proteins, which is also the responsibility of lysosomal proteinases which participate in intraluminal digestion in the distal portion of the small intestine.

It can be concluded from the results that in the period of milk feeding there is a proximo-distal gradient of activity of lysosomal proteases both in the mucosa and in the contents of the small intestine. The change from milk to definitive feeding is accompanied by disappearance of the proximo-distal gradient of lysosomal protease activity. It can be tentatively suggested that lysosomal proteases of enterocytes in the distal portion of the small intestine participate in intraluminal digestion at an early age.

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EFFECT OF β-PHENYLETHYLAMINE ON EVOKED POTENTIALS IN THE RAT NEOSTRIATUM

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The effect of intraperitoneal (70 mg/kg) and local (39μg) injections of β-phenylethylamine (βPEA) on evoked potentials (EP) in the caudate nucleus during stimulation of the compact zone of the substantia nigra in the frontal cortex was investigated in rats. For local application of βPEA, glutamate, and haloperidol a push-pull cannula system with simultaneous recording of EP was used. Definite specificity in the action of the drugs on EP of cortical and nigral origin was found. Intraperitoneal injection of βPEA caused a faster and stronger decrease in amplitude of the N_2-P_2 component in the response to stimulation of the substantia nigra than local application, but had very little effect on the amplitude of EP in response to stimulation of the frontal cortex. It was shown by the use of haloperidol that the N_2-P_2 component of EP in response to stimulation of substantia nigra is dopaminergic in nature. It is suggested that endogenous βPEA may be a regulator of the function of dopaminergic neurons in the nigro-neostriatal system of the rat brain.

KEY WORDS: β-phenylethylamine; dopamine; evoked potential; caudate nucleus; substantia nigra; frontal cerebral cortex.

It can be postulated on the basis of experimental data [2, 3, 11, 13] that β-phenylethylamine (βPEA) is an endogenous regulator of synaptic transmission effected by catecholamines. It is considered that βPEA acts

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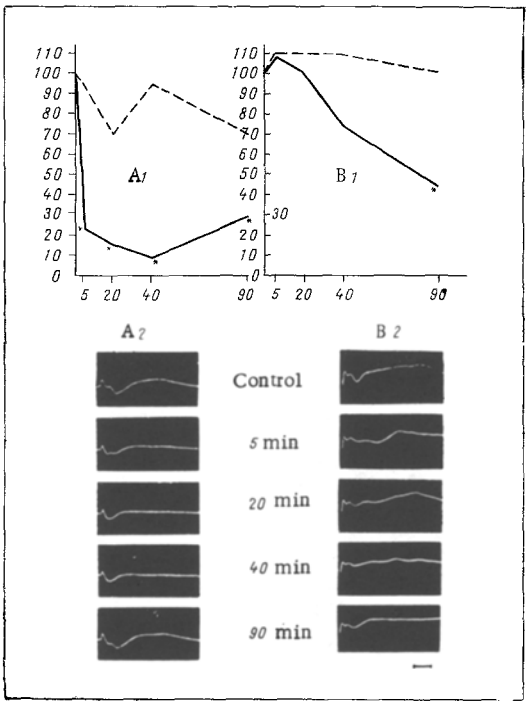

Fig. 1. Effect of βPEA on EP recorded in caudate nucleus to stimulation of SNC. A_1, B_1) each point represents mean amplitude (for several animals) of EP components at various times after injection of PEA; A_1) systemic injection of βPEA, B_1) local injection into caudate nucleus. Continuous line shows change in amplitude of component N_2-P_2; broken line, change in amplitude of component N_1-P_1. Asterisk indicates that amplitude of component differs significantly ($P < 0.01$) from normal amplitude. Abscissa, time after injection of βPEA (in min); ordinate, amplitude of component of EP (in percent of normal). A_2, B_2) averaged EP (16 realizations) for one animal under normal conditions (control) and at corresponding times after injection of βPEA: A_2) systemic injection, B_2) local injection. In control for local injection of βPEA, 1 μl Ringer's solution was injected. Here and in other figures, time calibration 10 msec. Negativity beneath active electrode corresponds to upward deflection.

both on the presynaptic [3, 6] and on the postsynaptic [2, 5] parts of catecholaminergic neurons. Considering that β-PEA is present in the caudate nucleus in relatively large quantities [5], that exogenous βPEA accumulates in the caudate nucleus [9], and that βPEA can liberate dopamine from dopaminergic terminals [3, 6], it was decided to study the effect of this compound on the functional activity of dopaminergic neurons.

