ABSTRACT
806

BRAIN OXYTOCIN RECEPTOR BLOCKADE INHIBITS PHARMACOLOGICALLY-INDUCED SEXUAL RESPONSES IN ANAESTHETISED MALE RATS

Pierre Clément[1], Magali Peeters[1], Jacques Bernabé[1], Miguel Laurin[1], Pierre Denys[2], François Giuliano[1,2*]

[1] PELVIPHARM Laboratories, Orsay, France [2] Raymond Poincaré Hospital, Neuro-Uro-Andrology Unit, Garches, France * e-mail address: giuliano@cyber-sante.org

ABSTRACT

Objectives: The present study was undertaken to clarify the role of brain, spinal, and peripheral oxytocin (OT) receptors in the control of ejaculation and erection. For this purpose we explored, in anaesthetised rats, the effects of an OT antagonist (OT antag) delivered through different routes on sexual responses elicited by intracerebroventricular (i.c.v.) 7-hydroxy-2-(di-N-propylamino)tetralin (7-OH-DPAT), a dopamine D_3 preferential agonist.

Material and methods: A cannula for i.c.v. injection was stereotactically implanted to sexually naive adult male Wistar rats anaesthetised with urethane. Seminal vesicle pressure and bulbospongiosus muscle (BS) electromyogram were recorded as physiological markers of, respectively, emission and expulsion phases of ejaculation. Intracavernosal pressure was measured as physiological marker of erection. The peptidergic selective OT antag ($d(CH2)_5^1$,$Tyr(Me)^2$,Orn^8)-Oxytocin) was delivered i.v. (0.5 and 1 µg/kg, n=10 each), i.c.v. (0.001, 0.01, and 0.1 µg, n=10 each), or intrathecally (0.1 µg i.t. at the 13th thoracic (T13) or 6th lumbar (L6) segment; n=10 each) prior to i.c.v. 7-OH-DPAT. Sexual responses were recorded over 30 min following 7-OH-DPAT administration.

Results: Whatever the dose tested i.v., the OT antag did not impair 7-OH-DPAT-induced sexual responses occurring in form of coordinated increases in seminal vesicle and intracavernosal pressures and rhythmic BS contractions sometime accompanied by expulsion of seminal material (i.e. ejaculation). When delivered i.c.v., the OT antag dose-dependently inhibited 7-OH-DPAT-induced sexual responses; the maximal i.c.v. dose tested (0.1 µg) resulting in abolition of ejaculation. When delivered i.t. (0.1 µg) at L6 but not at T13, the OT antag significantly reduced the duration of BS contractions and the occurrence of ejaculation without impairing erectile response.

Conclusions: From these results it is concluded that, in the 7-OH-DPAT model, (i) brain OT receptors mediate ejaculation and erection, and (ii) L6 spinal OT receptors have a modulating role on ejaculation but not on erection whereas (iii) peripheral OT receptors are not involved in either ejaculation or erection. In addition the present data support the existence of functional relationships between dopaminergic and oxytocinergic pathways in the central control of sexual responses.

References

➢Clément P, Bernabé J, Denys P, Alexandre L, Giuliano F. (2007) Ejaculation induced by i.c.v. injection of the preferential dopamine D(3) receptor agonist 7-hydroxy-2-(di-N-propylamino)tetralin in anesthetized rats. Neuroscience 145: 605-610.

PELVIPHARM
Parc d'Orsay, Orsay, France
Web site: www.pelvipharm.com

OBJECTIVE

➢ We aimed at clarifying the role of brain, spinal, and peripheral oxytocin receptors (OTR) in the control of ejaculatory and erectile responses using an already described pharmacological model in anaesthetised rats (Clément et al., 2007).

➢ For this purpose, ejaculatory and erectile responses were elicited by delivering the dopamine D3 receptor preferring agonist [R(+)7-hydroxy-2-(di-N-propylamino)tetralin; 7-OH-DPAT] into the cerebral ventricle (i.c.v.). The effects of a peptide OT antagonist administered via different routes [i.c.v., intrathecal (i.t.), i.v.] were tested on 7-OH-DPAT-induced sexual responses.

