Abstract N° 141:

Tamsulosin impairs bulbospongiosus muscle (BS) contractions induced by central injection of 8-hydroxy-2-(di-N-propylamino) tetralin (8-OH-DPAT) in anaesthetised rats while alfuzosin does not.

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ABSTRACT

Introduction & Objectives: Although alfuzosin and tamsulosin have similar efficacy for the treatment of symptomatic benign prostatic hyperplasia (BPH), the incidence of ejaculatory disorders is typically <1% with alfuzosin, whereas it is 4 to 18% with tamsulosin. The precise mechanism of action by which tamsulosin exerts its deleterious effect on ejaculation is still unclear. A central facilitator role of 8-OH-DPAT, a 5-HT1A agonist, on ejaculation is well documented in rats. The aim of this study was to compare the impacts of systemic delivery of tamsulosin and alfuzosin on the expulsion phase of ejaculation using the cerebrally injected 8-OH-DPAT-induced BS contractions experimental model.

Materials & Methods: Urethane-anaesthetised adult Wistar rats were stereotaxically implanted with a cannula aimed at the lateral cerebral ventricle. This cannula was used for i.c.v. injection of different doses of 8-OH-DPAT or combined injection of 8-OH-DPAT (20 µg) with WAY 100635 (20 µg), a 5HT1A antagonist, or raclopride (40 µg), a dopamine 2-like (D2-like) receptor subtype antagonist. Two silver electrodes were placed into the BS to record electromyograms. Tamsulosin (1 µg/kg) or alfuzosin (10 µg/kg) was injected (i.v.) 15 min before i.c.v. delivery of 8-OH-DPAT. The BS electrical activity was monitored for 30 min and quantified by determining, for each burst of BS contractions, the mean intensity and the area under the curve (AUC).

Results: Rhythmic BS activity was observed after i.c.v. injection of 8-OH-DPAT. The effect of 8-OH-DPAT on BS activity was dose-dependent (ED_{50}=19 µg). Co-injection (i.c.v.) of WAY 100635 did not inhibit 8-OH-DPAT effect (n=9) unlike co-injection of raclopride (n=8). Compared with i.v. saline (n=16) and alfuzosin (n=18), tamsulosin (n=24) resulted in lower AUC values (-31% and -28% respectively; ANOVA + Student-Newman-Keuls' *post-hoc* test, P<0.05) for BS contractions induced by 8-OH-DPAT (20 µg, i.c.v.). Conversely, alfuzosin did not impair BS contractions induced by 8-OH-DPAT when compared to saline.

Conclusions: The differential effect of systemic injection of tamsulosin and alfuzosin on BS activity induced by i.c.v. delivery of 8-OH-DPAT in rats might explain the ejaculation disorders reported in BPH patients receiving tamsulosin. This deleterious effect of tamsulosin on ejaculation could be mediated by cerebral D2-like receptors for which tamsulosin has a strong affinity.

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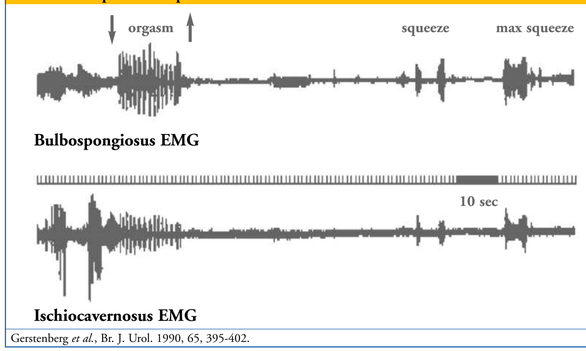
INTRODUCTION & OBJECTIVES

- Ejaculation consists of two distinct phases, emission and expulsion. Forceful expulsion of sperm contained in the prostatic urethra into the meatus is caused by rhythmic contractions of pelvic and perineal striated muscles. The bulbospongiosus muscles (BS) play a primary role in this process[1,2] (figure 1).
- Although alfuzosin and tamsulosin have similar efficacy for the treatment of symptomatic benign prostatic hyperplasia (BPH), the incidence of ejaculatory disorders is typically <1% with alfuzosin, whereas it is 6 to 30% with tamsulosin[3,4]. The precise mechanism of action by which tamsulosin exerts its deleterious effect on ejaculation is still unclear.
- Behavioural studies have shown that 8-OH-DPAT, the 5-HT1A agonist of reference, facilitates ejaculation in rats[5,6]. More recently, the effect of 8-OH-DPAT on ejaculation has been suggested to be mediated, at least in part, by D2-like receptors[7]. This is further supported by binding studies showing a moderate affinity of 8-OH-DPAT for D2-like receptors[8].
- Conversely to alfuzosin, tamsulosin displays a strong affinity for 5-HT1A and D2-like receptors. The 8-OH-DPAT-induced BS contraction was used as an experimental model mimicking the expulsion phase of ejaculation to test the effects of i.v. tamsulosin and alfuzosin.

