ABSTRACT # 27

ACUTE EFFECT OF DAPOXETINE ON EJACULATION INDUCED BY P-CHLOROAMPHETAMINE IN ANESTHETHIZED RATS

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ABSTRACT

Introduction and objective: Human premature ejaculation (PE) is under-recognized and under-treated whereas currently available data on the epidemiology of PE indicate this disorder as frequent and widespread. The efficacy of on-demand treatment of PE with serotonin selective re-uptake inhibitors (SSRIs) is still a matter of debate. In the present study we aimed at investigating the effect of acute i.v. delivery of dapoxetine, a short-acting SSRI, on emission and expulsion phases using an experimental model of pharmacologically-induced ejaculation in anesthetized rats: the p-chloroamphetamine (PCA)-induced ejaculation.

Methods: Male Wistar rats (n=40) were prepared for recording intra-seminal vesicle pressure (SVP) and bulbospongiosus muscles (BS) electromyogram as physiological markers of emission and expulsion phases respectively. Anesthetized rats were i.v. injected with vehicle or one of the three doses (1, 3 or 10 mg/kg) of dapoxetine tested and 30 min later PCA (5 mg/kg) was intraperitoneally delivered. Proportion of ejaculating rats as well as changes in SVP and BS activity were monitored over 30 min following PCA delivery. The area under the curve (AUC) of SVP rises and BS bursts of contractions induced by PCA was determined during the recording period to reflect the overall activity of these anatomical structures.

Results: Dapoxetine at the 3 doses tested dose-dependently and significantly reduced the proportion of rats displaying ejaculation after PCA from 78% in vehicle to 33%, 22%, and 13% in respectively 1, 3, and 10 mg/kg dapoxetine i.v. treated animals. At the 3 doses tested, dapoxetine significantly diminished AUC of SVP contractions induced by PCA (-78% in rats treated with either dapoxetine 1, 3, or 10 mg/kg). In the same way, AUC of BS bursts of contractions induced by PCA was dramatically reduced (-91% in rats treated with dapoxetine 1 and 10 mg/kg and -85% in rats treated with dapoxetine 3 mg/kg).

Conclusion: The present data demonstrate that acute treatment with dapoxetine is capable to inhibit PCA-induced ejaculation even at a dose of 1 mg/kg. It also appears that both emission and expulsion phases of ejaculation elicited by PCA are impacted by dapoxetine. These results provide pre-clinical evidence supporting the use of dapoxetine for the on-demand treatment of PE.

References

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- Rènyi L. (1985) Ejaculation induced by p-chloroamphetamine in the rat. Neuropharmacol. 24: 697-704.
- Yonezawa A., Watanabe C., Ando R., Furuta S., Sakurada S., Yoshimura H., Iwanaga T. and Kimura Y. (2000) Characterization of p-chloroamphetamine-induced penile erection and ejaculation in anesthetized rats. Life Sci. 67: 3031-3039.

INTRODUCTION & OBJECTIVE

- The efficacy of chronic treatment with serotonin selective re-uptake inhibitors (SSRIs) in delaying ejaculation is well documented although their ability to delay ejaculation after acute administration is still a matter of debate (McMahon and Touma, 1999; Waldinger et al., 2004).
- P-chloroamphetamine (PCA), an amphetamine derivative that liberates endogenous cathecolamines and serotonin, induces ejaculation in both conscious (Rènyi, 1985) and anesthetized rats by acting at spinal and/or peripheral levels (Yonezawa et al., 2000).
- The goal of the study is to investigate the effects of acute i.v. delivery of dapoxetine on PCA-induced ejaculation in anesthetized rats.

METHODS

Surgical preparation

All animal experiments were carried out in accordance with European Communities Council Directives on the use of laboratory animals.

Adult male Wistar rats weighing 250-300 g were anesthetized with isoflurane (1-2.5%), tracheotomized, and the carotid artery catheterized for blood pressure measurement.

Seminal vesicle pressure (SVP) was measured with a catheter, filled with mineral oil, inserted in the seminal vesicle through the apex.

A pair of stainless steel electrodes were placed within the bulbospongiosus muscles (BS) for recording BS electrical activity (BS EMG). Electrical signal from BS was amplified (gain, 10000; Low pass, 10 KHz; High pass, 300 Hz) before being digitized.