METHODS

Surgical preparation

Adult male Wistar rats weighing 250-300 g were anaesthetised with urethane (1.2 g/kg), tracheotomized, and the carotid artery catheterized for blood pressure measurement. All animal experiments were carried out in accordance with the European Community Council Directive (86/609/EEC) on the use of laboratory animals.

Intracerebroventricular cannula implantation

A guide cannula (22G) was stereotaxically placed above the cerebral ventricle (coordinates according to Paxinos and Watson rat brain atlas: 0.5 mm posterior to bregma, 1 mm lateral to midline, and 4 mm below the skull). The internal cannula (with 0.5 mm projection below the guide cannula) was connected to a Hamilton syringe placed in a micropump allowing delivery of microvolumes. At the end of the experimental session, methylene blue dye was injected through the cannula, and the brain, removed and grossly dissected, was inspected for the presence of blue dye in the ventricles.

Drugs

7-OH-DPAT and the peptide OT antagonist ($d(CH_2)_5^1$,$Tyr(Me)^2$,Orn^8)-Oxytocin) were dissolved in NaCl 0.9%. All i.c.v. treatments were delivered in a volume of 5 µl at a flow rate of 1 µl/min. I.t. and i.v. deliveries were performed in volumes of 10 µl and 1 ml/kg b.w. OT antagonist was administered (whatever the route) 15 min before i.c.v. 7-OH-DPAT (10 µg) and recording was continued over 30 min after 7-OH-DPAT delivery. Each route was tested in separate groups of 10 rats.

Intrathecal catheter implantation

For i.t. catheter insertion, the rat's head was placed in a stereotaxic frame, and was rotated nose downwards. The catheter was a polyethylene tubing (PE10) stretched to 150 % of its original length in hot water, and cut to the required length so that its distal opening reached the targeted levels of the spinal cord; i.e. 13th thoracic (T13) or 6th lumbar (L6) segment of the spinal cord. The atlanto-occipital membrane was opened and the catheter was carefully advanced in the caudal direction. The rostral free end of the catheter was secured with ligatures that closed the neck muscles and skin layers. The exact location of the caudal tip of the catheter was checked at the end of each experiment after sacrifice of the animal and exposure of the spinal cord.

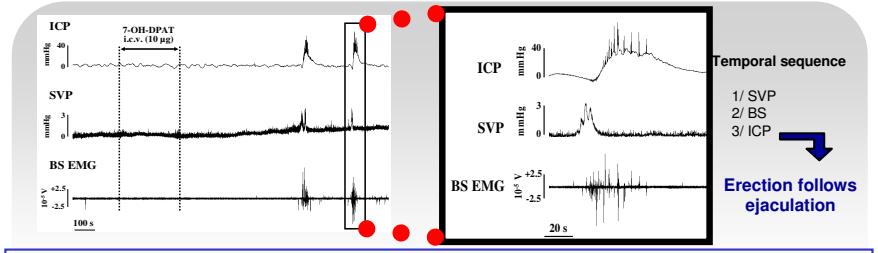
Recordings

Seminal vesicle pressure (SVP) was measured with a catheter, filled with mineral oil, inserted in the right seminal vesicle through the apex. Intracavernous pressure (ICP) was measured with a catheter inserted into one corpus cavernosum. Electrical activity of the bulbospongiosus muscle (BS) was recorded by passing a Teflon insulated stainless–steel wire laterally throughout the muscle with two 1-2 mm pieces (separated by 1-2 mm) of insulation stripped off. Electrical signal from the BS was amplified (gain, 10000; Low pass, 1 KHz; High pass, 10 Hz).