Figure 1: Bulbospongiosus and ischiocavernosus EMG in human male upon expulsion of sperm



Gerstenberg *et al.*, Br. J. Urol. 1990, 65, 395-402.

MATERIALS & METHODS

Surgery

- Wistar rats (200-250 g) were anaesthetised with urethane (1.2 g/kg) and the carotid artery was catheterised to allow blood pressure monitoring. The jugular vein was also catheterised when i.v. treatment was needed.
- Intracerebroventricular injections were performed via a cannula stereotaxically implanted in the lateral cerebral ventricle (coordinates according to Paxinos & Watson rat brain atlas: 0.5 mm anterior to bregma, 1.3 mm lateral to midline, and 4.5 mm below the skull).
- Electrical activity of BS was recorded by placing two thin bare silver electrodes spaced 1-2 mm apart into the muscles. The electrical signal from the BS was amplified (gain, 10000; Low pass, 10 KHz; High pass, 10 Hz) before being digitised.

Experimental procedures

- All study drugs were injected via the i.c.v. route in a volume of 12 µl (saline) at a flow rate of 2 µl/min and BS activity was monitored for 30 min.
- The effect of 5 doses (0.3, 3, 10, 30, and 90 µg) of 8-OH-DPAT (i.c.v.) on BS activity were tested and used to determine ED50.
- WAY 100635 (20 µg), a 5-HT1A antagonist, or raclopride (40 µg), a D2-like antagonist was i.c.v. codelivered with 8-OH-DPAT (20 µg) to identify the receptors mediating 8-OH-DPAT effects.
- Tamsulosin (1 µg/kg) and alfuzosin (10 µg/kg) were i.v. injected 15 min before i.c.v. delivery of 8-OH-DPAT (20 µg).

Data analysis

- Area under the curve (AUC), reflecting the energy (i.e. both amplitude and duration) of muscular contraction, of the recorded electromyographic signal during a burst of BS contractions was determined and averaged in each rat.
- Statistics: Proportions of responding rats were compared with Fisher's exact test and AUC values with one-way ANOVA followed, whenever P<0.05, by Student-Newman-Keuls' *post-hoc* test.

RESULTS: EFFECTS OF I.C.V. 8-OH-DPAT ON BS ACTIVITY

- Consistent and rhythmic contractions of BS were observed after i.c.v. delivery of 8-OH-DPAT in anaesthetised rats (figure 2).
- Quantification of BS activity by calculating AUC of BS contractions showed that the effect of 8-OH-DPAT was dose-dependent with an ED50 of 19 µg (figure 3).

Figure 2: Example of bulbospongiosus muscles EMG recorded following i.c.v. delivery of 8-OH-DPAT

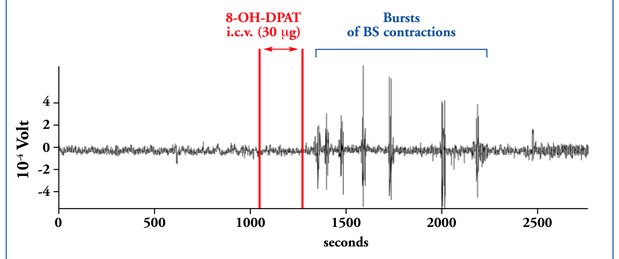
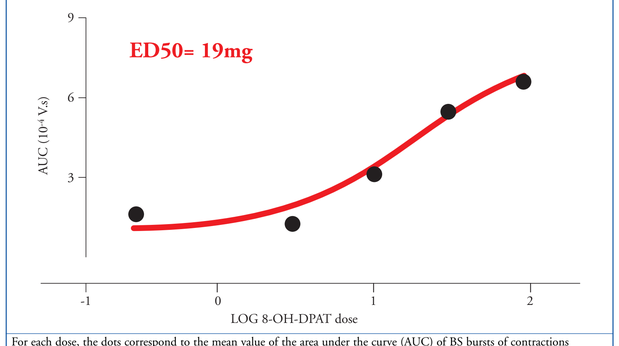


Figure 3: Dose-response curve of the effect of i.c.v. delivery of 8-OH-DPAT on bulbospongiosus activity



For each dose, the dots correspond to the mean value of the area under the curve (AUC) of BS bursts of contractions calculated in 5 or 6 rats

