functional activity affects the thyroid gland action as well. A noticeable decrease of the T_3 and T_4 blood serum concentration after external irradiation (Fig.2) and a significant lowering of the T_3 concentration after combined irradiation were observed. With the reduction of thyroid hormones level, the concentration of thyroglobulin was slightly but significantly decreased, indicating the disorders on the gland follicle level. Administration of neurotropin practically does not change these indexes. The ^{131}I action appears to cause pronounced alterations in the thyroid gland, lasting for 3 months. The prolonged hypofunction of the thyroid, connected with the direct action of ^{131}I, disorders on the follicle and hormonal secretion levels cannot be corrected by neurotropin through hypothalamus-mediated effects. Moreover, the pronounced drop of the insulin level, as well as the development of relative adrenal cortex insufficiency [6], support the proposals concerning disintegration of the central regulatory mechanisms. Thus, the results presented here indicate the development of stable and long-lasting disorders in the neurotransmitter and neurohumoral regulation processes when relatively low doses of external and, especially, combined irradiation were applied. These processes taking place in the CNS and, in particular, in the hypothalamus area provide the basis for formation of various autonomic disorders. In the case of additional ^{131}I administration the manifestation of the disorders is redoubled through direct and hypothalamus-mediated radioiodine action on the endocrine glands.

The normalization of the neurotransmitter adaptation processes, partially noted in the hypothalamus, is insufficient and, since the thyroid disturbances have already set in do not improve gland functional activity. In connection with the above, the correction of the revealed disorders must be carried out at earlier times after irradiation and supplemented with direct therapy of the affected organs and systems together with commonly accepted agents (adaptogens) used in the treatment of diseases characterized by a nonspecific component of pathogenesis.

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Myoclonic Hyperkinesia Induced in Rats by Repeated Injections of Picrotoxin Into The Neostriatum

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Using animal models, a number of symptoms occurring in neurological disorders of the human extrapyramidal system have been successfully reproduced by acting selectively upon neurotransmitter systems of the neostriatum. Most of the models are those of parkinsonism produced by causing malfunction of the

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dopaminergic nigrostriatal system [1, 3, 6]. It has proved much more difficult to produce in animals sustained states of an opposite nature, namely extrapyramidal subcortical hyperkinesias. The existing models involve either behavioral (phenamine-induced) stereotypy, which simulates most closely psychotic motor restlessness, or orofacial dyskinesias accompanied by vacuous chewing movements and tremor.

In this study, disorders whose signs particularly resembled those seen in choreomyoclonic hyperkinesia were produced and followed through their main stages by repeated (chronic) intracerebral administration of agents acting upon the GABA-ergic neostrital system whose role in the pathogenesis of extrapyramidal disorders is still poorly understood.

MATERIAL AND METHODS

The experiments were carried out on 30 male Wistar rats weighing 240-270 g. A conditioned reflex response of active avoidance in a shuttle box [6] was developed in all rats, after which a polyethylene cannula was implanted stereotactically into the rostral neostriatum of each rat on either side under hexenal (hexobarbital sodium) anesthesia. The rats were then allocated to six groups of 4 to 6 animals, and each group was microinjected through the indwelling cannulas with GABA (Serva, Germany), 15 μg or 45 μg per injection; bicuculline ("Sigma", USA), 5 μg; picrotoxin, 5 or 15 μg; or physiological saline. Details of the microinjection technique have been described previously [5].

The above preparations were injected daily (in a volume of 0.75 μl per injection) for 3 weeks. During this period, the behavior of the rats, which were kept in individual cages, was monitored for 2 or more hours after each injection. Their conditioned reflex responses were evaluated at minutes 15-30 postinjection; in addition, their behavior was assessed over a period of 2-3 weeks after the last injection to identify possible aftereffects of the treatments used. The rats were then killed under sodium hexobarbital anesthesia and histologic verification of the positions of the cannulas was carried out: their tips were seen to be located in the dorsal or central segments of the rostral neostriatum. The results were evaluated statistically by Student's *t* test using a PC/AT computer.

RESULTS

The rats given physiological saline (control) did not experience any motor disturbances. Their somewhat inaccurate conditioned responses after the first few microinjections could be attributed to consequences of the operative trauma (Fig. 1).

