EXPERIMENTAL STUDY OF POSSIBLE OPTIMIZATION OF BRAIN INTEGRATIVE ACTIVITY BY PSYCHOTROPIC DRUGS

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UDC 615.214.015.4:612.821.1/.3

KEY WORDS: psychotropic drugs; integrative mechanism; optimization.

During the formation of a system of conditioned reflexes and in the course of any nervous activity a special mechanism integrating all stimuli of a stereotype into a single entity is activated — the mechanism of dynamic stereotypy or the mechanism of a functional system [1, 2, 6, 7, 10, 11, 13]. It was interesting to assess the possibility of pharmacologic correlation of one of the leading mechanisms of higher nervous activity (HNA) responsible for the adaptive behavior of animals and capable of acting as a model of many human skills during work, sport, education, and so on.

The aim of this investigation was to study the action of certain neurotropic drugs on the integrative mechanism of HNA and to examine the role of various biochemical systems in integrative brain activity.

EXPERIMENTAL METHOD

Experiments were carried out on 10 dogs with systems of motor situational conditioned reflexes formed by the method in [5, 6]. In the "acoustic" rhythmic stereotype the positive (+) stimulus was a metronome with a frequency of 120 beats/min and the negative stimulus (—) one with a frequency of 60 beats/min. The "photo" stereotype included a 100 W lamp presented on the right (+) and left (—) sides of the feeding bowl. The stimuli were alternated in a fixed order. Altogether 20 stimuli were used in the system in the course of the experiment. Pieces of meat served as reinforcement. The model of short-term (under 7 days) disturbance of integration of nervous processes was reorganization of the stereotypes in the system. The effect of the following drugs on the integrative mechanisms of HNA was investigated: benactyzine (0.05-0.1 mg/kg) and amedin (1.5-2.0 mg/kg), blocking mainly central muscarinic acetylcholine receptors [12], pyrroxan (2-3 mg/kg), blocking adrenoreceptors (2-3 mg/kg) [4], pediphen (2-3 mg/kg), with nicotinic cholinolytic action [13], armin (0.005-0.01 mg/kg), exciting acetylcholine receptors, the psychostimulant sydnocarb (1-5 mg/kg) [8], and the GABA analog pyracetam (50-100 mg/kg) [3]. The drugs were given intramuscularly to the dogs 30 min before the experiment, except sydnocarb and pyracetam, which were given perorally 2 h before the experiment. The characteristics of the level of integration were determined in terms of a coefficient calculated by the equation suggested previously [9]:

$$Q = \frac{(n+) - (n-)}{\frac{S}{2}}.$$

In the test of integration of nervous processes, instead of the stereotype a positive stimulus was used and the number of visits in response to positive places (n+) and the number of visits in response to inhibitory places of the stereotype (—) were counted. S denotes the total number of stimuli applied, and was 60 in three tests. The total number of tests carried out was 245 (30 for each substance).

EXPERIMENTAL RESULTS

In intact dogs only benactyzine and amedin weakened integration processes down to the mean level (Table 1). Under the influence of the other drugs in doses with minimal action

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TABLE 1. Characteristics of Level of Integration of Conditioned Reflexes according to Values of Coefficient Q* during Action of Drugs on Intact Dogs and on Dogs with Disturbed Integration of Nervous Processes

Drug	Dose of drug, mg/kg	Intact dogs						Dogs with disturbed integration					
		Dzhim	Dzhek	Pushok	Druzhok	Seryi	Srednyaya	Chang	Chips	Belyi	Rudyi	Malysh	Srednyaya
Before administration of drugs	—	1,0	1,0	0,94	1,0	0,81	0,95	0,52	0,71	0,51	0,55	0,5	0,56
Benactyzine	0,1	0,6	0,58	0,52	0,42	0,33	0,49	0,27	0,33	0,19	0,17	0,33	0,26
Amedin	2,0	0,53	0,56	0,61	0,63	0,57	0,58	0,33	0,5	0,33	0,47	0,5	0,42
Pediphen	3,0	1,0	1,0	0,83	0,66	0,66	0,83	0,83	1,0	1,0	0,66	0,77	0,85
Armin	0,01	0,83	1,0	0,72	0,8	0,45	0,76	0,83	0,66	0,83	0,84	0,83	0,8
Pyrroxan	2,0	1,0	0,72	0,66	0,66	0,52	0,71	0,5	0,66	0,8	0,56	0,33	0,57
Sydnocarb	3,0	0,83	0,83	0,8	1,0	1,0	0,83	0,83	1,0	1,0	0,84	0,48	0,83
Pyracetam	50,0	1,0	1,0	1,0	0,86	0,83	0,93	1,0	0,93	1,0	0,92	0,93	0,96

*A coefficient between 0 and 0.3 corresponds to a low degree of integration, one from 0.31 to 0.6 to an average degree, and between 0.61 and 1.0 to a high degree of integration.

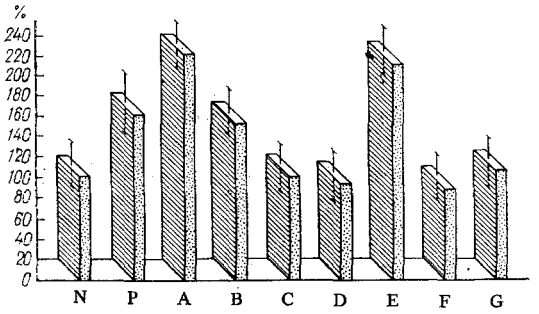

Fig. 1. Effect of drugs on latent periods of motor conditioned reflexes in dogs with disturbed integration of brain activity. Columns denote mean (of 150 measurements) latent period expressed as a percentage of normal (N), taken as 100%. P) Mean latent period in animals with disturbed integration and receiving benactyzine (A), amedin (B), pediphen (C), armin (D), pyrroxan (E), sydnocarb (F), and pyracetam (G).

on HNA the level of integration remained quite high (over 0.71). In animals with disturbed integration of nervous processes (Table 1) drugs blocking conduction of nervous impulses either did not change the level of integration (pyrroxan) or reduced it still further (benactyzine, amedin). The remaining drugs increased the level of integration and, despite different mechanisms of biochemical action, they had an optimizing effect on disturbed integrative activity.

