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Kynurenines and Audiogenic Excitement in Mice

IZYASLAV P. LAPIN

Laboratory of Psychopharmacology, Bekhterev Psychoneurological Research Institute, Leningrad, USSR

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LAPIN, I. P. *Kynurenines and audiogenic excitement in mice.* PHARMAC. BIOCHEM. BEHAV. 13(1) 9–15, 1980.—Adult male and female albino mice (SHR strain) responded to sound by locomotor excitement (73–81%), running fits (33–47%), clonic convulsions (15–25%), tonic extension (10–22%) and lethality (7–17%). Intraperitoneal injection of metabolites of tryptophan on the kynurenine pathway (Kynurenines): DL- and L-kynurenine sulfate, 3-hydroxyanthranilic, anthranilic, quinolinic, picolinic, nicotinic and xanthurenic acids (in doses of 200 and 400 mg/kg) decreased audiogenic excitement. Intraventricular injection of kynurenines (1–50 mcg), even in stimulating and convulsive doses, had no effect. Intraventricular injection did not induce an audiogenic response in C_{57} BL/6 and CC_{57}BR mice which are not normally susceptible to sound. Pentylenetetrazol and strychnine injected intraventricularly in up to lethal dosages did not modify audiogenic excitement. Decrease of audiogenic excitement by kynurenines is suggested to be partially related to lowering of body temperature.

Kynurenines Tryptophan metabolites Audiogenic excitement Convulsants

METABOLITES of tryptophan on the kynurenine pathway (kynurenines) possess various neurotropic activities [14–16]. They produce seizures in adult mice after intraventricular injection [17], and in immature rats during the first 10 days of postnatal ontogenesis after intraperitoneal injection [18]. The most active metabolites, dl-kynurenine and quinolinic acid, increased the interparoxysmal epileptiform discharges and electrographic correlates of the seizure on the EEG in frogs with epileptogenic focus induced by injection of penicillin into the primordial hippocampus [8]. So, kynurenines (except anthranilic acid which was inactive in all studies) attracted attention as endogeneous compounds which might be involved in the genesis of seizures [17,18]. Recently kynurenines have been determined in the human [10], rat [6,10] and mouse [7] brain. One of the current objectives in studying kynurenines in our laboratory was their interaction with convulsants, both chemical (strychnine, pentylenetetrazol, thiosemicarbazide, etc.) and physical (electric current and sound). The purpose of the present study was to find out whether kynurenines modify reaction to sound.

Throughout the last decade in our laboratory various studies [11, 12, 22, 23] on audiogenic seizures have been carried out using genetically susceptible adult rats, but for this study we have chosen mice of the SHR strain (bred from Swiss) because the major volume of information about convulsive effects of kynurenines has been obtained using this subject. It is well known that the most widely used subjects employed in studies of audiogenic seizures are mice of certain strains (e.g. DBA) and/or mice of various strains aged about 3 weeks of postnatal ontogenesis [5,24]. For the present study (taking into account the number of kynurenines, wide range of doses, and various procedures) we needed a great number of mice, and our source could supply only SHR adult mice. For this reason we tested these mice for susceptibility to sound in a chamber we used in our previous studies on rats. We expected that they would not respond to sound. Less than a quarter of the controls responded by clonic convulsions, but about two-thirds responded by locomotor excitement and more than one-third responded by running fits (wild running). These findings at the beginning of the present study fit our purpose to find out whether kynurenines enhance audiogenic seizures. Moreover, in agreement with our expectation we tested two strains of mice, which are not susceptible to sound, C_{57}BL/6 and CC_{57}BR, predicting that kynurenines probably would modify this nonsensitivity, like, e.g., acoustic priming [20,26]. Contrary to our expectations kynurenines modified motor excitement much more than seizures in SHR mice, therefore we focused our attention on audiogenic excitement.

