The "Nootropic" Approach to the Pharmacology of the Integrative Activity of the Brain[1,2]

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Abstract—The integrative activity of the brain is particularly related to the telencephalic level of CNS. Drugs affecting learning and memory usually interfere with the reticular or limbic system, and are either stimulants or sedatives. In contrast, Piracetam (U C B 6215) is an atoxic compound which, up to dosages such as g/kg, does not interfere with autonomic functions, general behavior, level of wakefulness, the limbic system, etc. Yet, in dosages such as mg/kg it improves several learning and memory abilities, protects against experimental amnesic agents, facilitates EEG recovery after severe hypoxia and also facilitates interhemispheric transfer (transcallosal evoked potential and learned behavior). Discussion is made on the basis of the particular neuropharmacology as well as on the available biochemical and human clinical correlations to emphasize the selectivity of this compound on telencephalic integrative mechanisms. Piracetam is presented as the first-comer of a new psychotropic class for which the term *nootropic* is proposed.

THE INTEGRATIVE ACTIVITY of the brain may be considered as the body of mechanisms which, in higher mammals, are related mainly to the telencephalic plasticity (Konorsky, 1967).

Learning and memory and integration of a new information in the amnesic background to make appropriate decisions, are some of the most usual aspects of the higher CNS-plasticity.

Many drugs were described that interfere with learning and memory (McGaugh and Petrinovich, 1965).

Most of them, as emphasized by Roy John (1967), influence only indirectly the integrative activity of the brain by interfering with mechanisms related to attention, perception or motivation.

In this short paper, I should like to draw your attention to a new drug, Piracetam.

We consider it as the first-comer of a new psychopharmacological class characterized by a direct interference with the higher, telencephalic integrative mechanisms of the brain.

Experimental Data

Leaving aside the actual chronology in which data were obtained during the nine-year-old study of this drug, out of the complex pharmacology of Piracetam, only the essential will be pre-

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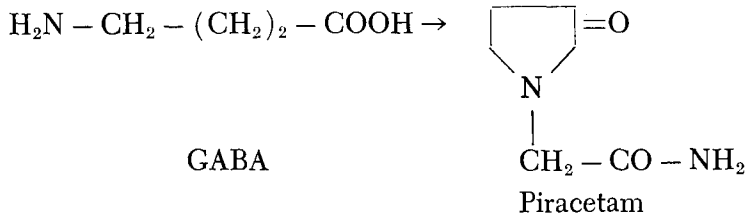
sented to support the telencephalic hypothesis on the mode of action of this drug.

Chemistry

Piracetam is a relatively simple compound chemically related to GABA:



GABA Piracetam

Lack of Usual Psychopharmacological Activities

The first, striking pharmacological impression when dealing with Piracetam is that of an inert compound. Indeed, up to dosages such as g/kg, no activities common to conventional drugs were ever seen in several animal species. This is based on about 30 classical psychopharmacological tests such as: *behavioural* observations (no sedation or tranquilization, no stimulation, no interference with synaptical transmitters, no acute or long-term (toxicity); *electrophysiological* investigations (no cortical or subcortical EEG changes, no interference with limbic after-discharges, reticular sensori or direct arousal threshold, etc.); *autonomic* tests (no changes of the cardiovascular, respiratory, gastrointestinal systems) (Giurgea *et al.*, 1967).

Protection Against Severe Hypoxia

In contrast with the above inactivities, Piracetam at mg/kg was shown in rabbits to facilitate recovery of a normal EEG after severe brain hypoxia.

The detailed method described elsewhere (Giurgea *et al.*, 1970) essentially consists in submitting animals to a progressive lowering of the oxygen content of the air by nitrogen perfusion in a closed chamber. Two main parameters were followed: a. the delay between the onset of the N_2 perfusion and the appearance of an isoelectric EEG tracing ("brain resistance") and b. the delay between readmission of normal air and the recovery of a normal EEG (brain recovery).

Table 1 shows Piracetam to enhance significantly brain-resistance and even more brain-recovery.