Experimental procedure

After a 5-min baseline recording period, saline or dapoxetine was delivered i.v. (volume 1ml/kg) and, 30 min later, PCA was injected intraperitonealy (5 mg/kg).

Seminal vesicle pressure (SVP) and bulbospongiosus muscles (BS) EMG monitoring was continued over a 30-min period after PCA delivery.

Each rat was injected with one of the three tested doses of dapoxetine (1, 3 or 10 mg/kg, i.v.).

Data analysis

The number of SVP increases induced by PCA was determined. The area under the curve (AUC) of each SVP rise (mean AUC) and all SVP rises (total AUC) was calculated.

The number of BS bursts of contractions induced by PCA was determined. The area under the curve (AUC) of each BS burst (mean AUC) and all BS burst (total AUC) was calculated.

Study sponsored by Johnson & Johnson Health Care Companies

RESULTS

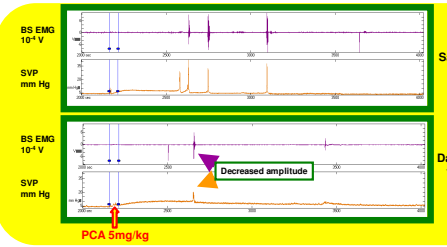

Figure 1: Typical recordings obtained after i.p. injection of PCA in rats treated i.v. with saline or dapoxetine.
Bulbospongiosus muscles (BS) EMG, and intra-seminal vesicle pressure (SVP) were monitored before and after i.p. delivery of PCA (5mg/kg) in anesthetized rats. BS burst of contractions and SVP increases were less intense in rat treated i.v. with dapoxetine.

Treatment i.v.	Rats ejaculating / Tested rats		Mean number of ejaculation	
Saline	8/10	*	1.9 ± 0.5	†
Dapoxetine 1 mg/kg	3/10	**	0.9 ± 0.4	
Dapoxetine 3 mg/kg	2/10		0.8 ± 0.3	
Dapoxetine 10 mg/kg	1/10		0.3 ± 0.2	

Table 1: Effect of acute i.v. delivery of dapoxetine on proportion of rats ejaculating and mean number of ejaculation induced by PCA i.p. delivery (5mg/kg).
A dose-dependent decrease in the proportion of rats ejaculating and the mean number of ejaculation was observed.

Statistics. Asterisks (one symbol, p<0.05; two symbols, p<0.01): Fisher's exact test. Dagger (p<0.05): ANOVA + Bonferroni's post-hoc test.

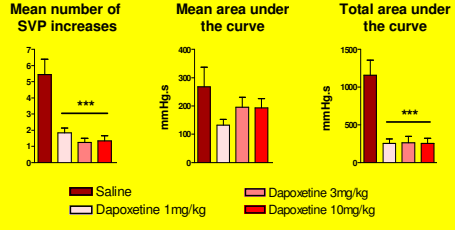

Figure 2: Effect of acute i.v. injection of dapoxetine on seminal vesicle pressure (SVP) measured after PCA i.p. delivery (5mg/kg).
The mean number of SVP increases and the total area under the curve of SVP increase were significantly diminished in rats treated with one of the three doses of dapoxetine tested.

Statistics. Asterisks (p<0.001): ANOVA + Bonferroni's post-hoc test.

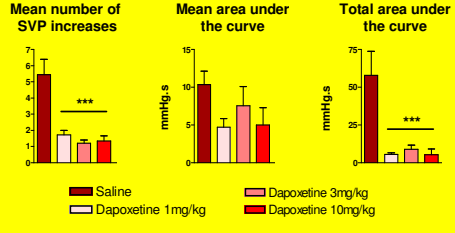

Figure 3: Effect of acute i.v. injection of dapoxetine on bulbospongiosus muscles (BS) burst of contractions measured after PCA i.p. delivery (5mg/kg).
The mean number of BS bursts and the total area under the curve of BS bursts were significantly diminished in rats treated with one of the three doses of dapoxetine tested.

Statistics. Asterisks (p<0.001): ANOVA + Bonferroni's post-hoc test.

CONCLUSION

- Acute i.v. delivery of dapoxetine is capable to inhibit PCA-induced ejaculation in anesthetized rats at a dose of 1 mg/kg.
- Acute i.v. dapoxetine impacts on both emission and expulsion phases of ejaculation by reducing the occurrence of PCA-induced seminal vesicle and BS contractions respectively.