LITERATURE CITED

1. É. M. Peganov, S. V. Revenko, B. I. Khodorov, et al., in: Molecular Biology [in Russian], No. 15, Kiev (1976), pp. 20-42.
2. R. Benaim, J. P. Denizeau, J. Melon, et al., Arch. Mal. Coeur, 69, 513 (1976).
3. F. A. Dodge and B. Frankenhauser, J. Physiol. (London), 143, 76 (1958).
4. N. Goupil and J. Lenfant, Eur. J. Pharmacol., 39, 23 (1976).
5. B. Hille, in: Biophysical Aspects of Cardiac Muscle, New York (1978), pp. 55-74.
6. B. Khodorov, L. Shishkova, E. Peganov, et al., Biochim. Biophys. Acta, 441, 409 (1976).
7. B. N. Singh and E. M. V. Williams, Br. J. Pharmacol., 39, 657 (1970).
8. G. R. Strichartz, J. Gen. Physiol., 62, 37 (1973).

EFFECT OF KYNURENINE AND ITS METABOLITES ON VASCULAR EFFECTS OF SEROTONIN, NORADRENALIN, AND ACETYLCHOLINE

I. P. Lapin and L. G. Umanskaya

UDC 615.225.2:547.757].015.4:615.217.32

KEY WORDS: kynurenines; serotonin; noradrenalin; acetylcholine.

The kynurenines – metabolites of tryptophan on the kynurenine pathway of intermediate metabolism – possess central and peripheral pharmacological effects [2] and, in particular, they interact with monoamines, their precursors, and psychotropic drugs. Kynurenine and its metabolites [1, 3, 4] lower blood pressure in rats. The effect of kynurenine on the vascular effects of serotonin, noradrenalin, and acetylcholine has been investigated in detail [1]. This paper describes a continuation of the study of its metabolites.

EXPERIMENTAL METHOD

Experiments were carried out on noninbred female rats weighing 200-250 g (from the Rappolovo nursery); the animals were anesthetized with urethane (0.7 ml of a 25% solution/100 g body weight, i.e., 1.75 g/kg, intraperitoneally). The systemic blood pressure was recorded by a mercury manometer in the carotid artery. The system of polyethylene tubes of the manometer was filled with heparin solution (1500 units/ml) to prevent the blood from clotting. The original pressure in different experiments varied between 90 and 120 mm Hg. All solutions were made up in fresh physiological saline immediately before injection into the femoral vein in a volume of 0.1 ml in the course of 3 sec. At the beginning of each experiment three or four control injections of physiological saline were given. Fluctuations of pressure caused by them were indistinguishable from those occurring spontaneously. Serotonin sulfate was injected in a dose of 0.5-5 μg, in most experiments in doses of 1 and 2.5 μg (the pressure was lowered by 8-21 mm Hg for 35-60 sec), noradrenalin bitartrate was injected in doses of 0.5-2 μg, in most experiments 0.5 and 1 μg (the pressure was raised by 4-8 mm Hg for 50-180 sec) and acetylcholine was injected in doses of 0.1 and 0.2 μg (the pressure was lowered by 9-14 mm Hg for 25-60 sec). Changes in the effects of serotonin and noradrenalin were determined in each experiment from the difference between the means of the three or four control tests before injection of the kynurenines, taken as 100%, and the mean of two tests after injection of the kynurenines, when the changes (in amplitude of duration) were maximal. The dose of kynurenines chosen in preliminary experiments as most effective for interaction with serotonin and noradrenalin, but not itself changing the blood pressure, was 200 μg. This last feature of the method is very important, for kynurenine and its metabolites [1, 3, 4] lower the blood pressure in rats over a wide range of doses.

Laboratory of Psychopharmacology, V. M. Bekhterev Leningrad Psychoneurological Research Institute.

(Presented by Academician of the Academy of Medical Sciences of the USSR V. V. Zakusov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 89, No. 6, pp. 704-706, June, 1980. Original article submitted October 13, 1979.

