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Piracetam as a Corrector of the Delayed Learning Disabilities Caused by Prenatal Alcoholization: the Importance of Times of Treatment

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The use of piracetam from the 8th to the 20th day of postnatal development prevents disruption of the elaboration of the conditioned bilateral avoidance reflex in the shuttle box in mature male offspring of rats which had received ethanol intragastrally from the 1st to the 20th day of gestation. When used for 13 days one month prior to conditioning, piracetam acts with less efficiency on mature animals, while the same duration of treatment just before conditioning does not affect the impairment of conditioned reflex elaboration.

Key Words: *alcoholization; active avoidance; correction; piracetam; ontogenesis*

Alcohol intake during pregnancy causes various disorders in the offspring, including intellectual disturbances which require treatment [2,8,13]. Among the pharmacological agents for the correction of mental disorders of different genesis in children, nootropics, and in particular piracetam, are widely used [11]. However, usually treatment is started only when there are already manifestations of developed pathology and so it does not always have a positive outcome. Preventive therapy would be more effective [3,7]. In experiments on animals the possibility of correcting cognitive disorders which are the delayed result of prenatal alcoholization was demonstrated with the aid of substances with nootropic activity administered during the early postnatal period [9, 10,12]. The goal of the present study was to compare the efficacy of nootropic agents used in the early postnatal period and in mature animals for the correction of learning and memory deficiencies induced by *in utero* alcoholization. The original

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nootropic piracetam was used as the prospective corrector.

MATERIALS AND METHODS

Experiments were carried out on 25 male offspring of outbred albino rats. From the 1st to the 20th day of gestation the animals were administered water (the 1st group) or 25% ethanol in a dose of 5 g/kg/day (the 2nd-5th groups) through a gastric tube. Intact rats (the 1st group) or prenatally alcoholized animals (the 2nd, 4th, and 5th groups) received 0.9% NaCl subcutaneously from the 8th to the 20th day of life. At the same times the offspring of the 3rd group were subcutaneously injected piracetam in a dose of 200 mg/kg/day. To the mature animals from the 4th group piracetam was administered subcutaneously in the same dose during 13 days. The last injection was given 30 min prior to elaboration of the conditioned reflex of bilateral avoidance (CRBA). Previously, testing in which a positive effect of nootropic compounds administered from the 8th to the 20th day of life was recorded was started 1.5 months after the treatment, that is, in mature animals [9,10,12]. Therefore, in the present study the 5th group received piracetam (200 mg/kg/day, subcutaneously) for 13 days so that the last injection would be performed one month prior to the end of conditioning. The conditioned reflex of bilateral avoidance was elaborated in males aged 3.5 months in a shuttle box (Ugo Basile). Sound was the conditioned signal, followed 4 sec later by electropain reinforcement (4 sec) delivered through the floor. The interval between sound signals was 12-19 sec. Every day 50 associations of the sound signal with pain reinforcement were presented. Elaboration of CRBA was continued until the criterion "8 avoidances in 10 presentations of the sound signal" was met, but no longer than 5 days.

RESULTS

Prenatal alcoholization resulted in the impairment of learning in the mature rats. The number of animals which attained the criterion of learning during the 5 days of CRBA elaboration in the 2nd group (untreated animals subjected to the influence of alcohol *in utero*) was smaller than in the 1st (intact offspring) with statistically reliable differences for the last 2 days (Fig. 1). The action of piracetam in the early postnatal period prevented the impairment of learning (3rd group).

Comparison of the influence of the nootropic under study on mature rats alcoholized *in utero* yielded unexpected results. When injected one month prior to conditioning (5th group), piracetam improved the elaboration of CRBA. The number of animals which achieved the learning criterion did not differ statistically from the control (1st group) during the entire 5 days or from the number of animals conditioned in the 3rd group (Fig. 1). However, in the 5th group this index was no different from that in the 2nd. Thus, in the 5th group CRBA was elaborated better than in the 2nd, but worse than in the 1st and 3rd groups; in other words, piracetam treatment was less effective for the mature rats than in the early postnatal period. Contrary to the corrective action of piracetam injected one month prior to conditioning, the 2-week administration of the nootropic just before conditioning did not improve CRBA elaboration. According to the number of animals which attained the criterion of learning the 4th group differed statistically both from the intact animals (the 1st group) and from the prenatally alcoholized and postnatally treated rats (the 3rd group, Fig. 1). Based on this we can draw the conclusion that the corrective effect of preparation manifests itself with time in the offspring alcoholized prenatally.

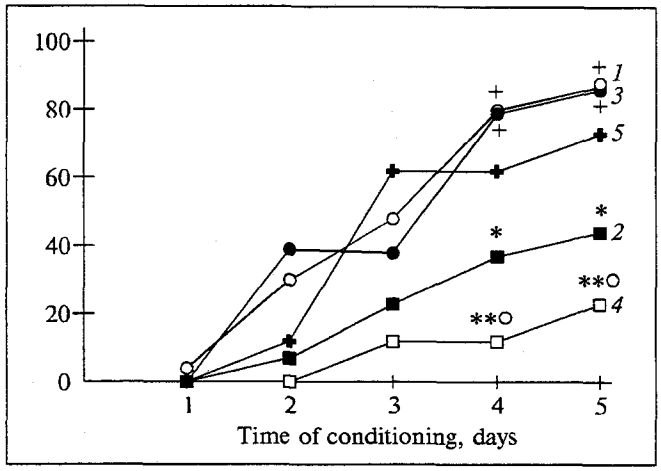

Fig. 1. Effect of piracetam in different age periods on the elaboration of the conditioned reflex of bilateral avoidance in offspring of alcoholized rats. Ordinate: percentage of animals attaining learning criterion by corresponding day of habit elaboration. The numbers of the curves correspond to the animal groups. *$p<0.05$, **$p<0.01$ compared to the 1st group; $p<0.05$: +compared to the 2nd group, °compared to the 3rd group according to the χ^2 test.

A two-phase nootropic action has been noted for piracetam in pediatric psychiatry. At the inception of therapy in children with psychopathiclike syndrome the preparation aggravated the psychotic phenomena and only later led to a therapeutic effect, improving attention and memory during the 3rd-4th week [1]. In the treatment of children with mental retardation the mental state declined 1.5 weeks after drug abolishment but then recovered spontaneously to the therapeutic level [5]. It is known that alco-

holic embryo-encephalopathy is attended by disinhibition and hyperactivity of children [13]. In the experimental setting this is expressed in an increase of emotional reactivity [10]. Piracetam, which has a stimulatory action, can in long-term use aggravate anxiety and affective tension in adults [4], while in children it can induce or exacerbate existing motor disinhibition, fussiness, general anxiety, and unbalanced state [6]. Such a similarity in the consequences of alcoholization and the initial effect of piracetam is evidently reflected in the preservation of the learning impairment in animals or in the initial aggravation of psychopathological simptoms in children. The nootropic effect of piracetam appears only in the course of time, after abolishment of the preparation or during its further use.

Thus, the data presented suggest that as early as possible prophylactic therapy with nootropics in children (perhaps even in newborns) whose mothers abused alcohol during pregnancy may be more effective in preventing the development of various intellectual ploblems than treatment of an already established pathological state at a later age. It must be remembered that the effect of the nootropic is delayed, and consequently in the first stage of treatment the mental state of the child may temporarily worsen. This may be due to specific properties of piracetam. Whether such a two-phase effect exists in other drugs and compounds with nootropic activity is a topic which calls for special investigation.

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