INTRODUCTION

The modulatory actions of glutamate, the main excitatory neurotransmitter in the central nervous system, are exerted via activation of metabotropic glutamate receptors (mGluRs) (1). Eight distinct mGluRs (mGluR1-8) have been classified into three groups (I-III) based on their sequence homology (2). Group II mGluRs (mGluR1, mGluR4, mGluR6, mGluR7 and mGluR8) are widely distributed throughout the central nervous system (3). It is unknown whether mGluRII plays a role in the regulation of neural mechanisms controlling the micturition reflex.

OBJECTIVES

To investigate supraspinal and spinal effects of L(+)-2-amino-4-phosphonobutyric acid (L-AP4), a selective mGluRII agonist, on the micturition reflex in urethane-anesthetized rats.

METHODS

Adult female Sprague-Dawley rats (weighing 238-261 g) were used. Rats were maintained under standard laboratory conditions with a 12-h light/12-h dark cycle and free access to food pellets and tap water.

Drugs

L-AP4, a selective mgLuRIII agonist, was dissolved in saline.

Intrathecal administration of L-AP4

Rats were anesthetized with isoflurane followed by urethane (1.2 g/kg subcutaneously).

A midline abdominal incision was made, and a transverse catheter (PE-60) with a fire-flared tip was inserted into the dome of the bladder and secured with silk thread for bladder filling and pressure recording. A 3-way stopcock was connected to the transversal catheter to monitor the bladder pressure.

Saline was continuously infused into the bladder for 2 hours at a rate of 0.04 ml per minute to record cystometrograms during a control period.

L-AP4 (1, 3 and 10 µg, n=8 per dose) was administered intrathecally to evaluate changes in bladder activity.

PE-10 Intrathecal catheter was directed caudally into the spinal subarachnoid space and positioned at the level of the L6-S1 spinal cord. The volume of fluid in the catheter was kept constant at 6 µl. Single doses of drugs were then administered in a volume of 2 µl, followed by a 6 µl flush with saline.

Cystometric parameters were recorded and compared before and after drug administration.

Intracerebroventricular administration of L-AP4

L-AP4 (1, 3 and 10 µg, n=8 per dose) was administered intracerebroventricularly.

Using a stereotaxic micro-injector, a 30 gauge needle attached to a 10 µl Hamilton syringe was inserted into the lateral ventricle, and single doses of drugs were administered in a volume of 2 µl during 2 minutes.

Cystometric parameters were recorded and compared before and after drug administration.

Statistics

Wilcoxon signed rank test was used to compare cystometric variables before and after treatment.

RESULTS

Intracerebroventricular administration of L-AP4 at doses of 1, 3 and 10 µg (n=8 per dose) increased intracerebroventricular intervals (ICI) in dose-dependent fashion, but did not affect maximum pressure (MP), basal pressure (BP), post void residual (PVR) at any doses tested.

Intrathecal administration of L-AP4 at doses of 1, 3 and 10 µg (n=8 per dose) also increased ICI in dose-dependent fashion, but did not affect MP, BP, PVR at any doses tested.

Intracerebroventricular or intrathecal administration of L-AP4 also increased threshold pressure (TP) in dose dependent fashion.

DISCUSSION

In urethane-anesthetized rats, intracerebroventricular or intrathecal administration of L-AP4 has an inhibitory effect on the micturition reflex, as shown by the observed increases in ICI and TP.

We postulate that the site of action may be the supraspinal and spinal sites.

CONCLUSIONS

The results of our study indicate that in urethane-anesthetized rats activation of mGluRII can inhibit the micturition reflex at supraspinal and spinal sites.

Thus mGluRII could be a potential target for the treatment of bladder dysfunction.

REFERENCES


Disclosures Statement

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