EVOKED POTENTIALS AND NEUROTRANSMITTER METABOLISM IN BRAIN STRUCTURES DURING CHRONIC HALOPERIDOL ADMINISTRATION

N. S. Popova, E. L. Dovedova, and O. S. Adrianov

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In order to discover the central mechanisms of the side effects of haloperidol, neurophysiological and biochemical processes were investigated in brain structures at various times after its administration.

EXPERIMENTAL METHOD

After the formation of a defensive reflex to six flashes of light (frequency 2 Hz), combined with above-threshold stimulation of the forelimb, i.e., after evoked potentials (EP) in the brain structures had acquired definite characteristics [9], haloperidol was injected intramuscularly into dogs until bradykinesia appeared. In order to record EP in the dogs electrodes were implanted in the motor cortex, in structures of the central visual system, and into the caudate nucleus, nucleus accumbens, and globus pallidus.

EP and their analogs (reproduction of EP in periods between stimulation, in the course of training) were recorded on a 9-loop oscilloscope (transmission band up to 2000 Hz, time constant 1 sec). The program used to analyze the experimental data envisaged semiautomatic calculation of the latent periods of onset of EP and the amplitude and duration of their negative components [9].

Rabbits also were used in the experiments. All the animals were divided into three groups. Each group consisted of five dogs and five rabbits. Group 1 was the control. Group 2 consisted of animals into which a single injection of haloperidol was given in a dose of 0.3-0.6 mg/kg body weight under control of EP (dogs) and of behavior (dogs and rabbits). All the rabbits were killed after 45 min to 1 h. Group 3 consisted of animals receiving a daily injection of haloperidol for 20-30 days. The rabbits were later killed.

Under the influence of haloperidol changes in behavior and neurotransmitter metabolism, similar in direction, were discovered in rabbits and dogs, but the time course of EP (according to their configuration) was more demonstrative in dogs. Biochemical parameters were studied in mitochondrial homogenates or fractions from the rabbit motor cortex and caudate nucleus. The protein concentration in the fractions was determined spectrophotometrically by Lowry's method, and type A monoamine oxidase (MAO) activity was measured at 250 nm (serotonin as the substrate), and type B MAO activity at 450 nm (paranitrophenylethylamide as the substrate), by the methods of Popov [13] and Gorkin [2] respectively. Concentrations of biogenic amines — dopamine (DA), noradrenalin (NA), serotonin (5′-HT), and its metabolite 5′-hydroxyindoleacetic acid (5′-HIAA), were determined in brain homogenates spectrofluorometrically by Kogan's method [4]. The results were expressed as percentages of the control.

EXPERIMENTAL RESULTS

A single injection of haloperidol (into dogs and rabbits) confirmed the previous conclusion that its action occurs in two phases: Phase 1 (20-55 min) is characterized by motor-emotional hyperactivity, and by enhancement of the parameters of EP, es-

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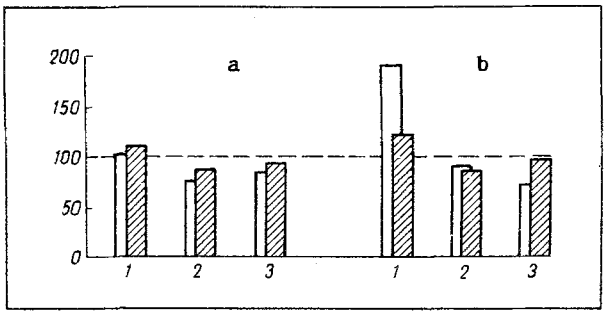

Fig. 1. Changes in relative activity of type A MAO (1), type B MAO (2), and AChE (3) in rabbit brain structures during single (a) and prolonged (b) administration of haloperidol. Unshaded columns — motor cortex, shaded columns — caudate nucleus. Ordinate, change in parameter (in per cent).

