TRANQUILIZING PROPERTIES OF SODIUM HYDROXYBUTYRATE

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Experiments on rats showed that sodium hydroxybutyrate in small doses inhibits the avoidance reaction to stimulation of the partner and motivated aggression in much smaller doses than it inhibits the conditioned defensive reflex and unmotivated aggression, it prevents the disturbance of attention and of a positive attitude toward the situation after responses of fear and rage, and it restores normal conditioned reflexes in rats with neuroses; these properties are evidence of its marked tranquilizing action.

KEY WORDS: emotional stress; sodium hydroxybutyrate; tranquilizing effect.

One way in which new pharmacological agents are created is by modifying the structure of biogenic substances. This line of attack has been pursued vigorously in the Institute of Pharmacology, Academy of Medical Sciences of the USSR, and as a result several neurotropic substances have been produced, among them sodium hydroxybutyrate [3]. From a clinical study of this compound, Banshchikov and Berezin [1] concluded that the spectrum of pharmacological activity of sodium hydroxybutyrate includes tranquilizing properties. However, no extensive clinical psychopharmacological study of sodium hydroxybutyrate has yet been undertaken and its comparative tranquilizing effect and its position relative to other tranquilizers in current use await investigation.

The writers showed previously that the experimental action of tranquilizers is characterized by depression of the avoidance reaction to stimulation of a partner and inhibition of the motivated struggle for territory by rats after administration of these substances in doses much smaller than those required to inhibit the conditioned defensive reflex and unmotivated aggressiveness [5, 6]; tranquilizers have also been shown to prevent the disturbance of attention and of a positive attitude toward the situation in cats after responses of fear and rage [4].

The object of this investigation was to study sodium hydroxybutyrate by the use of the above-mentioned tests in order to determine its tranquilizing action.

EXPERIMENTAL METHOD

An emotional response of avoiding a darkened room, which was convenient for them and which they were used to, but in which staying evoked painful electrical stimulation of another rat, was produced in 36 female albino rats [10]. The response was taken as positive if the rat went into the less attractive, lighter compartment for more than 3 min during a total exposure of 5 min [6].

A conditioned defensive reflex of jumping onto a bar and staying on it during the action of the conditioned stimulus (the ringing of a bell for 10 sec) accompanied by unconditioned electrical reinforcement, was produced in 10 rats until not less than 80% of correct responses was obtained.

The avoidance reaction to stimulation of the partner, if repeated for a long period, induced the develop-

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TABLE 1. Effect of Psychotropic Drugs on Conditioned Reflexes, Aggressiveness, and After-effects of Fear and Rage Responses

Drug	Inhibition of avoidance response to stimulation of partner, ED_{50} (in mg/kg)	Inhibition of conditioned defensive reflex, ED_{50} (in mg/kg)	Inhibition of motivated aggression (fighting for territory), ED_{50} (in mg/kg)	Inhibition of unmotivated aggression (fighting in response to unavoidable stimulation), ED_{50} (in mg/kg)	Attention in cats after responses of fear and rage (in % of total time of observation	positive attitude of cats toward situation after responses of fear and rage (in % of total time of observation)	Mean number of conditioned reflex jumps onto bar by rats with neurosis (in % of total no. of presentations)	Mean number of failures to press on the pedal in response to differential stimulus (in % of total number of presentations)
—					4,1	0,6	20,6	30
Sodium hydroxybutyrate	33,0	No effect up 100 mg/kg	3,7	90,0	48,6† (10)	7,8† (10)	49,5† (30)	100† (10)
Benactyzine	0,64	75,0 Gatti Bovet [12]	0,23	3,6	42,3† (0,5)	8,9† (0,5)	51,2† (0,5)	100† (0,5)
Diazepam	1,35	No. effect up to 5 mg/kg Delini—Stula [11]	0,16	5,6	50,1† (0,5)	9,4† (0,5)	39,9* (1)	100† (0,5)
Chlordiazepoxide	3,6	62 Vikhlyaev Klygul [7]	1,3	17,5	43,5†	6,7†	39,7*	100†
					(5)	(5)	(3)	(2,5)

*P < 0.05

†P < 0.01

Note. Numbers in parentheses show doses of drugs (in mg/kg) evoking the corresponding effect.

ment of neuroses in the rats, and this made it difficult to produce a defensive reflex. The reflex of jumping onto the bar was produced in 50 rats with neurosis and 10 control rats in the course of 10 days with daily presentation of 10 stimuli. The number of correct responses in the course of the experiment was counted. The substances were injected daily during these experiments.