It is to be recalled that, in the CNS, higher nervous structures are the most sensitive ones to lack of oxygen (Sugar and Gerard, 1938) and it will be seen below that Piracetam protects against hypoxia in other experimental situations as well.

TABLE 1. Effect of Piracetam on Brain Resistance and Brain Recovery

	Dose mg/kg	Number of animals	Brain Resistance (mean time)	Brain Recovery (mean time)
Controls (saline)	20 ml/40′	16	32′ 16″	±30 min
Piracetam	80 to 1,000	11	36′ 20″	±17 min

Learning and Memory Facilitation; Resistance to "Amnesic" Agents

Table 2 gives a list, by now incomplete, of statistically–significant, repeatedly-done experiments with Piracetam in relation with learning and memory (with the references to previous papers).

Attention will be drawn here only to experiments with rats dealing with so-called retrograde amnesia in one-trial, passive-avoidance learning procedure. Figure 1 shows the principle of the experimental procedure.

TABLE 2. Piracetam and Its Relationship with Learning and Memory

Test	Criteria	Amnesic agent	Results with Piracetam	References
Water maze	–Speed of performance –errors	–	–increase –decrease	Giurgea and Mouravieff-Lesuisse, 1972
Y maze	acquisition	–	facilitation	Wolthuis, 1971
Drink test	acquisition	–	facilitation	Wolthuis, 1971
Spinal fixation	time	–	shortening	Giurgea and Mouravieff-Lesuisse, 1971
Operant conditioning (multiple trial)	active avoidance responses	hypoxia	anti-amnesic	Giurgea et al., 1971
Passive avoidance (one-trial)	a. retention	hypoxia electroshock cerebral oedema	anti-amnesic	Giurgea, 1972; Sara Lefevre, 1972
	b. retention	electroshock pentylene-tetrazol	no effect	Wolthuis, 1971

As seen in Figures 2 and 3, pre-trial injections of Piracetam, but also to some extent post-trial injection, efficiently prevented "amnesia" produced in rats by post-trial application of electro-convulsive seizures (ECS) or hypoxia.

These data are given here in more detail since they are apparently controversial to those of Wolthuis (1971). Indeed, while generally supporting our findings with Piracetam on learning facilitation, Wolthuis reports negative results in a one-trial passive-avoidance procedure, that were true even if Piracetam was given in pre-trial injections. The controversy might simply be due to experimental procedures which were different in the two laboratories. Therefore the generality of both Wolthuis negative and our positive results is somehow limited by the experimental model itself.