Rats receiving 45 mg of GABA exhibited a more marked reduction of conditioned reflex activity during the early period of treatment (Fig. 1). At the end of the first week, elements of stereotyped behavior appeared such as frequent rising on the hind paws and sniffing; on days 10-11 this behavior lasted almost continuously for several hours postinjection except for the time taken up by the conditioned avoidance responses themselves. The stereotypy became less strongly marked during the third week and had disappeared almost completely by the time of the last injection. Chronic activation of the neostrital GABA-ergic system was also manifested in a tendency of these rats to adopt a frozen posture for prolonged periods [2]: when the observer took a rat in his hands, it became motionless and was hanging passively in this state for 30-40 s

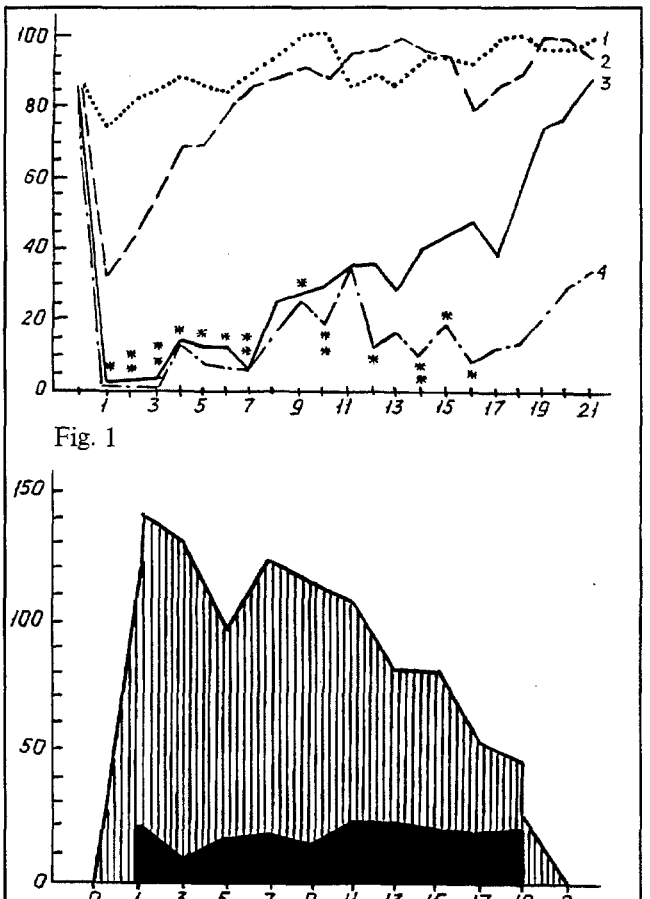

Fig. 1. Time-course of active avoidance responses in rats during chronic administration into the rostral neostriatum of physiological saline (*1*), 45 μg GABA (*2*), 5 μg picrotoxin (*3*), or 5 μg bicuculline (*4*). Abscissa: proportion of correct responses (expressed as % of the presented conditioned signals). Ordinate: experimental days in which the drug was injected. One and two asterisks indicate the days when the parameter concerned differed significantly from its control value at $p<0.05$ and $p<0.01$, respectively.

Fig. 2. Time-course of neuromotor dyskinesias in rats during chronic administration of 5 μg picrotoxin into the neostriatum. Abscissa: experimental days; ordinate: latent period of dyskinesias (blackened area) and duration of hyperkinesia (hatched area) (average values per group per minute).

(control rats remained stuporous for 10 s at most). During the third week, such pathological stupor of several minutes in duration could be observed over a period of 2 to 2.5 h postinjection, and in 4 of the 6 rats in this group it was also seen on the following day before the next injection. This test was strongly positive throughout the first day after the last injection and less so during the subsequent 2 to 4 days. The effects mentioned above were all also seen in the 15-μg GABA group but well-defined vertical activity was shown by only 3 to 5 rats and was of lower intensity while the stuporous state did not last for more than 60 sec and was never observed on the following day.

In the group receiving 5 μg of picrotoxin, significant deterioration of the conditioned reflex responses was in evidence during the first week of treatment only (Fig. 1). On day 1, the rats exhibited psychomotor excitation during which twitching of the facial musculature, vacuous chewing movements, and vertical head movements were observed (at minute 20 postinjection on average). During the next 25-30 min, the twitching became rhythmical, the amplitude of head movements increased, and their frequency rose to 40-60 per minute. The hyperkinesia reached its maximum on minutes 45-70 postinjection, persisted unabated until minutes 90-100, and then decreased markedly. After 2 or 3 days of treatment, the pathological movements took less time to develop and rhythmical twitching of a forepaw was added: the rat raised the paw rapidly over the floor and started to swing it as if in unison with the head movements, clenching and unclenching the paw from time to time.