METHOD

Animals

Adult albino SHR mice (bred from Swiss) of both sexes from the Rappolovo farm were used. We do not know the exact age of the animals, but according to information received from the farm and their body weights (Table 1), the mice were about 7–9 weeks old. In one series of experiments adult male mice C_{57}BL/6 and CC_{57}BR weighing 21–23 g and 27–30 g, respectively, were used. Their age was approximately 11–12 weeks.

Sound Chamber

A chamber made from transparent Plexiglas (28×47×50 cm) with an electric bell of the S-6 No007 type on the top was used. The bell sounded for 1 min at a level of 100 db.

TABLE 1
AUDIOGENIC EXCITEMENT IN SHR MICE (CONTROL)

Sex	Body weight* (g) mean ± SE	Season	Number of mice					
			Total	LE	RF	CC	TE	L
Male	16.8 ± 0.4	June–July 1978	270 (100%)	220 (81.4%)	127 (47%)	64 (23%)	46 (17%)	28 (10%)
Male	20.9 ± 0.6	November 1978–February 1979	160 (100%)	117 (73.1%)	63 (33.4%)	25 (15.6%)	17 (10.6%)	11 (6.9%)
Male	23.2 ± 1.1	June–July 1977	496 (100%)	154 (31%)	131 (26.4%)	75 (15.1%)	not registered	38 (7.7%)
Female	22.0 ± 1.2	October 1978–February 1979	80 (100%)	59 (73.7%)	33 (41.2%)	20 (25%)	18 (22.5%)	14 (17.5%)

Abbreviations: Audiogenic excitement: LE—locomotor excitement, RF—running fit, CJ—compulsive jumping, CC—clonic convulsions, TE—tonic extension, L—lethality.
*Mean body weight was calculated for groups of 100 male mice and 80 female mice.

Semiautomatic Apparatus

Intraventricular injections to conscious mice were made by means of the apparatus [28] used in our previous studies on kynurenines [17]. Kynurenines were injected in water solutions in a volume of 0.005 ml into the right cerebral ventricle. Their solutions had pH's of about 4.0–6.5. Highest concentrations (2%) of DL- and L-kynurenines and quinolinic acid had pH's of about 2.0. Control injections of solutions of HCl (pH 2.0–6.0) did not produce any effect. Controls were injected with saline. Each experiment began with a testing of accuracy of injection in 5–6 mice using a 0.25% solution of methylene blue. One min after injection these mice were decapitated. Homogenous distribution of methylene blue in a system of brain ventricles testified accurate injection.

Drugs

All kynurenines, except nicotinic acid (which is supplied from a drug store), were supplied from Sigma or Calbiochem Chem. Co. They were used in water solutions. Intraperitoneal injections were made in a volume of 0.01 ml/g. Controls were treated with the same volume of distilled water.

Imipramine hydrochloride (Melipramine, Egypt), haloperidol (Gedeon Richter), adrenergic drug AW 151129 (imidazo-quinazoline derivative, Wander A.G.) [27] were injected 1 hr prior to nicotinic acid (Table 4) or 1 hr prior to apomorphine hydrochloride, or the reserpine-like drug benzoquinolizine derivatives Ro 4-1284 (Hoffmann La Roche) (Table 5). All drugs were used in water solutions.

Procedure

Mice were placed into the sound chamber 10 min after intraventricular injection of kynurenines (Table 3) or 30 min after their intraperitoneal injection (Table 2) or injection of apomorphine or Ro 4-1284 (Table 5). In some experiments the time interval between intraperitoneal injection and sound chamber treatment was 1 hr (Table 5). Rectal temperature was measured by a medical electrothermometer. The last measurement of body temperature was made immediately prior to placing mice into the chamber. Animals were placed in the chamber in groups of 4. After a 30 sec adjustment period the sound was switched on for 1 min. Room temperature and temperature in the chamber was 19–20°C (if not, other temperature was noted—Table 6). The following responses to sound were recorded: (1) locomotor excitement (LE), (2) running fits (RF) or wild running, (3) compulsive jumping (CJ) on walls, (4) clonic convulsions (CC), (5) tonic extension (TE) and (6) lethality (L). Latency to begin responses and survival time was also recorded by a stopwatch. Mice were tested in the chamber only once, except in a series where the offset-procedure [3] was used.