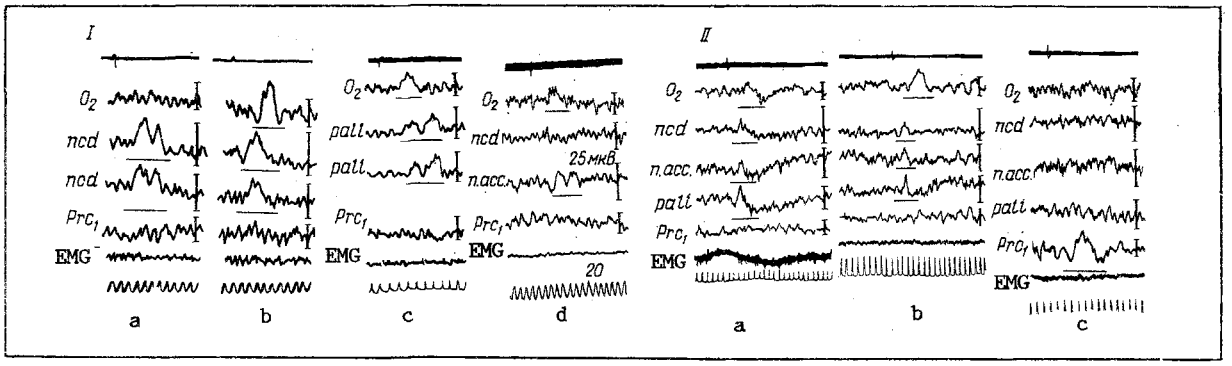

Fig. 2. EP in dog brain structures. I) After consolidation of defensive avoidance reaction; II) against the background of chronic haloperidol administration (13-30 days). EMG) Electromyogram, top line — marker of photic stimulus, bottom line — time (in msec).

pecially in the visual cortex (accompanied by shortening of their latent period); Phase 2 (60-120 min) is characterized by lowering of muscle tone, reduction of motor activity, and a decrease in the parameters of EP in the brain structures tested. A decrease in activity of the enzyme of acetylcholine utilization (acetylcholinesterase, AChE) and a decrease in activity of type B MAO were observed, more especially in the motor cortex (Fig. 1a). Changes observed in behavior, EP, and neurotransmitter metabolism were evidently interlinked, for we know that AChE blockade is connected with increased emotional activity [5, 6], whereas depression of motor activity is associated with inhibition of dopamine metabolism.

During chronic haloperidol administration (10-12 days), before any motor disturbances had occurred, the parameters of EP in the visual cortex became very variable: for instance, the latent period of EP varied from 25 to 50 msec. The coefficient of variation rose from 5.8 to 31%. In deep brain structures (caudate nucleus, globus pallidus, nucleus accumbens), uniform EP similar in configuration were recorded (Fig. 2, II), by contrast with the normal situation (Fig. 2, I). Their latent period was shortened (25-28 msec). These changes in EP, as was shown previously, are evidence of limitation of the inflow of afferent complexes, induced by movements, to the brain structures [3, 9]. Under these circumstances activation of type A MAO was observed, especially in cortical synaptosomes (Fig. 1b). Consequently, changes in neurotransmitter processes in the brain structures (based on inadequacy of the motor afferent complex) were combined initially with activation of serotonin metabolism. This was confirmed by information on the potentiation of serotoninergic processes in the early period of motor deprivation [8]. Under these circumstances AChE activity and also the motor-emotional responses of the animals returned to normal, demonstrating a connection between these processes.

