Selective antagonism of dopamine D3 receptor specifically inhibits the expulsion phase of ejaculation in anaesthetised male rats

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ABSTRACT

Objective: The role of dopaminergic 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 D3 selective antagonist on seminal vesicle pressure (SVP) and bulbospongiosus muscle (BS) responses elicited by intravenous (i.v.) 7-hydroxy-2-(di-N-propylamino)tetrinalin (7-OH-DPAT).

Methods: Male sexually mature adult Wistar rats were anaesthetised with isoflurane. Seminal vesicle pressure (SVP) and bulbospongiosus muscle (BS) responses were used as physiological markers of the ejaculatory process and of the expulsion phase of ejaculation. Pressure in the corpus cavernosum (ICP) was also measured as a physiological marker of erection. The D3 selective antagonist [1-piperazinyl[buty1]-9H-fluorene-2-carboxamide; NGB2904] was administered i.v. in anaesthetised rats.

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 0.003 mg/kg treated rats, incidence of ejaculation (expulsion of seminal plug) was significantly reduced and there was a 40% 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 decrease in BS contractions. The incidence of BS contraction was not altered by NGB2904. The present results demonstrate that D3 receptors specifically control the expulsion phase of ejaculation and that blockade of D3 receptors results in elevated ejaculation latency in a pharmacological model of ejaculation in anaesthetised rats. The results obtained may have significant therapeutic potential for the development of pharmacological agents for the treatment of ejaculatory disorders, particularly premature ejaculation.

Conclusions: The present results demonstrate that D3 receptors specifically control the expulsion phase of ejaculation and that blockade of D3 receptors results in elevated ejaculation latency in a pharmacological model of ejaculation in anaesthetised rats. The results obtained may have significant therapeutic potential for the development of pharmacological agents for the treatment of ejaculatory disorders, particularly premature ejaculation.

OBJECTIVE

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

RESULTS

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)tetrinalin; 7-OH-DPAT]. The effects of a highly selective D3 antagonist [1-piperazinyl[buty1]-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. Electrophysiological 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 2%. NGB2904 was injected i.v. 10 min before i.v. 7-OH-DPAT (1 mg/kg) and recording was continued for 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.

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.