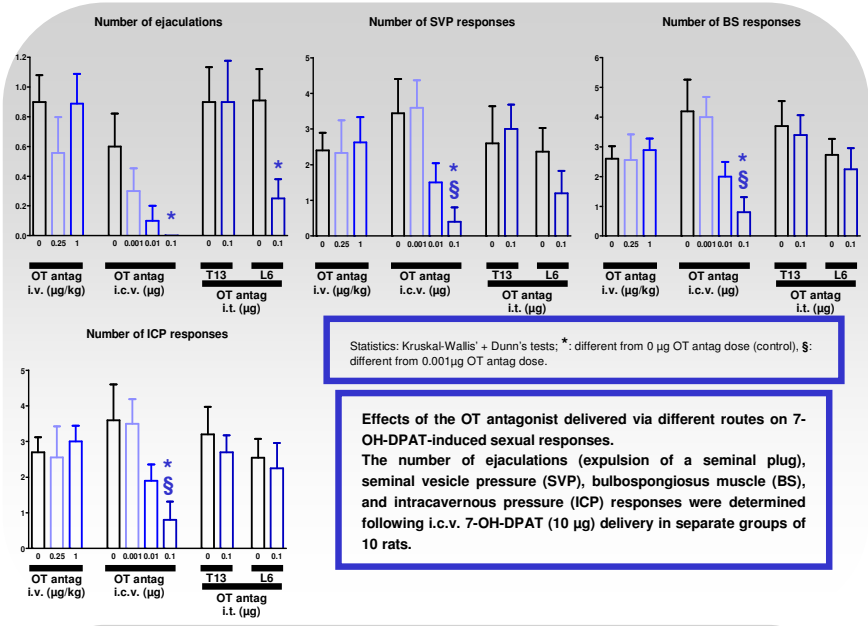
CONCLUSIONS

➢In the 7-OH-DPAT model, erections (reflected by ICP responses) are likely reflexive.
➢Delivered i.v. the OT antagonist has no effect on 7-OH-DPAT-induced sexual responses.
➢Delivered i.c.v. the OT antagonist dose-dependently inhibits 7-OH-DPAT-induced sexual responses.
➢Delivered i.t. at L6 but not T13 level the OT antagonist has a modulatory role on 7-OH-DPAT-induced ejaculation.
➢The results indicate the key role that brain OT receptors may play in ejaculation.

RESULTS

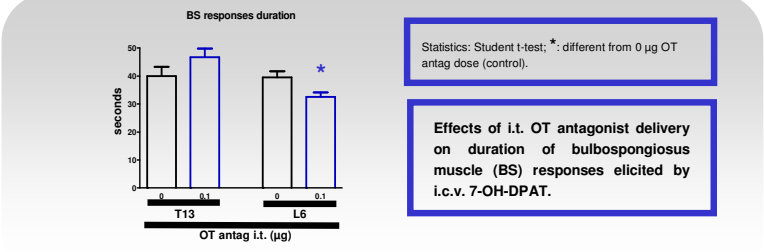


Sample of recording of intracavernous pressure (ICP), seminal vesicle pressure (SVP), and bulbospongiosus muscle EMG (BS EMG) obtained in anaesthetised rats after i.c.v. delivery of 7-OH-DPAT.



Statistics: Kruskal-Wallis' + Dunn's tests; *: different from 0 µg OT antag dose (control), §: different from 0.001µg OT antag dose.

Effects of the OT antagonist delivered via different routes on 7-OH-DPAT-induced sexual responses.
The number of ejaculations (expulsion of a seminal plug), seminal vesicle pressure (SVP), bulbospongiosus muscle (BS), and intracavernous pressure (ICP) responses were determined following i.c.v. 7-OH-DPAT (10 µg) delivery in separate groups of 10 rats.



Statistics: Student t-test; *: different from 0 µg OT antag dose (control).

Effects of i.t. OT antagonist delivery on duration of bulbospongiosus muscle (BS) responses elicited by i.c.v. 7-OH-DPAT.