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Oxiracetam increases the release of endogenous glutamate from depolarized rat hippocampal slices

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Nootropics are drugs employed to improve cognitive functions, particularly learning and memory ability, and to prevent their impairment following cerebral damage (Moos et al., 1988). Oxiracetam (4-hydroxy-2-oxopyrrolidinoacetamide) has been reported to enhance learning and memory in normal animals as well as in animals bearing different types of cerebral impairment. Clinical effects of oxiracetam on cognitive processes are also well documented (for references see Pugliese et al., 1990). However, as for other nootropics, little is known about the mechanism of action of this drug at the neurochemical level.

Several findings, both in experimental animals and in humans, emphasize the importance of the hippocampus for memory. As to the neurotransmitters involved, a major role has been attributed to acetylcholine and, more recently, to glutamic acid. Interestingly, long-term potentiation (LTP), a form of synaptic plasticity which occurs prominently in the hippocampus and may represent a physiological substrate of learning and memory processes, involves activation of glutamatergic neurotransmission (see Collingridge and Bliss, 1987 and references therein).

Since LTP has been reported to be associated with an increase in glutamate release (see, for instance, Errington et al., 1987), we have investigated a possible interaction of oxiracetam with glutamatergic transmission in the hippocampus by examining the effects of the drug on the release of the excitatory amino acid from rat hippocampal slices. We studied the release of both [^{3}H]D-aspartate ([^{3}H]D-ASP), a well known marker for excitatory amino acid containing pathways, and endogenous glutamic acid.

Hippocampal slices (0.4 mm thick) were prepared from male Sprague-Dawley rats. The slices were prelabeled with [^{3}H]D-ASP (10 min; 0.1 μM final concentration) and subsequently transferred to a multi-chamber superfusion apparatus (two slices per chamber). Superfusion was started (0.6 ml/min) with standard medium of the following composition (mM): NaCl 125; KCl 3; $MgSO_4$ 1.2; $CaCl_2$ 1.2; NaH_2PO_4 1.0; $NaHCO_3$ 22; glucose 10 (aeration with 95% O_2 and 5% CO_2 at 37°C); pH 7.2-7.4. Two 3-min periods of depolarization (35 mM KCl substituting for an equimolar concentration of NaCl) were applied after 38 (S_1) and 66 (S_2) min of superfusion, respectively. Fractions were collected from min 35 or from min 63 according to the following scheme: two 3-min samples (basal release) before and after one 6-min sample (K^+-evoked release). The amount of radioactivity released into each fraction was expressed as a percentage of the total tritium present in each slice at the start of the respective collection period. The K^+-evoked overflow was estimated by subtracting the basal outflow from the evoked release. The first stimulation period (S_1) was always the control; oxiracetam was added to the superfusion medium 8 min before the second stimulation period (S_2). In order to quantify the effect of the

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