For this purpose the effect of βPEA on evoked potentials (EP) recorded in the caudate nucleus in response to stimulation of the substantia nigra (SN), was studied.

EXPERIMENTAL METHOD

Noninbred male rats weighing 300-400 g were used. The animals (40 rats altogether) were divided into two groups.

In the animals of Group 1 the systemic action of βPEA on EP recorded in the caudate nucleus to stimulation of SN in the midbrain and the frontal cortex was studied. In the course of a preliminary operation, stimulating electrodes were implanted, using stereotaxic coordinates from Fifkova and Marsal's atlas, in the compact zone of SN (SNC) (AP = +4.5, V = 8.2, L = 1.8) and the frontal cortex (AP = −2, L = 1), and a recording electrode was inserted into the head of the caudate nucleus (AP = −1.5, V = 4.5, L = 2.5). The experiment began 5-7 days after the operation: During its course EP in the caudate nucleus to stimulation of SN and the frontal cortex were recorded by a monopolar technique. The reference electrode was located in the nasal part of the skull,

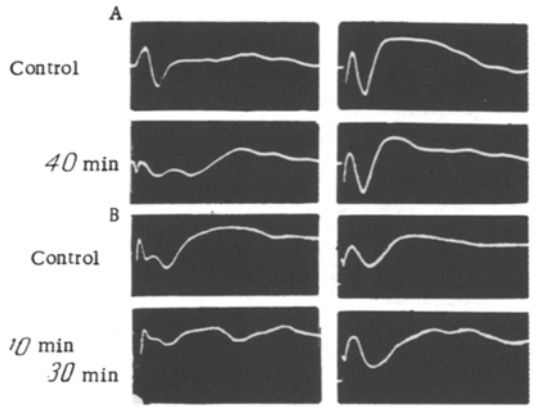

Fig. 2

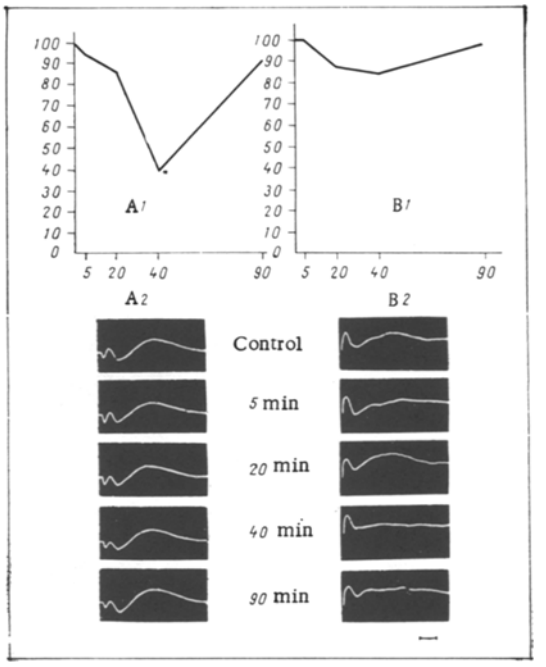

Fig. 3

Fig. 2. Averaged EP recorded in caudate nucleus at specified time after local injection of haloperidol (A) and glutamate (B). EP to stimulation of frontal cortex shown on right, to stimulation of SNC on left.

Fig. 3. Effect of βPEA on amplitude of EP recorded in caudate nucleus to stimuation of frontal cortex. A_1, A_2) systemic injection of βPEA; B_1, B_2) local injection of βPEA into caudate nucleus. Remainder of legend as in Fig. 1. Data for same groups of animals as in Fig. 1.

and the whole system of electrodes was secured to the skull by means of self-hardening plastic. The animals were unrestrained during the experiment. EP were led through a low-noise cable to a 4-ÉÉG-1 electroencephalograph and recorded on an SDR-4I analog tape recorder after frequency modulation of the signal. Processing of EP consisted of averaging by the "biocode-neuron" system (Special Design Bureau for Biological Instrumentation, Pushchino). The averaged EP were then led to a photographic recorder. The EP were recorded both under normal conditions and 5, 20, 40, and 90 min after administration of βPEA. βPEA-HCl was injected intraperitoneally in a dose of 70 mg/kg.

