Life Sciences Vol. 19, pp. 1479-1484, 1976. Pergamon Press
Printed in the U.S.A.

DEPRESSOR EFFECT OF KYNURENINE AND ITS METABOLITES IN RATS

I. P. Lapin

Laboratory of Psychopharmacology
Bekhterev Psychoneurological Research Institute
Leningrad 193019 USSR

(Received in final form June 19, 1976)

Summary

Kynurenine in doses of 0.2 ng to rats weighing 160-240 g elicited a measurable decline in blood pressure. The depressor effect increased with dosage and reached a maximum of about 30 mm Hg at a dose of approximately 100 ug. At higher doses (400 to 2000) ug kynurenine elicited a pressor response of about 15 mm Hg. Other kynurenines tested also lowered blood pressure. It is possible that the increased formation of kynurenine and its metabolites is involved in disturbances of circulation under stress, when the formation of these compounds is increased by activation of liver tryptophan pyrrolase.

Previous studies describing the influence of kynurenine on the vascular effects of biogenic amines (1,2,3) yielded preliminary results suggesting that kynurenine itself lowered the systemic blood pressure of rats. The present study shows that very low doses of kynurenine do indeed elicit a hypotensive response.

Methods

Albino rats of both sexes (mainly females), weighing 160-240 g (Rappolovo farm), were anesthetized with urethane (1.75 g/kg) administered IV. Blood pressure was measured via the carotid artery, utilizing a system of polyethylene tubes filled with a solution of 1500 units of heparin per ml of saline.

Kynurenine (free base or the sulfate monohydrate) and the following metabolites were studied: 3-hydroxykynurenine (free base), 3-hydroxyanthranilic acid, anthranilic acid, nicotinic acid, quinolinic acid and picolinic acid. Each compound was dissolved in water and adjusted with sodium hydroxide to approximately pH 7 for injection in 0.1 ml of vehicle into the femoral vein. The injection time was 3 seconds or less.

Results and Discussion

Of the substances tested, kynurenine itself exibited by far the greatest depressor effect and detailed studies were restricted to this substance.

The threshold dose of kynurenine which produced a measurable

hypotensive effect was 0.2 ng (mean of 34 animals - all doses cited in text and figures represent amount per rat). This dose varied between animals but was reproducible in the same animal. In all tests the response differed markedly from control values; the mild decrease in blood pressure produced by the injection of saline alone (1-3 mm Hg) lasted only 5 to 7 seconds. Threshhold doses of other kynurenines were as follows: picolinic and quinolinic acids, 1.0 mg; 3-hydroxykynurenine, 3-hydroxyanthranilic acid, anthranilic acid and nicotinic acid, 2.0 mg.

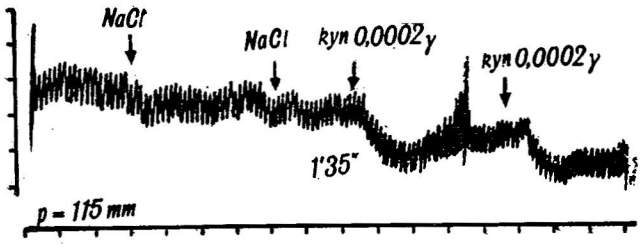

FIG. 1

Depressor Effect of the Threshold Dose of Kynurenine (0.2 ng).

Scale: blood pressure; 10 mm Hg increments; time, 5 second intervals. Initial blood pressure level was 115 mm Hg. Speed of drum was 1 cm/sec. Total duration of the depressor effect was 1 minute, 35 seconds.

The duration of the depressor effect of kynurenine increased with dosage and a peak response of 20-32 mm Hg was elicited by doses of about 100 ug.

TABLE 1

Depressor Effect of Kynurenine on Systemic Blood Pressure in Rats

	Dose (ng)	Depressor Action (mm Hg)	Duration (sec)
Threshold Effect	0.2 (0.01 - 2.0)	11.5 (10.4 - 12.1)	60 (10 - 100)
Maximum Effect	1.25×10^5 (0.8×10^5 - 2×10^5)	19.7 (15 - 32)	380 (300 - 480)

At higher doses (400-2000 ug) kynurenine produced a diphasic response. A transient hypotensive response (4-6 mm Hg) for 10-15 seconds was followed by a rise in blood pressure (12-16 mm Hg) which persisted two to three minutes.

In doses of 20-200 ng kynurenine produced hypotension which was similar to that produced by acetylcholine and serotonin (Fig. 2). However, at higher doses the latter two substances produced considerably greater hypotensive effects than did kynurenine.

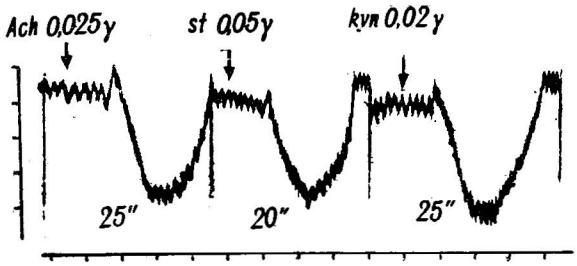

FIG. 2

Comparison of Depressor Effects of Kynurenine, Acetylcholine, and Serotonin

Scale: blood pressure, 10 mm Hg increments; time, 5 second intervals. Initial blood pressure level was 115 mm Hg. Speed of drum was 1 cm/second. Total duraction of the depressor effects of kynurenine (kyn), acetylcholine (ach) and serotonin (st) were 25, 20 and 25 seconds respectively.

