

## THESES

### ROLE OF THE N-METHYL-D-ASPARTATE RECEPTOR IN THE ENHANCEMENT OF INHIBITORY AVOIDANCE RETENTION INDUCED BY ADDITIONAL TRAINING (ABSTRACT)\*. DISSERTATION. PORTO ALEGRE, 1996.

RAFAEL ROESLER \*\*

The N-methyl-D-aspartate (NMDA) type of glutamate receptor channel has been shown to be involved in learning and memory, probably through NMDA receptor-dependent long-term potentiation (LTP). NMDA receptor antagonists such as dizocilpine (MK-801) and aminophosphonovaleric acid (AP5) affect memory of several tasks and block LTP in several brain areas. Both memory and NMDA receptor-dependent LTP are also blocked by the gamma-aminobutyric acid type A (GABA<sub>A</sub>) receptor agonist muscimol.

Memory of the inhibitory avoidance task may be enhanced by additional training, and the neurochemical mechanisms underlying memory enhancement remain unclear. In the present study, we evaluated the role of a NMDA receptor-dependent mechanism in the enhancement of retention induced by additional training in an inhibitory avoidance task in rats. Additional experiments were carried out to verify the role of hippocampal NMDA receptors in memory of a two-way active avoidance task and to evaluate the effects of NMDA receptor antagonists on glucose utilisation by the hippocampus.

To investigate the effects of the noncompetitive NMDA antagonist MK-801 on the enhancement of inhibitory avoidance retention, adult female Wistar rats were submitted to an only (0.4 mA footshock) or two (0.2 mA footshock) training sessions followed by a test session in a step-down inhibitory avoidance task (24 h interval between sessions). MK-801 (0.0625 mg/kg, i.p.) impaired retention when given 30 minutes before, but not immediately after, the only training session. It also blocked the enhancement of retention caused by additional training when given 30 minutes before, but not immediately after, the second session. A control experiment showed that the effect was not due to analgesia. It may be concluded that NMDA receptors are critical for the acquisition of an inhibitory avoidance task.

In another set of experiments, we evaluated the effects of NMDA receptor blockade and GABA<sub>A</sub> activation in the hippocampus on the enhancement of retention of inhibitory avoidance task. Adult male Wistar rats surgically implanted with cannulae aimed into the CA1 area of the dorsal hippocampus were submitted to two training sessions followed by a test session of inhibitory avoidance task (0.2 mA footshock, 24 h interval between sessions). Immediately after the second training session, animals received a bilateral intrahippocampal 0.5 µl microinjection of vehicle, AP5 (5.0 µg), or muscimol (0.03 µg). All three experimental groups showed an improvement of retention test performance. There were no significant differences between groups. The results suggest that the enhancement of inhibitory avoidance retention induced by additional training does not depend on NMDA receptors and is not sensitive to GABA<sub>A</sub> receptor activation in the hippocampus.

We also investigated the role of hippocampal NMDA receptors in the acquisition of a two-way active avoidance task. Adult male Wistar rats were trained and tested in a two-way active avoidance task (30 trials, 0.5 mA footshock, 24 h training interval). Immediately before or after the training session, AP5 (5.0 µg) or its vehicle (0.5 µl) were infused bilaterally into the dorsal hippocampus. Pretraining, but not posttraining, treatment with AP5 impaired performance of animals in the test session. The results suggest that hippocampal NMDA receptors participate in acquisition of two-way active avoidance conditioning, possibly through NMDA receptor-dependent LTP.

Neurochemical experiments were designed to evaluate the effects of MK-801 and AP5 on hippocampal metabolism. These experiments showed that glucose utilisation by hippocampal slices from female Wistar rats was not affected in vitro by AP5 (500 µM), MK-801 (50 µM), or by intraperitoneal administration of MK-801 (0.05 or 0.5 mg/kg).

Collectively, the experiments reported in the present study suggest that: (1) a NMDA receptor-dependent mechanism in brain areas other than the hippocampus is involved in the enhancement of inhibitory avoidance retention; (2) hippocampal NMDA receptors are critical for acquisition of a two-way active avoidance task; and (3) NMDA receptor antagonism by AP5 or MK-801 does not affect glucose utilisation in hippocampal slices.

**KEY WORDS:** NMDA receptor, hippocampus, long-term potentiation, memory.

\* Papel dos receptores N-metil-D-aspartato no reforço da memória induzido por treino adicional em esquiava inibitória (Resumo). Dissertação de Mestrado, Universidade Federal do Rio Grande do Sul, Departamento de Bioquímica (Área: Bioquímica). Orientadora: Maria Beatriz Cardoso Ferreira.

\*\* Address: Departamento de Bioquímica, Instituto de Ciências Básicas da Saúde, Universidade Federal do Rio Grande do Sul (Campus da Saúde), 90035-003 Porto Alegre RS, Brasil. FAX 051 316 5535. E-mail: quevedo@vortex.ufrgs.br