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SELECTIVE ANTAGONISM OF DOPAMINE D3 RECEPTOR SPECIFICALLY INHIBITS THE EXPULSION PHASE OF EJACULATION IN ANAESTHETISED MALE RATS

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ABSTRACT

Objectives: The role of dopamine D3 receptors in the control of ejaculation is not fully elucidated. The present study was undertaken to clarify this role by using a pharmacological model of ejaculation in anaesthetised rats. For this purpose we explored the effects of a highly D3 selective antagonist on sexual responses elicited by i.v. 7-hydroxy-2-(di-N-propylamino)tetralin (7-OH-DPAT), a dopamine D3 preferential agonist.

Material and methods: Sexually naive adult male Wistar rats were anaesthetised with isoflurane. Seminal vesicle pressure (SVP) and bulbospongiosus muscle (BS) electromyogram were recorded as physiological markers of, respectively, emission and expulsion phases of ejaculation. Pressure in the corpus cavernosum (ICP) was also measured as physiological marker of erection. The D3 selective antagonist (N-[4-[2,3-Dichlorophenyl)-1-piperazinyl]butyl]-9H-fluorene-2-carboxamide; NGB2904) was delivered i.v. (0.03, 0.3 and 3 mg/kg; n=6 each) 10 min prior to i.v. 7-OH-DPAT (1 mg/kg). Sexual responses were recorded over 20 min following 7-OH-DPAT administration.

Results: The recordings in rats treated with NGB2904 showed that BS contractions induced by 7-OH-DPAT were temporarily inhibited whereas SVP and ICP responses were not altered. In NGB2904 3 mg/kg treated rats, incidence of 7-OH-DPAT-induced ejaculation was reduced and there was a 4-fold increase in the first ejaculation latency to occur following 7-OH-DPAT injection as compared to vehicle animals. This was associated with a significant delay in the first BS response to occur after 7-OH-DPAT delivery and a significant diminution of BS contractile activity. The other sexual responses evoked by 7-OH-DPAT and monitored in this study i.e. increases in SVP and ICP were not altered by NGB2904.

Conclusions: The present results demonstrate that D3 receptors specifically control the expulsion phase of ejaculation and that blockade of D3 receptors results in increased ejaculation latency in a pharmacological model of ejaculation in anaesthetised rats. These observations open new avenues for the development of pharmacological agents for the treatment of ejaculatory disorders, especially premature ejaculation.

OBJECTIVE

➢ We aimed at clarifying the role of dopamine D3 receptors in the ejaculatory process using a pharmacological model in anaesthetised rats.

➢ For this purpose, ejaculatory as well as erectile responses were elicited by delivering i.v. the dopamine D3 receptor preferring agonist [R(+)7-hydroxy-2-(di-N-propylamino)tetralin; 7-OH-DPAT]. The effects of a highly selective D3 antagonist [1-piperazinyl]butyl]-9H-fluorene-2-carboxamide; NGB2904)] i.v. administered was tested in this model.

METHODS

Surgical preparation

Adult male Wistar rats weighing 250-300 g were anaesthetised with isoflurane (1-1.2%) and the carotid artery catheterised 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.

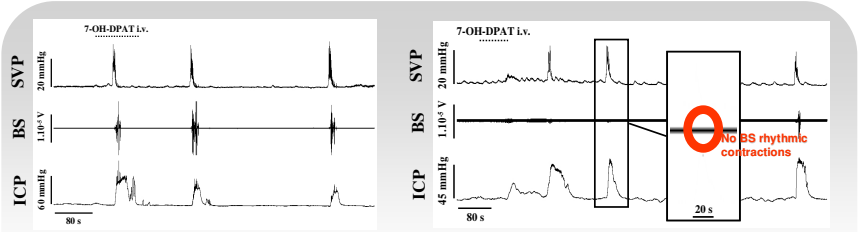
Recordings

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).