0007-4888/80/8906-0794$07.50

TABLE 1. Changes in Depressor Effect of Serotonin Produced by Kynurenine and Its Metabolites

Preparation (200 μg)	Number of experiments	Change in effect of serotonin, % (mean value)	
		amplitude	duration
Kynurenine	8	—26,3 (5) +84,5 (2)	—30,4 (5) +37,7 (3)
3-Hydroxyanthranilic acid	7	—20,5 (4)	—34,2 (5) +56,5 (2)
Anthranilic acid	10	—51,8 (6) +62,0 (3)	—49,8 (5) +146,0 (2)
3-Hydroxykynurenine	5	—45,3 (3) +40,0 (2)	—44,1 (2) +107,0 (3)
Nicotinic acid	10	—44,2 (5) +133,0 (4)	—39,6 (5) +114,0 (1)
Quinolinic acid	5	+49,8 (5)	0 (5)
Picolonic acid	4	+66,3 (3) —21,8 (1)	+101,0 (3)

Legend. Number of experiments in which a change in the effect of serotonin was observed is shown in parentheses.

TABLE 2. Changes in Pressor Effect of Noradrenalin Produced by Kynurenine and Its Metabolites

Preparation (200 μg)	Number of experiments	Change in effect of noradrenalin, % (mean value)	
		amplitude	duration
Kynurenine	7	+107,0 (4) —14,3 (3)	—32,6 (5) +29,0 (1)
3-Hydroxykynurenine	5	+47,1 (3) —25,0 (2)	—54,1 (2) +80,0 (1)
Anthranilic acid	3	+18,2 (2) —57,0 (1)	+58,0 (1)
Nicotinic acid	9	+34,7 (4) —36,8 (3)	—50,7 (8)
3-Hydroxyanthranilic acid	7	—28,3 (3) +52,1 (1)	—26,4 (5) +91,1 (2)
Picolinic acid	1	—12,5 (1)	—25,0 (1)

Legend. Number of experiments in which a change in the effect of noradrenalin was observed is shown in parentheses.

EXPERIMENTAL RESULTS

A common feature of all the results was, first, that the kynurenines differed from each other qualitatively and quantitatively as regards their influence on the effects of serotonin and noradrenalin and, second, that the same preparation, in the same dose, had a different, often opposite, action. The depressor effect of serotonin was mainly reduced by some kynurenine, whereas by others it was mainly increased (Table 1). The depressor effect of acetylcholine was unchanged by kynurenines in doses of 200, 500, and 1000 μg. Contractions of the isolated guinea pig intestine induced by acetylcholine were unchanged by injection of kynurenine [1]. The pressor effect of noradrenalin was potentiated under the influence of most kynurenines (Table 2). It was noteworthy that the changes in amplitude of the effect of noradrenalin and in its duration were different. For that reason, conclusions regarding the change in this effect could differ if it was estimated only on the basis of one indicator (amplitude or duration alone). Higher doses (500 and 1000 μg) of kynurenine, 3-hydroxykynurenine, and 3-hydroxyanthranilic acid potentiated the effect of noradrenalin more considerably and more uniformly. Potentiation of the pressor effects of noradrenalin and adrenalin by high doses of kynurenine has been observed previously [1]. In this investigation no attempt was made to confirm the truth of a previous observation [1] that kynurenine has a biphasic action on the effect of noradrenalin: antagonism during the first hour after injection of kynurenine and potentiation in the second hour.

The opposite action of the same dose of some kynurenines in different experiments is in harmony with the results of our experiments to study the effects of kynurenine on serotonin uptake by platelets. The opposite effect of the same dose of a metabolite in different individuals could perhaps depend on differences in the level of this endogenous kynurenine, as a result of which the addition of exogenous kynurenine would create a different final concentration in the body.

The different action of individual kynurenines on the vascular effect of serotonin and noradrenalin is evidence that the final effect of the elevation of the kynurenine level observed in stress and in various pathological states [2] on blood pressure will depend on the ratio between the levels of the various kynurenines. In order to predict the hemodynamic consequences of a rise in the kynurenine level in the body, as well as its other complications [2], the concentrations of as many kynurenines as possible must be determined.

LITERATURE CITED

1. I. P. Lapin, Tr. Leningrad. Nauch.-Issled. Psikhonevrol. Inst., 53, 113 (1970).
2. I. P. Lapin, Zh. Vsesoyuz. Khim. Obshch., No. 2, 151 (1976).
3. I. P. Lapin, in: Symposium on Pharmacological Agents and Biogenic Amines in the Central Nervous System, Budapest (1973), p. 149.
4. I. P. Lapin, Life Sci., 19, 1479 (1976).