A dose response relationship was observed for all kynurenines tested, but in only about half of the experiments. This was also true for acetylcholine and serotonin. Perhaps systemic blood pressure is too complex a phenomenon to reflect accurately a dose-response relationship.

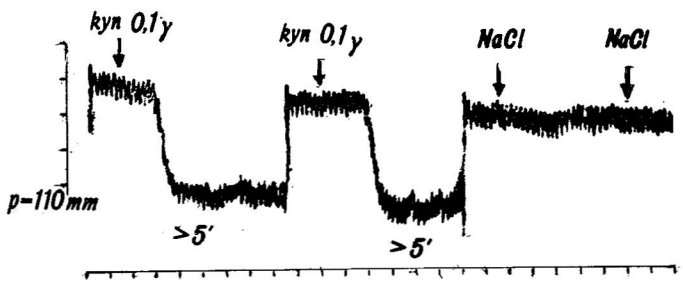

FIG. 3

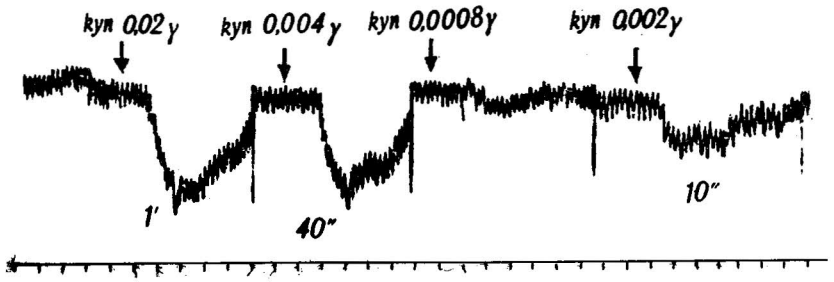

FIG. 3

Possible Dose-Response Relationship for the Depressor Effect of Kynurenine. Low Dose Range

Scale: blood pressure, 10 mm Hg increments; time, 5 second intervals. Initial blood pressure level was 110 mm Hg. Speed of drum was 1 cm/sec. Total duration of the effect of various doses of kynurenine show was greater than 5 minutes; 1 minute; 40 seconds; etc.

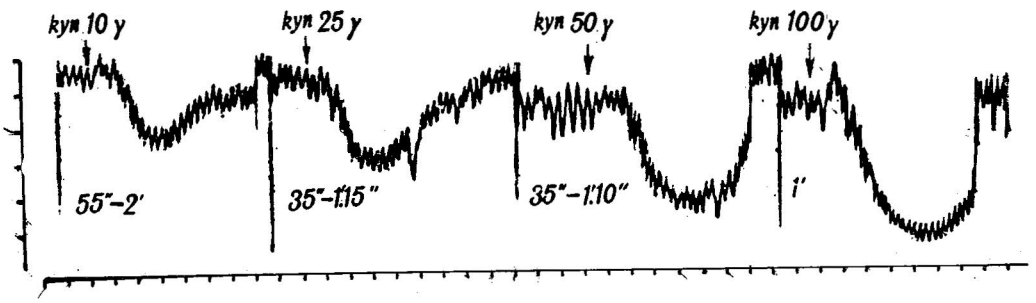

FIG. 4

Possible Dose-Response Relationship for the Depressor Effect of Kynurenine. High Dose Range

Scale: blood pressure, 10 mm Hg increments; time, 5 second intervals. Initial blood pressure level was 105 mm Hg. Speed of drum was 1 cm/sec. The two times shown for each dose represent the end of the initial reaction effect (e.g., 55 seconds) and the return of blood pressure to pretest level after slow elevation (e.g., 2 minutes).

The hypotensive response to kynurenine was not affected by bilateral vagotomy or pretreatment with atropine (10 mg/kg IP, 1 hour before kynurenine). Thus the lowered blood pressure may result from a direct action on the blood vessels. However, the hypotensive action was antagonized by scopolamine (in doses of 25-50 ug per rat, IV) in four of eight experiments. Antiserotonins methysergide (50 and 100 ug), LSD-25 (10-25 ug) and MCE (1,6-dimethyl-8-p carbo-benzylhydroxy-aminomethyl-10-alpha-ergolin, 1-20 ug) did not prevent the depressor effect of kynurenine.

A comparison of kynurenine metabolites in experiments using doses of 5.0, 6.0 and 7.0 mg showed that the order of decreasing effectiveness is as follows: nicotinic acid, quinolinic acid, 3-hydroxykynurenine, anthranilic acid, picolinic acid, and 3-hydroxyanthranilic acid.

In conclusion, the data show that kynurenine in very low doses lowers the blood pressure of rats. The formation of kynurenine is enhanced under stress conditions, through the activation of liver pyrrolase by corticosteroids (4). Thus the possibility exists that kynurenine (and probably its metabolites) are involved in the disturbances of circulation which occur under stress conditions.

References

1. I. P. LAPIN, In: Proceedings of the First Congress of Hungarian Pharmacological Society, Budapest, October 18-22, 1971. Akadémiai Kiadó, 149 (1973).
2. I. P. LAPIN, Psychopharmacologia 26 237 (1972).
3. I. P. LAPIN, Pharmakopsychiatr. Neuropsychopharmakol. 6 273 (1973).
4. F. M. CHIANCONE, Acta Vitaminol. Enzymol. 21 37 (1967).