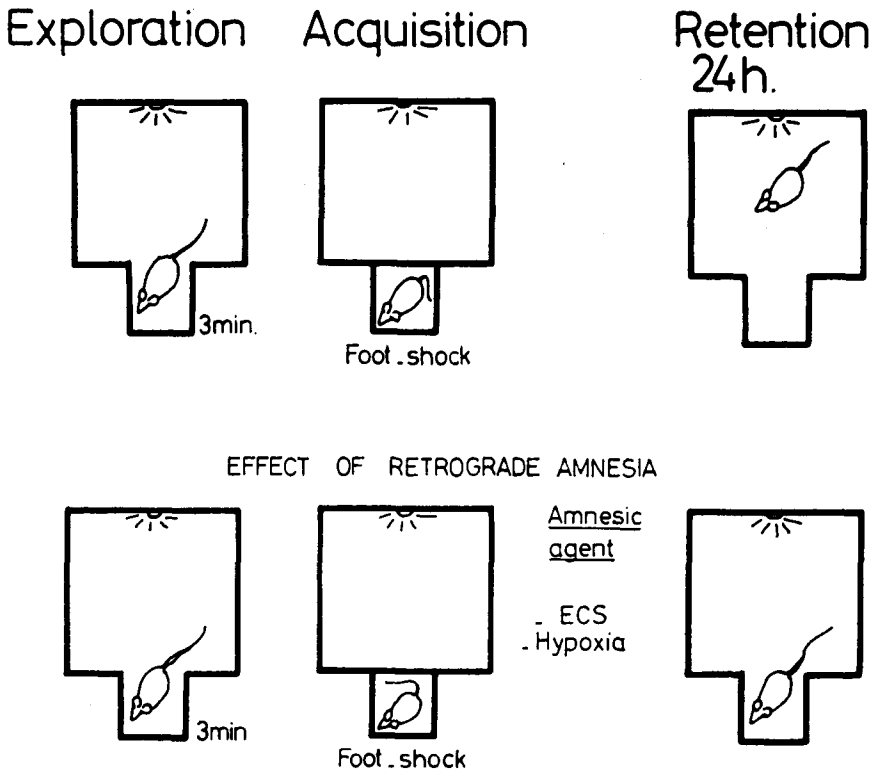


FIG. 1. *One trial learning:* (A.) *Principle;* (Bures and Buresova, 1968). The cage consists of a small dark compartment and a large brightly illuminated one. *Exploration;* A rat prefers to stay most of the allowed time (3 min) in the small cage. *Acquisition:* A painful unescapable foot-shock is given to the animal in the dark closed compartment. *Retention:* 24 hr later when placed into the cage, only a very small percentage of the 3 minutes is spent in the dark compartment. (B.) *Effect of retrograde amnesia:* When producing retrograde amnesia by hypoxia or electroconvulsive shock immediately after the foot-shock, retention is decreased very significantly and the rat returns to the dark cage 24 hours later.

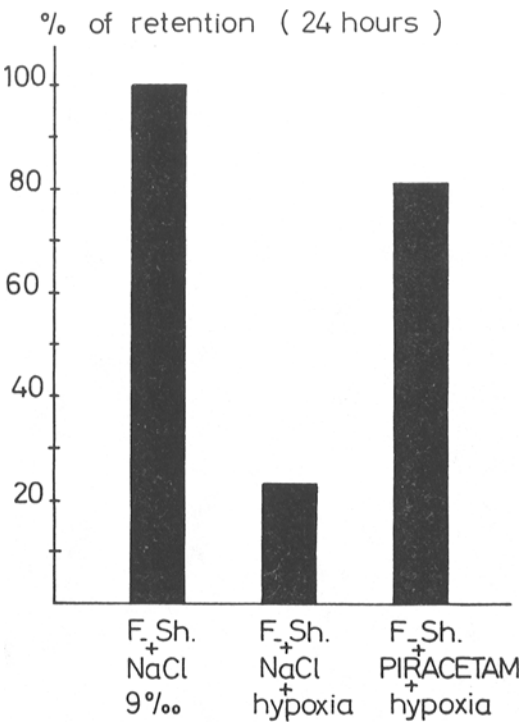


FIG. 2. Effect of PIRACETAM on retention in the one-trial passive avoidance test. F sh : + NaCl 9°/°° (group I) Rats having had foot-shock in the small compartment, spend most of the time 24 hours later in the brightly illuminated cage indicating retention. To simplify comparison with the other groups their retention was considered as 100 per cent, although 25 per cent of the 3 minutes was occupied by exploration of the environment. These rats were put into the hypoxia cage without being submitted to hypoxia. Injection of NaCl 9°/°° was made 30 minutes before training. F sh + NaCl + hypoxia (group II) Same experimental procedure as group F sh + NaCl 9°/°° but these rats underwent hypoxia in the hypoxia cage. Note their retention is about 25 per cent as compared to group I. F sh + PIRACETAM + hypoxia (group III) (100 mg/kg). Same as in group II but here an oral Piracetam injection replaced the NaCl injection of group II. Note the good retention (80 per cent) as compared to group I and protection against hypoxia *vs* group II.

