New Endogenous Dipeptide Cycloprolyl-Glycine Is Similar to Piracetam by Its Mnemotropic Selectivity

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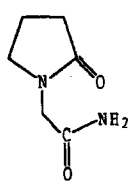
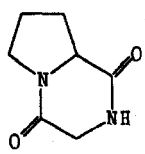
The effects of endogenous dipeptide cycloprolyl-glycine on learning and memory in the model of postconvulsive retrograde amnesia of passive avoidance response in rats depended on the administration schedule. The dipeptide prevented retrograde amnesia, when injected prior to learning, had no effect after postlearning administration, and aggravated amnesia, when injected immediately before retrieval. These data suggest that cycloprolyl-glycine is similar to the standard nootropic piracetam by its mnemotropic activity.

Key Words: *cycloprolyl-glycine; piracetam; antiamnesic activity*

Cycloprolyl-glycine (CPG) is an endogenous compound which improves acquisition of passive avoidance reaction (PAR) in doses of 0.1-1 mg/kg [11,12]. Structurally, this compound is a topological analog of the standard nootropic piracetam [4]: the similarity between their electron surfaces is about 90% (P. Mezly, personal communication). This suggests that piracetam is a peptidergic mimetic of natural CPG.



Piracetam



Cycloprolyl-Glycine

To assess the functional similarity between piracetam and CPG we compared their effects on retention of PAR using different administration schedules.

MATERIALS AND METHODS

CPG was synthesized as described elsewhere [2] with the following constants: melting point 199-201°C, $[\alpha]_D^{20}$=209°C (water). Piracetam was purchased from UCB.

Experiments were carried out on outbred male albino rats weighing 180-240 g (Krukovo Breeding Center of the Russian Academy of Medical Sciences).

The drugs were tested on the model of retrograde amnesia induced by electroconvulsive shock (ECS) and were administered according to 3 schedules: 1) CPG 15 min and piracetam 45 min prior to conditioning; 2) both immediately after learning; and 3) CPG 15 min and piracetam 45 before retrieval session.

The drugs were dissolved in 0.9% NaCl and injected intraperitoneally. Control animals received saline and either true or sham ECS. One-trial passive avoidance conditioning [9,15] was performed in a Laffaet Instrument apparatus, which consisted of a 25×7 cm illuminated start platform connected through a sliding door with a 40×40×40 cm dark compartment with an electrified floor. The rat was placed onto the start platform facing away from the entrance to the dark compartment, 3 min after entering this compartment it received 8 unescapable foot shocks (0.45 mA, 1 sec each) through the floor. Immediately after that the rat was taken out of the apparatus and subjected to transcorneal ECS (70 V, 300 msec). Memory retention was tested after 24 h by placing the animal on the illuminated platform and measuring the latency (L) of first

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TABLE 1. Effects of CPG and Piracetam on Learning and Memory in Passive Avoidance Task Followed by ECS

Group	Administration schedules					
	before learning		immediately after learning		before retrieval	
	L, sec	AA, %	L, sec	AA, %	L, sec	AA, %
NaCl	91±34 (14)		90±19 (20)		70±20 (16)	
NaCl+ECS	19±8° (12)		36±11° (19)		39±15° (16)	
CPG, 0.1 mg/kg+ECS	73±26* (16)	+76*	44±14 (22)	+15	7±1** (16)	-100**
NaCl	113±14 (18)		107±15(18)		113±12 (20)	
NaCl+ECS	49±15° (60)		69±8° (60)		48±11° (31)	
Piracetam, 200 mg/kg+ECS	98±14* (10)	+77*	77±7* (20)	+21*	31±14 (10)	-26

Note. *$p<0.05$, **$p<0.01$ in comparison with rats receiving ECS+NaCl;°$p<0.01$ in comparison with rats receiving NaCl; in parentheses: the number of rats.

visiting the "dangerous" compartment. Antiamnesic activity (AA) was calculated by formula [11]:

$$AA = \frac{L(ECS+drug)-L(ECS+NaCl)}{L(NaCL)-L(ECS+NaCl)} \times 100\%,$$

where L(ECS+NaCL) is the mean latency in the group receiving ECS and saline, L(ECS+drug) the mean latency in the group receiving ECS and drug injection, L(NaCl) the mean latency in the group receiving NaCl and sham ECS. The data were analyzed statistically using the Mann—Whitney *U* test.

RESULTS

Injection of CPG before learning reduced the level of ECS-induced amnesia by 76%, administration immediately after learning did not affect retention scores. Administration of CPG immediately before retrieval session produced a strong amnesic effect (Table 1).

The standard nootropic piracetam showed similar AA after prelearning administration. Its postlearning administration slightly reduced amnesia, while administration immediately before retrieval session produced amnesia (Table 1).

Thus, on the model of ECS-induced amnesia of PAR both compounds showed similar effects.

We used a one-trial passive avoidance model, which allowed us to time the drug administration to a distinct phase of learning and to assess its effect on different memory stages. It is generally accepted that prelearning administration affects all memory stages and especially the acquisition process [12,14]. Postlearning administration considerably interferes memory consolidation without affecting acquisition, and administration before retrieval session modulates retrieval only.

Piracetam improved acquisition, had no effect on consolidation, and impaired retrieval (Table 2).

Vasopressin and its principal brain metabolite improved both consolidation and retrieval. Pyroglytamyl dipeptides constructed as piracetam peptide analogs [5] similarly to piracetam improved acquisition without affecting consolidation, but differed from piracetam in their effects on retrieval.

Thus, with regard to the effects on memory stages piracetam corresponded to the new endogenous dipeptide CPG rather than memory peptide vasopressin and

TABLE 2. Effects of Nootropic Dipeptides and Piracetam on Memory Stages in Passive Avoidance Task

Compound	Mnemotropic activity after administration		
	before learning	after learning	before retrieval
Piracetam [8]	+	0	—
L-pGlu-L-Asn-OH [7]	+	0	0
L-pGlu-L-Asn-NH_2 [7]	+	0	+
[Phe^3Arg^8]AVP_{1-9} [12]	n. d.	+	+
AVP_{4-9} [10]	n. d.	+	+

Note. Mnestic(+) and amnesic(—) activity; 0 — no effect, n.d. — no data.

its main metabolite. These data suggest that piracetam is a mimetic of the CPG nootropic neuropeptide.

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