CHANGES IN BEHAVIOR OF CATS AFTER INTRACEREBRAL MICROINJECTIONS OF KYNURENINE AND QUINOLINIC ACID

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Activity of kynurenines – endogenous tryptophan metabolites – on the nervous system, the study of which began in the USSR [4, 10], is at present being investigated intensively in many laboratories of the world. Most information on this subject relates to convulsions and the role of kynurenines as endogenous convulsants [11]. Only isolated data can be found on the effect of kynurenines on behavior. For instance, the most active metabolites, namely kynurenine itself (KYN) and quinolinic acid (QA), if injected into the cerebral ventricles of rats [7] or mice [5, 6], induce locomotor excitation, which is prevented by diazepam [6]. Intraventricular injection of large doses of KYN into rats causes a phenomenon of rotation around the sagittal axis – "rolling like a barrel" [7], whereas QA, if injected into the hippocampus, causes motor excitation, stereotypy, and shaking [13]. Antagonism of KYN with serotonin precursors and with tryptamine has been found in behavioral tests [9]. The effect of KYN on behavior has not been studied in cats. All that is known is that intraperitoneal injection of KYN did not change the behavior of chronically alcoholized cats [3], but considerably increased preferential ethanol intake (rather than water).

Following our experience with the study of behavioral changes in cats under the influence of neurotropic drugs [1], we decided to study the effect of KYN and QA on the behavior of animals of this species, which is characterized by the strongest manifestations of emotions. Choice of the neostriatum as the target structure for the study of behavioral effects of KYN and QA was not accidental, but was due, first, to the high concentration of serotonin and certain of its metabolites in the tissues of the caudate nucleus [8], and second, to the active role of the caudate nucleus in the regulation of various forms of behavior [1, 2, 8].

EXPERIMENTAL METHOD

Experiments were carried out on 15 cats weighing 2.2-4.7 kg. Cannulas 0.8 mm in diameter, made of stainless steel, were inserted into all animals under pentobarbital anesthesia (40 mg/kg), into the caudate nuclei at coordinates A17-15, L2-4, and H15-17, taken from the atlas [14]. Microinjections of the substances were given by means of an automatic microinjector of our own design. L-Kynurenine sulfate (KYN) was given in doses of 50, 125, 250, 500, and 1000 μg, QA in doses of 20, 50, 100, 250, and 500 μg and, in some experiments, 1000 μg (both substances were obtained from Sigma, USA). The maximal volume of a microinjection was 100 μl, its average 25-50 μl, and the rate of injection was 10 μl/min. The substances were dissolved in physiological saline, and the pH of both KYN and QA was 2.0-2.5. The intervals between microinjections were 2-4 days and the largest number of injections given to one animal was four. In the control microinjections of the solvent and of dopamine (250 and 500 μg, respectively, pH 4.0) were given. Behavioral effects were recorded visually and separate fragments were recorded on an "Élektronika" video recorder. The location of the cannulas was verified in frontal brain sections.

EXPERIMENTAL RESULTS

On the whole changes under the influence of KYN were rare and nonspecific. They occurred 1-3 min after the microinjection, were almost independent of the dose of KYN, and they consisted essentially of the appearance of sedation, a sphinx-like posture, periodic

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grooming, and infrequent regular ipsilateral head turning through 60-120°. Myoclonia and convulsions did not occur. These changes differed only a little from those after intracerebral injection of the solvent, they were unstable, and they disappeared 10-15 min after the microinjection.

After injection of 20-250 μg KYN a series of rhythmic or tonic contralateral head turns through 120-150° occurred immediately, accompanied by elevation of the head, looking around, and alertness. These responses were identical with the effects of high-frequency electrical stimulation of the caudate nucleus [1]. In many cases these head turns ended with a series of stereotyped movements in the contralateral direction. The animals at this period became affectionate and moved actively. These responses lasted 2-5 min, after which the animal became quiet and lay down, and fell into a drowsy state. Similar cycles of behavioral activation were repeated every 5-15 min for 30-60 min.

Behavioral responses to microinjections of 500 and 1000 μg QA were much more varied. Immediately or 1-2 min after its injection series of head turns in the contralateral direction began, and changed into stereotyped movements. Many cats developed choreoathetoid hyperkinesias of the contralateral forelimb, withdrawing and protruding the claws, turning the limb around the longitudinal axis, and drawing it inward. Emotionally expressive manifestations consisted essentially of alertness, straining, unease, and fear, with its characteristic features: intensive mydriasis, tachypnea, a facial expression of panic horror, plaintive mewing turning into crying, shrinking, and hiding in a corner of the experiental room. No behavioral convulsions developed.