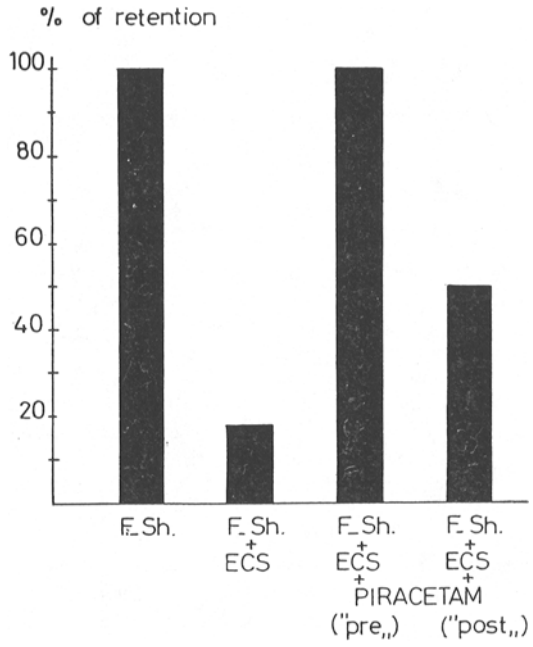


FIG. 3. One trial: Retention at 24 hours. Same criteria as in Figure 2. Retrograde amnesia is produced here by a maximal electroshock seizure (ECS). ECS is given immediately after the foot-shock. Piracetam "Pre" intraperitoneal injection of PIRACETAM 100 mg/kg 1 hour before training. Piracetam "Post:" intraperitoneal injection of PIRACETAM 100 mg/kg immediately after ECS. *Note:* 1. impairment of retention by ECS. 2. complete protection of retention by PIRACETAM "pre" of ECS rats. 3. partial protection by PIRACETAM "post."

Discussion

To summarize the above presented data, Piracetam is a compound which has no overt behavioral, autonomic or EEG (cortical-subcortical) activities up to dosages such as *g/kg* and yet it is able to protect against severe brain hypoxia and to enhance learning and memory in several experimental models at mg/kg dose levels.

Piracetam is therefore a CNS-active drug, but the questions are: *at which level* (where?) and *how?*

Evoked potentials (EP_s) studies in cats showed that out of several cortical responses we have investigated, only the transcallosal response was enhanced by the compound. It should be noted that this is an event that takes place in a cortical associative area. Fig. 4 illustrates this effect on EP_s (Giurgea & Moyersoons, 1972).

Bures and Buresova (personal communication) obtained an interesting behavioral confirmation of our electrophysiological findings. They have used their elegant model of learning with monocular input and cortical spreading depression (CSD). The authors have shown that Piracetam significantly enhances the "writing-in" callosal interhemispheric transfer of information. (Giurgea, 1972).

Consequently, as an answer to the question "where," we propose Piracetam as a compound selectively acting a telencephalic level and this for three main reasons: 1. it interferes positively with learning and memory and speeds up cortical EEG-recovery after severe brain hypoxia; 2. it does not interfere with the activities of peripheral as well as reticular, limbic or thalamic structures we have investigated; 3. it selectively facilitates one of the main mechanisms the callosal transmission that contributes to the harmonious, functional synchronization of the two brain hemispheres.

The second question, *how* does it act? is even more difficult to answer but at least we know that it enhances the ATP/ADP ratio in the brain and so promotes energy reserves (Pede *et al.*, 1971).

Other data are available (Gobert, 1972) but they will be left aside: nor shall the abundant clinical favorable results obtained in pediatrics, geriatrics, toxicomania, etc. be taken into account (Sivadon, 1971).

The last point is *how to classify* such a drug, whose activity could be summarized as follows: a. direct activation of the higher integrative mechanisms, b. telencephalic selectivity, c. particular efficiency to restore deficient higher nervous activity. Obviously such a drug does not fit into any described class of psychotropic drugs.

