i.p. daily with methamphetamine for three weeks and the effects on erectile function compared to untreated, age matched control animals. An escalating dose regimen was necessary to prevent animal fatality (2.5 mg/kg (1st week), 5 mg/kg (2nd week), and 10 mg/kg (3rd week)). A representative trace showing the ICP in treated and untreated animals is shown in Figure 4. There was no significant difference in systemic blood pressure between the control and the methamphetamine treated animals. There was a significant difference in the ICP/BP ratio which corresponded to visibly poorer erections in the methamphetamine treated group compared to the control group (Figure 4 and 5). Following cavernous nerve stimulation there was an increase in spontaneous partial erections in the methamphetamine treated group, similar in nature to those observed in the acutely treated animals (Figure 4). When animals chronically administered with methamphetamine were treated with tadalafil one hour prior to the determination of ICP/BP, erectile function was improved to a level that it was not significantly different to control animals that were not treated with methamphetamine (Figure 5).

Discussion

Our studies are the first to utilize an animal model for investigating the effect of both chronic and acute methamphetamine use on erectile physiology. These studies have implications to adult patients being clinically treated with methamphetamine or amphetamine and who suffer impotence, and also to patients who abuse these substances. Prior to the experiments reported here, the majority of studies done on the effects of methamphetamine on animal physiology have been performed on the mouse, with fewer being performed on the rat. However, the fine surgery necessary to measure ICP/BP is technically difficult in such a small rodent as the mouse. Our data suggests that the rat is an appropriate model for assessing the effect of methamphetamine on erectile function in that it supports anecdotal reports suggesting that methamphetamine results in ED in humans. Both acute and chronic methamphetamine use results in ED in the rat animal model, as indicated by decreased ICP/BP response following cavernous nerve stimulation.

Although we have not investigated the biochemical mechanisms by which methamphetamine results in ED, the most likely pathway is impaired relaxation of corporal smooth muscle through the action of methamphetamine on the sympathetic nervous system which causes increased norepinephrine levels (5, 6). However, methamphetamine has been demonstrated to have several effects on other systems which could also affect corporal smooth muscle tone. For example, the MaxiK potassium channel has been shown to play an important role in relaxation of corporal smooth muscle tissue (Christ, et al., 2009, Werner, et

al., 2005), and recently methamphetamine was shown to directly affect activity of this channel (Wang, et al., 2013). Intracellular Ca^{2+} is also a critical regulator of corporal smooth muscle tone and at least in cardiomyocytes methamphetamine directly accelerates contraction rates by increasing Ca^{2+} entry via L-type Ca^{2+} channels, independent of the involvement of neurotransmitter mechanisms (Sugimoto, et al., 2009).

There are several reports suggesting that other drugs impacting the adrenergic system can affect erectile function. Chronic cocaine administration to rats has been shown to result in ED (Kendirci, et al., 2007). There is a high incidence of erectile dysfunction in men using cocaine (Cregler and Mark, 1986), however, paradoxically there are reports where cocaine use has been associated with priapism (Altman, et al., 1999). A possible explanation is that during acute use of cocaine there is activation of the adrenergic system but with chronic use there is depletion of norepinephrine from neurons, leading to priapism (Munarriz, et al., 2003). At present there are no reports that methamphetamine use (in the absence of other confounding factors) is associated with priapism in humans.

The PDE5i, tadalafil, improved the erectile response to cavernous nerve stimulation in both chronic and acute methamphetamine treated animals. The biochemical mechanism of action of other orally administered erectogenic agents (such as sildenafil, avanafil and vardenafil) is also primarily through PDE5 inhibition, and are therefore likely to have the same qualitative physiological effect. An erection is initiated through neuronal stimuli that inhibit the release of norepinephrine from sympathetic nerves and trigger the release of other neurotransmitters, such as nitric oxide (NO) initiate an erection (Dean and Lue, 2005). NO raises the concentration of cyclic guanosine monophosphate (cGMP) which leads to relaxation of vascular and cavernosal smooth muscle cells, resulting in increased blood-flow through the helicine arteries and into the corpus cavernosum inducing erection. It is well established that a major pharmacological effect of PDE5i is to increase cGMP levels in cavernosal smooth muscle tissue following neural stimulation, and thereby initiate an erection (Moreland, et al., 2001, Waldkirch, et al., 2005). The ability of tadalafil to overcome the effects of methamphetamine on the adrenergic system resulting in erectile dysfunction are likely mediated by sufficiently up-regulating the activity of the NO-cGMP pathways activated by cavernous nerve stimulation.