RESULTS: PHARMACOLOGICAL CHARACTERISATION OF BS CONTRACTIONS INDUCED BY I.C.V. 8-OH-DPAT

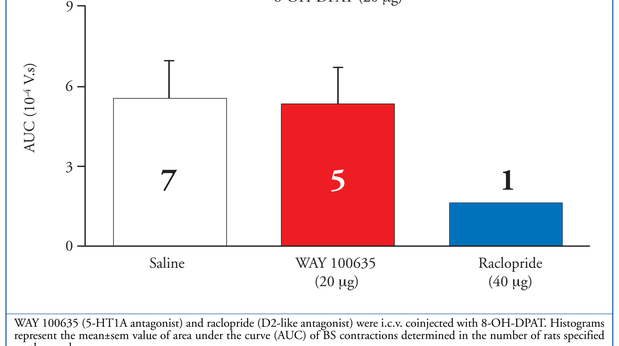
- Co-injection of WAY 100635 (20 µg), a 5-HT1A antagonist, and 8-OH-DPAT (20 µg) failed to reduce significantly the proportion of rats exhibiting at least one burst of BS contractions (responding rats) while co-injection of raclopride (40 µg), a D2-like antagonist and 8-OH-DPAT (20 µg) almost completely abolished the 8-OH-DPAT-induced BS contractions (table 1).
- The AUC value of BS contractions was unchanged when 8-OH-DPAT was i.c.v. codelivered with WAY 100635 while it was dramatically decreased when it was i.c.v. codelivered with raclopride (figure 4).

Table 1: Effects of co-injecting (i.c.v.) 8-OH-DPAT with WAY 100635 or raclopride on the proportion of rats exhibiting at least one burst of rhythmic BS contractions (responding rats).

I.C.V. treatment 8-OH-DPAT (20 µg) +	Responding rats	
Saline	7/9	78%
WAY 100635 (20 µg)	5/9	56%
Raclopride (40 µg)	1/9*	11%

Statistics: Fisher's exact test; * P<0.05 compared to saline.

Figure 4: Reversion of the bulbospongiosus muscle contractions induced by 8-OH-DPAT



WAY 100635 (5-HT1A antagonist) and raclopride (D2-like antagonist) were i.c.v. coinjected with 8-OH-DPAT. Histograms represent the mean±sem value of area under the curve (AUC) of BS contractions determined in the number of rats specified on the graph.

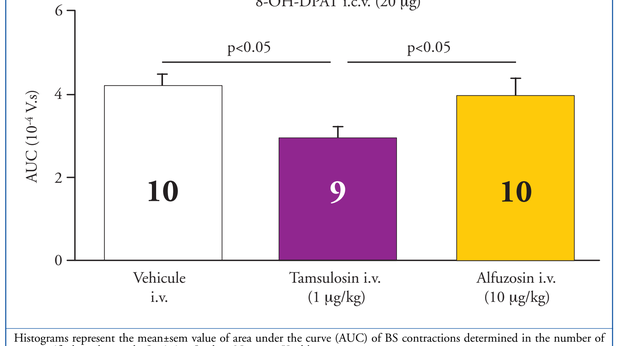
RESULTS: EFFECT OF I.V. INJECTION OF TAMSULOSIN AND ALFUZOSIN ON BS CONTRACTIONS INDUCED BY I.C.V. 8-OH-DPAT

- Tamsulosin (i.v., 1 µg/kg) had a greater impact than alfuzosin (i.v., 10 µg/kg) on the proportion of rats exhibiting at least one burst of BS contractions (responding rats), although no statistical significance was reached compared to vehicle (Fisher's exact test, P=0.20) (table 2).
- The AUC value of BS contractions induced by i.c.v. delivery of 8-OH-DPAT was significantly lower in rats treated with tamsulosin (i.v., 1 µg/kg) than in rats treated with vehicle or alfuzosin (i.v., 10 µg/kg) (ANOVA, P=0.02; Student-Newman-Keuls' test, P<0.05) (figure 5).

Table 2: Effect of i.v. tamsulosin and alfuzosin on the proportion of rats exhibiting at least one burst of rhythmic BS contractions (responding rats) after i.c.v. delivery of 8-OH-DPAT

I.C.V. 8-OH-DPAT (20 µg) +	Responding rats	
vehicle i.v.	10/16	63%
Tamsulosin (1 µg/kg)	9/24	38%
Alfuzosin (10 µg/kg)	10/18	56%

Figure 5: Effect of tamsulosin and alfuzosin on bulbospongiosus muscle contractions induced by 8-OH-DPAT



Histograms represent the mean±sem value of area under the curve (AUC) of BS contractions determined in the number of rats specified on the graph. Statistics: Student-Newman-Keuls' test

CONCLUSION

- In anaesthetised rats, 8-OH-DPAT induced contractions of BS in a dose-dependent manner by acting centrally, thereby mimicking the striated muscular activity occurring during expulsion of sperm. The effect of 8-OH-DPAT was likely mediated by cerebral D2-like receptors. The 8-OH-DPAT-induced BS contractions can be used as an experimental model of the expulsion phase of ejaculation.
- The activity of BS in response to i.c.v. delivery of 8-OH-DPAT was diminished in rats treated with tamsulosin but not in rats treated with alfuzosin. This inhibitory effect may be due to the interaction of tamsulosin with D2-like receptors. This result may explain the differential deleterious effects of tamsulosin and alfuzosin on ejaculation reported in clinical studies.

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