In three cats with cannulas in medial zones of the caudate nucleus on the boundary with the septum and fornix (levels A15-14 according to the atlas), 5-10 min after microinjection of 500 μg QA a state of panic terror arose, with growling and hissing, rushing about the room, attacking objects placed in the room, aggressive attempts to escape, with biting and scratching, intermingled with series of stereotyped running in the contralateral direction with a frequency of about 40/min, with hyperkinesias of the contralateral hind limb followed by paresis and dragging of the limb. During this period strong mydriasis, tachypnea, defecation, and mewing, changing into malicious crying, arose. This state lasted about 2 h, and was followed by muscle relaxation. The cats lay down, while remaining, however, in a malicious and peevish mood, and if an attempt was made to touch them, they scratched and bit. Fragments of emotional negativism were still present even 1 or 2 days after the experiments. There were no convulsions. This state was conventionally described as the QA syndrome.

Microinjections of dopamine into the same zones of the caudate nucleus in doses of 250 and 500 μ, as well as of the solvent of QA, evoked no emotional disturbances.

Of the two kynurenines studied only QA caused emotional changes and motor excitation, described as the QA syndrome. This syndrome differed qualitatively from the effects of QA mentioned above on rats [7, 13] and mice [5, 7, 11]. The typical QA syndrome, as well as its less marked but similar emotional manifestations in other cats, has definite similarity, in our view, to the clinical manifestations of dysphoria in epileptic patients. It may be that certain kynurenines and QA in particular may form not only a convulsive syndrome [11], but also emotional disorders characteristic of epilepsy.

A special feature of the behavioral changes in cats was the wide range of vivid emotional disorders. It was probably the successful choice of object which enabled these effects of QA to be recorded, although they did not appear in rats and mice – animals with a less expressive emotional sphere. The structure also was important – the caudate nucleus. Previously this formation, which plays an active role in the regulation of movements, mental processes, and the emotional sphere [1, 2, 8], has not been studied from the point of view of neuroactivity of KYN.

Conditional comparison of doses of QA on cats, rats, and mice, allowing for body weight (about 3 kg, 200 g, and 20 g, respectively) and the weight of the brain (about 31.4, 1.8, and 0.4 g, respectively) shows that doses of 500 and 1000 μg, which induced the QA syndrome in these experiments, correspond approximately to excitatory and convulsant doses of QA by intraventricular injection: 2.5-5 μg in experiments on mice [7, 11] and 10-20 μg in experiments on rats [7, 13].

Inactivity of KYN as regards behavior in cats may be due, first, to an inadequately high dose. By intracerebral injection KYN is less active than QA, by about 10-20 times as regards provocation of excitation [7] and about 40 times as regards provocation of convulsions in rats [7, 12, 13]. Consequently, if probable species differences are omitted, for comparison with effective doses of QA, doses of KYN for cats of between 5000 and 10,000 μg ought to be given. It is impossible to give such a dose because of limitations on the volume of solution which can be injected and the solubility of the compound. Meanwhile the results of investigations of KYN on other species of animals show that it may be promising to inject it into other brain structures in cats, for example, into the hippocampus or cortex. Thus the cat is the most convenient of all species of laboratory animals so far studied for further research into behavioral effects of neuroactive metabolites of trypotophan.

LITERATURE CITED

1. É. B. Arushanyan, V. A. Baturin, Yu. A. Belozertsev, et al., Pharmacologic and Physiologic Study of the Functions of the Caudate Nucleus [in Russian], Chita (1981).
2. É. B. Arushanyan and Yu. A. Belozertsev, Zh. Vyssh. Nerv. Deyat., No. 1, 55 (1974).
3. N. F. Baskina and I. P. Lapin, Farmakol. Toksikol., No. 1, 70 (1982).
4. I. P. Lapin, Zh. Vses. Khim. Obshch. im. D. I. Mendeleeva, No. 2, 151 (1976).
5. I. P. Lapin, Khim.-farm. Zh., No. 3, 395 (1983).
6. I. P. Lapin, Byull. Éksp. Biol. Med., No. 8, 206 (1984).
7. I. B. Prakh'e, I. P. Kiseleva, and I. P. Lapin, Fiziol. Zh. SSSR, No. 11, 1516 (1982).
8. A. Dray, Prog. Neurobiology, 14, 221 (1980).
9. I. P. Lapin, Psychopharmacologia, 26, 237 (1972).
10. I. P. Lapin, Trends Pharmacol. Sci., 1, 410 (1980).
11. I. P. Lapin, Epilepsia, 22, 257 (1981).
12. A. Pinelli, C. Ossi, R. Colombo, et al., Neuropharmacology, 23, 333 (1984).
13. R. Schwarcz, G. S. Brush, A. C. Foster, et al., Exp. Neurol., 84, 1 (1984).
14. R. S. Snider and W. T. Niemer, A Stereotaxic Atlas of the Cat Brain, Chicago (1961).