In the animals of group 2, the local action of βPEA on EP recorded in the caudate nucleus to stimulation of SN and the frontal cortex was studied under pentobarbital (40 mg/kg, intraperitoneally) anesthesia. The procedure was similar to that used with the animals of group 1. For local microinjection of the drugs, a push-pull cannula system of the writers' own design, with an electrode for recording brain electrical activity from the region of injection, was used. The operation of this cannula was fully described previously [1]. The injection cannula, connected with an electrode for recording EP, was introduced into the head of the caudate nucleus (AP = −1.5, V = 4.5, L = 2.5). The following substances were injected: βPEA-HCl (39 μg/μl), glutamate (10^{-10} M), and haloperidol (4 μg/μl). The solutions of the substances were injected in a volume of 1 μl for 1 min to avoid damage to the brain through pressure. EP recorded under normal conditions and at different time intervals (5, 20, 40, and 90 min) after microinjection of each drug were averaged. Statistical analysis was by Student's t-test. The amplitude of the components of EP was measured from peak to peak. At the end of the experiment the position of the electrodes and injection needle in the animal's brain was verified morphologically.

EXPERIMENTAL RESULTS

The effect of βPEA on EP recorded in the visual cortex of animals to flashes was investigated previously [12]. However, the components of these EP have a complex and heterogeneous origin, which makes them difficult to analyze. Unlike Sabelli et al., [12] we studied the effect of βPEA on nigral and cortical inputs to the caudate nucleus, whose monosynaptic nature enables the results to be interpreted more clearly. EP in the caudate nucleus to stimulation of SN consisted of two components: early (N_1-P_1) and late (N_2-P_2), which differ in origin.

Under the influence of haloperidol and βPEA, the first component of EP was virtually unchanged, probably because of its presynaptic origin. Mainly the second component (N_2-P_2) of EP, with a latent period of 7-12 msec and a duration of 15-20 msec, responded to the substances used. Systemic injection of βPEA in a dose of 70 mg/kg to the rats caused a sharp decrease in amplitude of the second component of EP in the caudate nucleus to stimulation of SN after 5 min (Fig. 1). An EP of reduced amplitude continued for 90 min. Local injection of 35 μg/μl of βPEA caused a slower decrease in amplitude of the N_2-P_2 component of the nigral EP, becoming significant 90 min after the injection. It was this component which responded by a decrease in amplitude to local injection of haloperidol, which blocks dopaminergic postsynaptic receptors [8], into the caudate nucleus (Fig. 2). These observations indicate that the N_2-P_2 component of EP is probably dopaminergic in nature and that it was reduced because of exhaustion of dopamine (DA) in the nerve endings under the influence of βPEA [6]. There are several possible explanations of the greater effectiveness of action of βPEA when injected intraperitoneally. First, after intraperitoneal injection of βPEA, the drug affected all parts of the neuron (body, axon terminals, dendrites). Second, βPEA could affect other monoaminergic brain systems on which the activity of nigro-striatal neurons depends. In the case of local injection of βPEA, the drug penetrates by passive diffusion [10] only into the neuron terminal, where it probably disturbs the deposition of DA in granules and, consequently, causes the more rapid liberation of mediator into the synaptic space and a decrease in the DA concentration in the nerve endings. However, the intact neuron body in SN compensates for these deficiencies, and only the prolonged action of βPEA can give rise to the observed decrease in amplitude of the second component of EP 90 min after injection.

EP of cortical origin consisted of one component (N_1-P_1) with a latent period of 5-7 msec and a duration of 15-20 msec. Local injection of βPEA had virtually no effect on the amplitude of EP, but systemic injection of 70 mg/kg βPEA caused a transient decrease in amplitude of EP at the 40th minute (Fig. 3). The cause of this effect is not quite clear. It was perhaps mediated through dopaminergic terminals modulating the activity of cortical afferents, but the direct action of βPEA on cortical neurons cannot be ruled out, for the cerebral cortex can also accumulate exogenous βPEA [9]. Haloperidol, when applied to the caudate nucleus, did not affect EP of cortical origin (Fig. 2). Unlike haloperidol, glutamate, which according to some workers [4], plays the role of mediator in the neuron system of the cortico-striatal pathway, led to opposite changes in EP to stimulation of the frontal cortex and SN: EP of cortical origin were significantly increased in amplitude. EP of nigral origin were reduced. Depression of the amplitude of the EP of nigral origin points to a depressant effect of glutamate on activity of nigral afferents in the caudate nucleus. In experiments with local injection of βPEA, glutamate, and haloperidol into the caudate nucleus, definite specificity in the response of the frontal cortex and SN was thus discovered. These experiments revealed a specific action of βPEA on activity of the nigro-striatal system, reflected in a specific decrease in amplitude of EP of nigral origin. However, these results do not rule out a direct effect of βPEA on EP of nigral origin, not mediated through exhaustion of DA from presynaptic terminals.

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