For the experiments with motivated aggression, 42 male albino rats were trained individually to run into a box measuring 8 × 8 × 6 cm in response to painful electrical stimulation of the paw; after training they were kept in pairs in a room and the presence or absence of fighting for control of the box was recorded. The number of cycles of fighting by 42 rats was recorded during unavoidable painful electrical stimulation [5].

Electrical stimulation of the brain to induce a response of fear or rage was given to six cats with electrodes implanted into the anterior hypothalamus in accordance with the coordinates of a stereotaxic atlas [14]. The parameters of stimulation and manifestation of the emotional responses arising to threshold stimulation were described previously [4]. The level of attention of the animals and their positive attitude toward the situation (purring, walking about, lifting the tail, rubbing by the cats 1 min after responses of fear and rage, as described previously [14]) were determined by a method of recording individual motor acts [13]. A defensive reflex of pressing on a pedal in response to the ringing of a bell, followed after 15 sec by electrical reinforcement, and with differentiation to a pure tone of 100 Hz, was produced in three of these cats. Differentiation was disturbed in 70% of cases after responses of fear and rage ($P < 0.001$).

The pharmacological agents were injected intraperitoneally into the rats 30 min before, and into the cats 1 h before the experiment. ED_{50} was calculated by the method of Litchfield and Wilcoxin [2]. For statistical analysis, the significance of the difference of sample means was determined by Fisher's criterion and the significance of differences between fractions by the "phi" method [9].

EXPERIMENTAL RESULTS

Sodium hydroxybutyrate (GHBA) inhibited the avoidance reaction to stimulation of the partner and fighting for territory in the rats (ED_{50} was 33.0 and 3.7 mg/kg, respectively). The conditioned defensive reflex of jumping onto the bar was unchanged even after administration of GHBA in a dose of 100 mg/kg and the number of bouts of fighting in response to unavoidable stimulation was reduced by half only after a dose of 90 mg/kg (Table 1).

After emotional responses of fear and rage there was no depression of attention or of the positive attitude to the situation in cats receiving sodium hydroxybutyrate in doses of 10 and 20 mg/kg, and the threshold for appearance of the fear and rage responses was increased on the average by 0.8 ± 0.4 V ($P < 0.01$). With the same doses, differentiation of the conditioned defensive reflex was restored to normal after responses of fear and rage.

In rats with neuroses arising after prolonged repetition of avoidance during stimulation of the partner, chronic administration of GHBA in a dose of 30 mg/kg restored the normal conditioned reflex of jumping onto the bar, which occurred in 49.5% of presentations. In rats with neuroses it occurred in response to 20.6% of presentations, and in the control animals to 36.2% ($P < 0.05$).

As Table 1 shows, the restoration of normal conditioned-reflex activity under the influence of GHBA took place in doses comparable with those of the other tranquilizers studied, namely benactyzine, diazepam, and chlordiazepoxide, which were close to ED_{50} as determined by tests revealing the tranquilizing effect (motivated aggression, avoidance during stimulation of the partner).

GHBA thus inhibits the avoidance reaction to stimulation of the partner and motivated aggression in much smaller doses than it inhibits the conditioned defensive reflex and unmotivated aggression, a characteristic feature of tranquilizers [5, 6]. Prevention of the depression of attention and of the positive attitude toward the situation arising after responses of fear and rage, which was observed following administration of GHBA, is also a characteristic effect of tranquilizers [4].

The depriming action of GHBA on negative emotions is also manifested as its ability to restore normal conditioned reflexes in animals with neuroses and after powerful emotional responses.

It can be concluded that sodium hydroxybutyrate, in small doses, has a marked tranquilizing action and prevents the effect of negative emotions on the animals' behavior.

The fact that sodium hydroxybutyrate raises the threshold for the appearance of emotional responses of fear and rage to electrical stimulation of the hypothalamus is evidence that the compound acts on the hypothalamic trigger mechanisms of negative emotions, another characteristic feature of tranquilizers [3, 4].

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