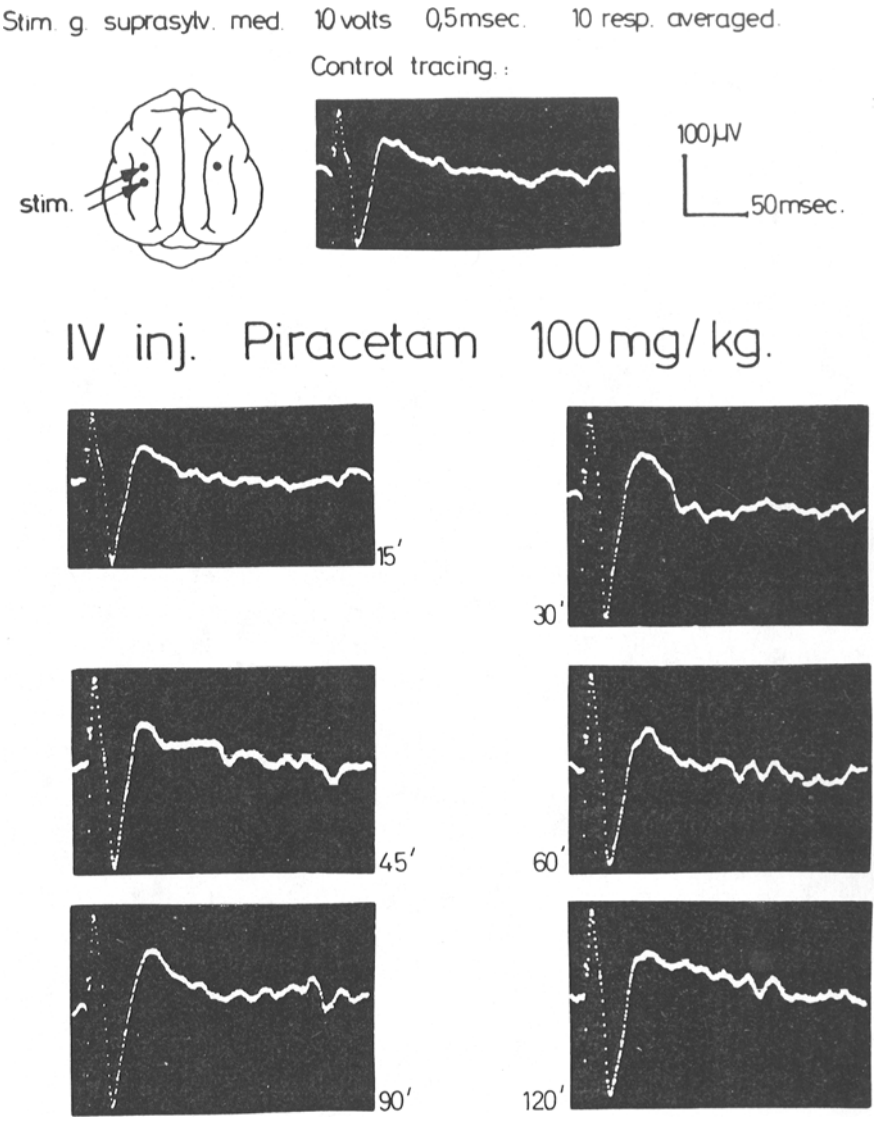


FIG. 4. Effect of Piracetam on the Transcallosal Response. Curarized cat, artificial ventilation. Bipolar stimulation of median suprasylvian gyrus. One stimulation every 5 seconds (±2). Monopolar recording of the transcallosal evoked potential (TEP) at the homotopic point of the other hemisphere. Each tracing is the average of 10 responses made by a data retrieval computer. Note the increase of the amplitude of the TEP after intravenous injection of 100 mg/kg Piracetam. Almost no change of the morphology of the wave form can be observed. Two hours after the injection there is still no return to the control amplitude.

A new class is therefore to be considered for which we propose the term *Nootropic* (from Noos—mind, and tropein—towards).

In conclusion, the long-term perspectives of studies along the Nootropic line might be to find other drugs that *specifically, di-*

versely and *beneficially* will interfere with the integrative activity of the brain. It is to be reminded that, phylogenetically, this integrative activity is probably the main factor in the evolution towards "Homo sapiens" (Penfield, 1966).

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