The picture of hyperkinesia was best developed after 5-10 days of picrotoxin treatment (Fig. 2). Twitches appeared 10 to 15 min postinjection and during the next 20-30 min became fairly rhythmical and of constant frequency (about 20 per minute), involved the whole limb, and came to resemble swinging choreic hyperkinesia in amplitude. In approximately half of the cases, choreiform movements were also performed by the other foreleg and by the head (in some cases the ipsilateral hind leg was involved). After 80-90 min, movements increased in frequency to 40 per minute and became so strong as to cause the rat to fall on its side or back. In most instances the same limb was affected time and again in rats with unilateral hyperkinesia, but occasionally the contralateral rather than ipsilateral limb was affected after an injection. It should be noted that psychomotor excitation was only observed in the first few days of picrotoxin treatment and never thereafter. The hyperkinesia, unless generalized, did not interfere with food taking by the rat and its free movement within the cage. When the observer took a hyperkinetic rat in his hands, the twitching became less intense but did not cease. During the second week of treatment, hyperkinesia remained well-defined for several hours, whereas in the fourth week its duration did not exceed 60-70 min. When microinjections were discontinued (or omitted for some reason), no hyperkinesia was observed.

The picrotoxin dose of 15 μg led to neurotoxic effects. After the first few microinjections, myoclonic twitchings of the facial and foreleg muscles spread rapidly to involve the trunk musculature and were succeeded by clonic convulsions. Of the 5 rats in this group, 3 died on days 1 to 3 of treatment, apparently of respiratory spasm. The remaining rats displayed the same hyperkinetic behavior as did those receiving the 5 μg dose.

Bicuculline, unlike picrotoxin, did not elicit hyperkinetic abnormalities, but its impact on conditioned avoidance responses was more pronounced (Fig. 1). Such differences between the effects of these two GABA antagonists can be explained by their binding to distinct GABA receptors [4]. The action of picrotoxin is more complex and involves the chloride channels and benzodiazepine portion of the GABA receptor system, which is likely to be of crucial importance in the causation of neuromotor dyskinesias by picrotoxin.

The effects produced by picrotoxin after the first 2-3 microinjections were very similar to those after its single administration and consisted of impaired conditioned avoidance responses and orofacial dyskinesia. Such effects have been reported to occur following pharmacological blockade of the GABA-ergic nigrostriatal system [7]. We have succeeded in prolonging selective inhibition of the GABA-ergic neostriatal system, which resulted in qualitatively different motor disturbances such as a high-amplitude hyperkinesia involving the limbs and trunk of the animal. While orofacial dyskinesias and limb hyperkinesia have a common striatal origin, they differ substantially in terms of the neurotransmitter agents concerned. A major role here appears to be played by the dopaminergic system. There is evidence that dyskinesias of facial and masticatory musculature are triggered via dopamine-1 receptors of the neostriatum and myoclonic hyperkinesias of extremities, via its dopamine-2 receptors, these two subtypes of dopamine receptor being functional antagonists [8]. It may assumed that during the development of chronic picrotoxin effects, different components of the dopaminergic system become sequentially involved in neurotransmission reorganizations, and that the respective neuromotor dyskinesias appear as a result.

The time-course of hyperkinesia described above, with its distinct generalization phase, resembles the

progressive course of Huntington's chorea or of chorea minor during a rheumatic attack. This suggests that our experiments reproduced a particular stage in the pathogenesis of those diseases. Moreover, the procedure we employed makes in possible to control the course of pathological events and is convenient to use in the testing of therapeutic agents.

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Effect of Reserpine on the Parameters of Rat Grooming Behavior

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The pharmacological approach in studying the neuronal mechanisms of grooming behavior (*i.e.* specialized reflexes for skin cleaning) is widely used [9]. In this investigation reserpine (a neuroleptic agent) was used for such a purpose. It is known that the use of reserpine has led to fundamental discoveries in studies of the mechanisms of action of the monoamines (MA). Reserpine depresses the active transport of MA, and in particular of dopamine (DA), into vesicles, and prevents the formation of norepinephrine (NE) from DA. The resulting deficiency of the transmitter depresses the effects of the central and peripheral adrenergic structures [2, 7, 11]. The typical symptoms of reserpine action are as follows: a decrease of locomotor activity, an increase of muscle tonus, and tremor in the case of systematic administration of the drug [10].

Table 1. Effect of reserpine on the grooming behavior of rats.

Kinds of groomi	Variation of grooming parameters, %					
	number			duration, sec		
	Days of injection					
	1	2 - 3	4 - 5	1	2 - 3	4 - 5
washing	+40	+50	-40	-	+71	0
licking	-50	+30	-100	-63	+150	-
biting	-90	+250	-80	-50	+240	0
scratching	-63	+133	-62	-16	+21	0
shaking off	-55	+515	+1075	0	+75	+150

In studies of the neuronal mechanisms of grooming with the use of pharmacological agents, the graphic recording of grooming [1] opens up wide possibilities for an objective estimation of all the parameters of the different movements of which grooming consists.

MATERIAL AND METHODS

The study was performed on 10 adult albino male rats, aged two months, which were allowed to move freely. The motor activities of both the intact and experimental rats, which were placed in different actographs, were

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