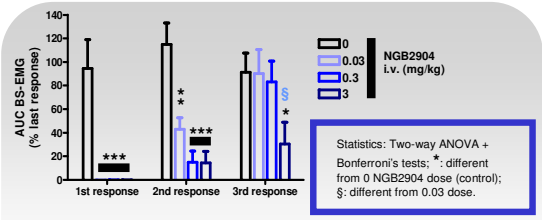
Drugs

7-OH-DPAT was dissolved in NaCl 0.9%. The D3 selective antagonist NGB2904 was dissolved in 2-hydroxypropyl-β-cyclodextrin 25%. NGB2904 was injected i.v. 10 min before i.v. 7-OH-DPAT (1 mg/kg) and recording was continued over 20 min after 7-OH-DPAT delivery. Three doses of NGB2904 (0.03, 0.3, and 3 mg/kg) were tested in separate groups of 6 rats.

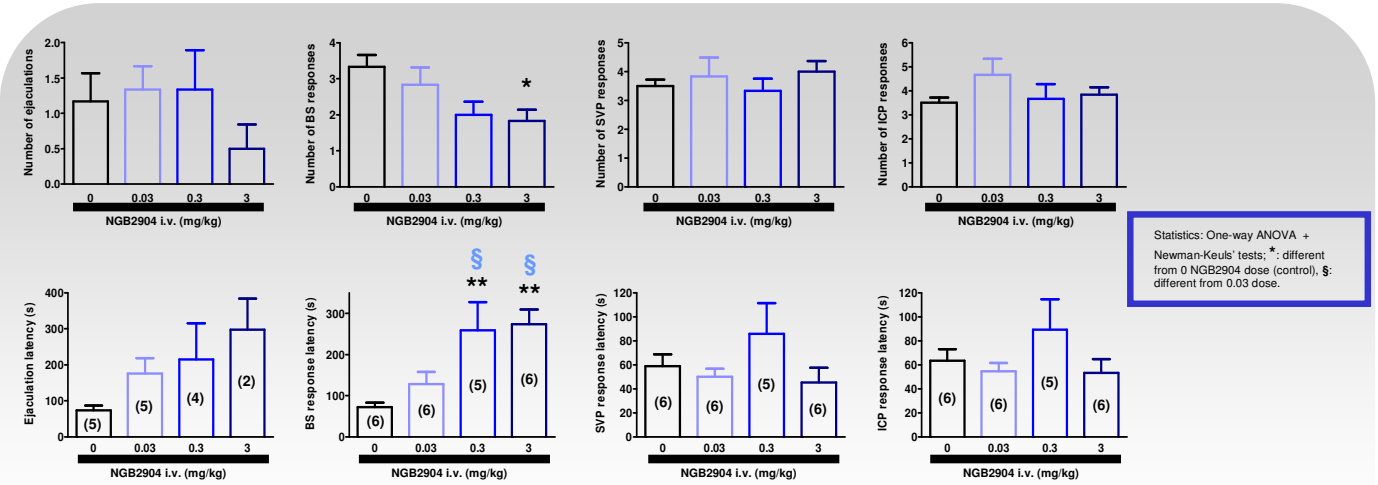
RESULTS



Sample of recording of seminal vesicle pressure (SVP), bulbospongiosus muscle EMG (BS), and intracavernous pressure (ICP) obtained in anaesthetised rats after i.v. delivery of 7-OH-DPAT (1 mg/kg). Left panel, rat was i.v. pre-treated with NGB2904 vehicle; right panel, rat was i.v. pre-treated with 3mg/kg NGB2904.



Effects of i.v. NGB2904 on area under the curve (AUC) of bulbospongiosus muscle (BS) responses elicited by i.v. 7-OH-DPAT. AUC values are expressed as % of the last response.



Effects of the D3 selective antagonist NGB2904 on 7-OH-DPAT-induced sexual responses.
Upper panel: The number of ejaculations (expulsion of a seminal plug), bulbospongiosus muscle (BS), seminal vesicle pressure (SVP), and intracavernous pressure (ICP) responses were determined following i.v. 7-OH-DPAT (1 mg/kg) delivery in separate groups of 6 rats. Lower panel: The latency of the first sexual response was determined in (n) rats displaying such response.

CONCLUSIONS

➢ In the 7-OH-DPAT model, selective antagonism of D3 receptor impairs ejaculation by specifically altering the expulsion phase of ejaculation.

➢ These results open new avenues for the development of pharmacological management of premature ejaculation.

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