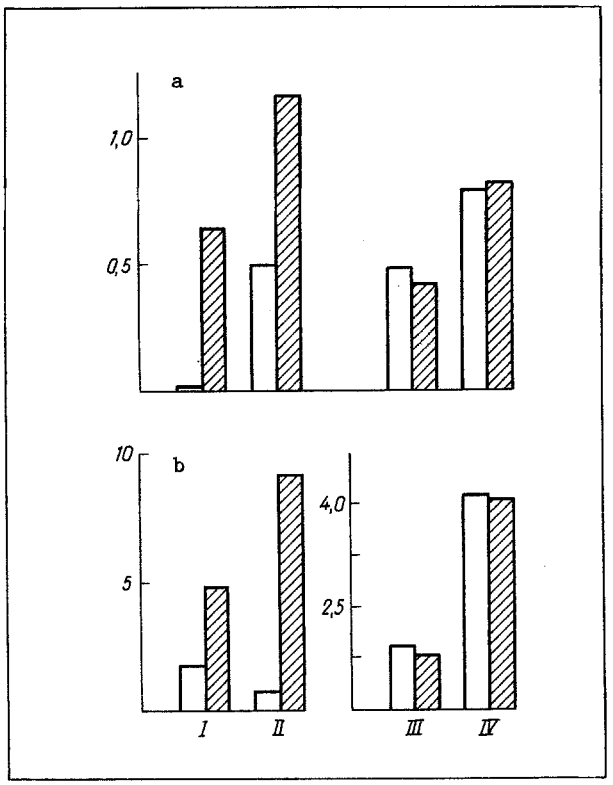

Fig. 3. Concentration of biogenic amines in rabbit brain structures during administration of haloperidol for 30 days. a) Motor cortex, b) caudate nucleus. I) DA, II) NA, III) 5′-HT, IV) 5′-HIAA. Shaded columns indicate haloperidol, unshaded — normal conditions.

During further administration of haloperidol (3-4 weeks), when bradykinesia developed, distortion of neurophysiological processes was observed in the motor cortex: high-amplitude analogs of EP were recorded, and the amplitude and duration of EP were increased (Fig. 2, II, c), and this was combined with lengthening of their latent period (X = 45.7). In deep brain structures EP to flashes were no longer recorded (Fig. 2, II, c). At the same times of action of haloperidol, irregular accumulation of DA and NA took place in the cortical and deep brain structures. For instance, the DA level in the motor cortex was increased more than sixfold, and in the caudate nucleus threefold; the NA level was increased twofold and ninefold respectlvely (Fig. 3). Incidentally, during this period the levels of 5′-HT and its metabolic product 5′-HIAA were virtually identical with normal values. Catecholamine accumulation was evidently associated with aggravation of the deficit of motor afferentation, for in any event, prolonged motor deprivation is accompanied by analogous changes in neurotransmitter metabolism [8].

On the basis of the view that the basal ganglia transform sensory signals into a form suitable for the construction of motor programs [12, 14], it can be postulated that under the influence of haloperidol this function is performed in the presence of a deficiency of afferent influences induced by movements. As a result, an incomplete sensory-motor integral reaches the final common path, and this leads to distortion of processes in the motor cortex. Moreover the atypical nature of processes in the motor cortex may also reflect another mechanism of bradykinesia, namely the transfer of motor automatisms to the cortical level, which is not adapted for this purpose. On withdrawal of haloperidol the changes described above may diminish. However, during longer administration of haloperidol irreversible changes may develop [1, 10, 11], connected with degeneration of nigrostriatal structures and of the tegmentum mesencephali [7]. The possibility cannot be ruled out that one cause of the degenerative changes may be accumulation of an excess of catecholamines in the deep brain formations, which was found at the above-mentioned times of action of haloperidol.

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SURFACE-ACTIVE PROPERTIES OF DIMETHYLETHANOLAMINE AND ITS EFFECT ON ECTO-ATP-ASE ACTIVITY OF PLASMA MEMBRANES

V. K. Rybal'chenko, S. A. Lukoshko, G. V. Ostrovskaya, and N. V. Kulikova

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Dimethylethanolamine (DMEA) belongs to the class of amino alcohols. The compound is widely used in the production of polymers, dyes, and perfumes [3, 6]. As an intermediate in the synthesis of phosphatidylcholine in the liver DMEA plays an essential role in biochemical processes and gives rise to numerous pharmacological effects [8, 9, 11, 15]. The wide spectrum of application of this substance provided the basis for determination of maximal allowable concentrations (MAC) of the amino alcohol in the air of inhabited places in regions where it is manufactured and used.

One of the most sensitive parameters of the cytotoxic effect of chemical compounds is a change in activity of the ecto-enzymes that are located on the outer surface of plasma membranes (PM). Activity of ecto-enzymes is mainly determined by the lipid microenvironment, on which, in turn, toxic substances, especially those possessing surface activity, exert their influence [4, 7, 13].

Guided by the fundamental principles of toxicity, namely that for damage to occur, the toxic substance must interact with the plasma membrane of the cells of the damaged tissue [2], we investigated the surface activity of DMEA, which has not previously been investigated. Using the ecto-ATPase activity of a suspension of smooth-muscle cells as the example, we studied the effect of DMEA on PM function. With this type of experimental approach it is possible to evaluate the reversible and irreversible effects of the mechanism of toxicity.

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