Effect of Tryptophan Metabolites on Activity of the Epileptogenic Focus in the Frog Hippocampus

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With 5 Figures

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Summary

In frogs with the epileptogenic foci made by injection of penicillin (1000 U in 0.4 ml) in the primordial hippocampus it was shown that preliminary administration of two kynurenines quinolinic acid (0.1 µg) and d,l-kynurenine (1 µg), in the foci region, and their injection in the functioning epileptogenic foci led to a strong increase of the interictal epileptiform discharges and of the electrographic correlates of fits on the EEG. Anthranilic acid (0.1, 1.0 and 5.0 µg) did not influence the activity of epileptogenic foci. Serotonin (1 µg) and 5-methoxytryptamine (1 µg) essentially decreased it. Provocating effect of kynurenines on neurons in epileptogenic foci is supposed to play a certain role in pathogenesis of epilepsy.

Introduction

It has been shown that kynurenines—the major in quantity metabolites of aminoacid tryptophan (TRY)—possess a neurotropic activity (Lapin, 1973; Lapin, 1976). In the brain tissue both the tryptophan pyrrolose (TP) activity (Gal, 1974) and kynurenine (Joseph, 1977) have been found. However, direct influence of kynurenines on brain structures were not studied neither in physiological nor pathologic conditions. Meanwhile, this problem is of great importance and interest because firstly there are no evidence for direct action of kynurenines on the CNS (with the only exception—
Lapin, 1978 a, b), and secondly kynurenines are reported to be antagonists of many neurotropic effects of serotonin (5-hydroxytryptamine; 5-HT)—another important metabolite of TRY. It is known that 5-HT, its precursors and analogs are able to decrease the activity of epileptogenic foci in man and experimental animals (Saradzishvili and Bibileishvili, 1972; Gusel, 1975; Grigorieva, 1975). At the same time in epileptic patients it has been demonstrated an increase of excretion of kynurenines (Rudzit, 1973; Hansson, 1968), which was not related to a deficit of pyridoxine (Hansson, 1968).

Idea of this study stemmed from the finding (Lapin, 1978 a, b), that kynurenines injected either into brain ventricles in mice or intraperitoneally in immature rats provoke seizures.

Thus, the aim of the present work was to study the influence of three kynurenines (d, l-kynurenine – KYN; quinolinic acid – QA; and anthralinic acid – AA) on the activity of epileptogenic foci in frog hippocampus, in comparison with effects of 5-HT and an agonist of 5-HT—5-methoxytryptamine (5-MT).

Frog is chosen as an experimental subject, in the first, because in frogs there is no hormonal induction of TP (Lapin, 1976) and therefore the experimental procedure with its and design of the epilepsy will not lead to any increase of the synthesis of endogenous kynurenines and will not interfere the evaluation of effects of exogenous kynurenines; in the second, it is technically easier to induce the epileptogenic foci in the hippocampus and to administer drugs into it in frogs than in mammals and, in the third, in frogs brain 5-HT is the major monoamine transmitter (Lapin et al., 1967) and one may expect that all processes which are associated with activation and inhibition of serotoninergic systems will be manifested more distinctly.

Design of the epileptogenic foci just in the hippocampus is because of great importance of both this structure in the pathogenesis of epilepsy (Vinogradova, 1975), and serotoninergic processes in regulation of functional activity of hippocampus.

Methods

Experiments (1 experiment on 1 frog) were made on winter-spring season on 102 male (mainly) frogs (Rana temporaria) weighing 35—40 g and living in Leningrad region. Frogs were fixed after urethane anaesthesia (5 mg/g). Frog’s skin during all experiment lasted 2—3 hours was covered by a humid gauze which was moistened with Ringer solution (pH 7.6). The skin was cut on the middle line of the head and then the skull bones were removed with care in order to prevent damage of the brain meninges.