Particular features of the action of the drugs on HNA of the dogs were as follows. Elevation of the level of integration induced by pyracetam was accompanied by normalization of all motor activity: latent periods of motor responses were reduced and their rate of performance increased to the initial values (Fig. 1) and differentiation between stimuli was impaired (Fig. 2). In dogs with disturbed integration, the latent periods after administration of armin or sydnocarb were even shorter than normally (Fig. 1), purposive motor activity increased, but so also did the number of intertrial responses. Benactyzine, amedin, and pyrroxan not only lowered the level of integration, but also aggravated existing disturbances of HNA: they lengthened latent periods, delayed motor conditioned reflexes, and impaired differentiation of acoustic and photic stimuli (Fig. 2).

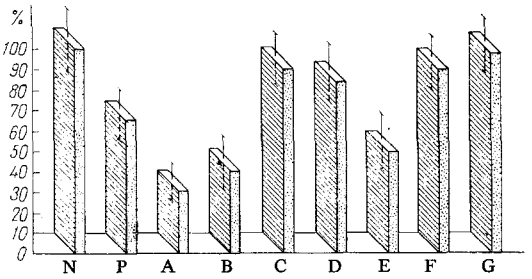

Fig. 2. Effect of drugs on differential inhibition in dogs with disturbed integration of brain activity. Columns denote percentage of differentiation of conditoned stimuli (of 150 applications). N) Normal, P) in animals with disturbed integration and receiving benactyzine (A), amedin (B), pediphen (C), armin (D), pyrroxan (E), sydnocarb (F), and pyracetam (G).

All the drugs tested, despite their different mechanisms of pharmacological action, affected disturbed integration of brain activity. The special integrative mechanism forming a system of nervous processes corresponding to the external stereotype of stimuli, was inhibited by muscarinic cholinolytes and adrenolytics. Blocking nicotine-sensitive acetylcholine receptors by pediphen, or their stimulation by armin and also by sydnocarb, improved integration and the course of systems of conditioned reflexes.

Pyracetam, which selectively optimized HNA, proved to be particularly effective in animals with disturbances of integration. The therapeutic action of pyracetam is the result of its direct effect on integrative brain mechanisms. According to data in the literature it accelerates learning, improves memory, and enhances mental activity [3, 14, 15]. The possibility of optimizing disturbed integration by action directed toward different chemoreceptors is evidence of the chemical heterogeneity of the integrative mechanisms of the brain.

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NEUROSENSITIZATION IN RESUSCITATED ANIMALS AND ITS CORRECTION BY PYRACETAM

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UDC 616-036.882-08-06:616.831-085.214.3:547.745

KEY WORDS: brain; postresuscitation period; neurosensitization; pyracetam.

The most general principles governing injury to and restoration of the functions of organs and systems during dying and resuscitation have now been established [4]. Post-resuscitation brain pathology, known in the literature as postanoxic encephalopathy, resuscitation-induced encephalopathy, the respiratory brain, postresuscitation encephalopathy, and so on, is particularly interesting. In most publications on this matter the role of hemodynamic disorders, metabolic changes, and neurophysiological mechanisms in the genesis of the cerebral changes has been examined [3, 4, 11]. Meanwhile the possible role of immune mechanisms in postresuscitation brain pathology has been studied quite inadequately [8]. Further investigations also are required into the problem of correction of these disturbances by drugs.

The aim of the present investigation was to study neurosensitization in animals recovering from a terminal state and the effect of pyracetam, a drug which has begun to be used in resuscitation practice [10], on this process.

EXPERIMENTAL METHOD

Experiments were carried out on Wistar rats in which clinical death was induced under superficial ether anesthesia by the method of external cardiac tamponade [2]. The resuscitation measures included closed cardiac massage and artificial ventilation of the lungs. There were two series of experiments, differing in the duration of the terminal state: 4-5 min in series I, 7-8 min in series II. Under the experimental conditions used, the number of animals successfully resuscitated in these series of experiments was 53.8 and 33.6% of the total number of resuscitated rats respectively. The state of neurosensitization was evaluated by the following methods: the complement fixation test in the cold [1], tests of activation of spontaneous rosette formation [9], and tests of inhibition of migration of cells from splenic fragments [5]. Antigens for the immunologic studies were saline extracts from the cerebral cortex and skeletal muscle tissues of rats. Lymphocytes were isolated from the blood in a Ficoll—Verografin density gradient and their viability was determined by the trypan blue test. These experiments were carried out on intact animals and also on animals resuscitated on the 7th, 14th, 21st, and 30th days after the terminal state. In some experiments, starting with the 1st day after resuscitation, the animals were treated with pyracetam (100 mg/kg, subcutaneously) for 10 days.

EXPERIMENTAL RESULTS

The experiments showed that clinical death induced a state of neurosensitization in the animal. The development of this phenomenon proceeded in two ways: humoral and cellular. Immunologic reactions of humoral type were reflected in the discovery of antibrain antibodies in the blood of the resuscitated rats. It follows from the data given in Table 1

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 0007-4888/83/9501-0072$07.50