We also noted that methamphetamine resulted in increased numbers of spontaneous erections in both acutely and chronically treated animals. The average duration of these spontaneous erections was one minute, which is similar in duration to a reflexive erection, or an apomorphine-induced erection in the rat (Bernabe, et al., 1999). There are several potential mechanisms by which methamphetamine might cause spontaneous erections. It might involve a similar mechanism described above for priapic episodes mediated by cocaine, where extended administration depletes norepinephrine, resulting in heightened sensitivity of corporal smooth muscle tissue to “relaxant” signals (Munarriz, Hwang, Goldstein, Traish and Kim, 2003). Alternatively methamphetamine could directly activate smooth muscle relaxation mechanisms, by modulating potassium or L-type calcium channel activity as described above. There may also be an “upstream” effect, whereby methamphetamine generates stimulatory nerve impulses within the central nervous system.

The therapeutic dose of methamphetamine for ADHD or narcolepsy ranges from 10-40 mg daily and blood concentrations are commonly 0.02-0.05 mg/L, although levels can reach 0.2 mg/L. Abusers of methamphetamine typically use 100-1000 mg daily, but can take up to 5000 mg during chronic binges. Blood levels in methamphetamine abusers are typically 0.01-2.5 mg/L with a mean of 0.6 mg/L. (<http://www.nhtsa.gov/people/injury/research/job185drugs/methamphetamine.htm>). The rats used in our studies weighed on average 250g and were given up to 10 mg methamphetamine, which would equate to the doses taken by abusers rather than therapeutic doses. However, the ability of tadalafil to restore erectile function even at these high levels would suggest that it would also have efficacy in patients taking the drug therapeutically. Our studies did not consider the reversibility of ED following chronic methamphetamine use. However, histopathology of corporal tissue after 3 weeks of methamphetamine administration to rats showed no significant pathology compared to controls (data not shown), suggesting that after the withdrawal of methamphetamine a functional penile architecture remains.

Overall our data suggests that the rat is a suitable animal model to study the physiological effect of methamphetamine on erectile function. Our work also provides a rationale for treating patients that report ED associated with therapeutics containing methamphetamine or amphetamine with PDE5i.

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Figure 1.

A typical tracing showing the intracorporal pressure of a rat following cavernous nerve stimulation before and one hour after the administration of 10 mg/kg methamphetamine. Lower panel is a recording of systemic blood pressure. Note the occurrence of spontaneous erections following methamphetamine administration indicated by unstimulated transient increases in ICP.

Figure 2.

The effects of acute high dose i.p. injection of methamphetamine on erectile function. Prior to methamphetamine injection seven animals had their ICP/BP determined at increasing levels of cavernous nerve stimulation (0, 0.75, 4 and 6 mA). Animals were then injected with 10 mg/kg methamphetamine and the ICP/BP determined following cavernous nerve stimulation determined one or two hours after exposure. The bars represent the mean ICP/BP for a particular cavernous nerve stimulation. Error bars represent the SEM.

*=significant decrease in ICP/BP compared to pre-treatment ($P < 0.05$).

Figure 3.

Tadalafil treatment improves erectile response in methamphetamine treated rats. The ICP/BP following cavernous nerve stimulation at 0, 0.75, 4 and 6 mA was measured in seven rats one hour after administration of tadalafil. In a second set of seven animals methamphetamine was co-administered (at the same time) with tadalafil (2.5mg/kg p.o.). Error bars represent the SEM. *=significant increase in ICP/BP compared to methamphetamine ($P < 0.05$).

Chronic methamphetamine effects

Figure 4.

Representative tracing of ICP of control animals (A) or after chronic methamphetamine treatment (B). Lower panel is a recording of systemic blood pressure. Animals were injected i.p. daily with methamphetamine for three weeks with an escalating dose regimen 2.5 mg/kg (1st week), 5 mg/kg (2nd week), and 10 mg/kg (3rd week). Note chronic exposure to methamphetamine results in spontaneous erections following cavernous nerve stimulation.

Figure 5.

The effect of chronic i.p. injection of methamphetamine on erectile function. Animals were injected i.p. daily with methamphetamine for three weeks with an escalating dose regimen 2.5 mg/kg (1st week), 5 mg/kg (2nd week), and 10 mg/kg (3rd week). Control animals were not treated with methamphetamine. N= 7 rats per group. The ICP/BP was determined following cavernous nerve stimulation. The bars represent the mean ICP/BP for a particular level of cavernous nerve stimulation. Error bars represent the SEM. *=significant difference ($P < 0.05$) in ICP/BP compared to control group.