RESULTS

Control adult male and female SHR mice appeared to be susceptible to strong sound responding by the same behavioral reactions: LE, RF, CC, TE (Table 1) as strains and ages particularly sensitive to sound, e.g. DBA and 21–22 days old mice. The younger mice (those having lower body weights), displayed a higher percentage of animals responding in all reaction categories. Female SHR mice seem to be slightly more susceptible to sound than males (Table 1). Audiogenic seizures (CC and TE) were observed in 10–25% of the animals while LE and RF were much more frequent.

Control adult male C_{57}BL/6 and CC_{57}BR mice did not respond to sound, although some individuals exhibited slight or moderate LE.

Kynurenines in doses of 0.1–100 mg/kg, IP did not modify behavioral responses to sound in SHR mice. Doses of 200 and 400 mg/kg IP diminished those responses (Table 2). A dose of 200 mg/kg was effective for nicotinic, anthranilic, picolinic and quinolinic acids (in a declining order of potency). This dose of effective kynurenines lowered body temperature (Table 2). The same dose of ineffective kynurenines: DL- and L-kynurenine, xanthurenic and

TABLE 2

EFFECT OF INTRAPERITONEAL INJECTION OF KYNURENINES ON AUDIOGENIC EXCITEMENT

Kynurenines	Dose mg/kg IP	Mice total	Audiogenic excitement (number of mice) LE	RF	CC	TE	L	Hypothermia $-\Delta t°C$ mean ± SE
—	—	270 (100%)	220 (81.4%)	127 (47%)	64 (23%)	46 (17%)	28 (10%)	—
—	—	24+	19.5	11.3	5.7	3.8	2.0	—
—	—	16+	13	7.5	4	2.3	1.7	—
DL-K	200	16	10	3	2	1	1	2.3 ± 0.2
	400	16	5*	2*	0*	0	0	4.2 ± 0.6
L-K	200	24	13	8	4	2	1	2.4 ± 0.3
	400	16	2†	2*	0*	0	0	4.5 ± 0.5
QA	200	24	9†	8	5	2	1	4.5 ± 0.7
	400	15	11	5	1	1	1	2.0 ± 0.3
PA	200	24	10†	4*	4	3	1	7.5 ± 0.9
	400	16	7*	3	1	1	1	7.5 ± 0.7
NA	200	56	18†	4‡	3†	1†	0†	4.8 ± 0.3
	400	16	4†	0‡	0‡	0†	0†	6.6 ± 0.2
XA	200	16	8	3	1	1	0	1.9 ± 0.2
	400	16	7	0	0	0	0	3.7 ± 0.5
3-HAA	200	16	8	4	2	1	1	2.6 ± 0.4
AA	200	46	12‡	7‡	2†	2†	1*	3.6 ± 0.2
	400	16	2‡	0‡	0†	0*	0*	6.4 ± 0.3

Abbreviations: Kynurenines: DL-K—DL-kynurenine sulfate, L-K—L-kynurenine sulfate, 3-HAA—3-hydroxyanthranilic acid, AA—anthranilic acid, PA—picolinic acid, QA—quinolinic acid, XA—xanthurenic acid, NA—nicotinic acid, NAM—nicotinamide.

*$p<0.05$; †$p<0.01$; ‡$p<0.001$

+Calculative means for 24 and 16 mice of controls, respectively.

3-hydroxyanthranilic acids lowered body temperature to a lesser degree. A dose of 400 mg/kg was effective for all kynurenines tested (this dose was not tested for 3-hydroxyanthranilic acid) except quinolinic acid which was the least hypothermic (Table 2). A dose of 400 mg/kg was more hypothermic than a dose of 200 mg/kg (for quinolinic acid that was not the case). The most marked diminution of behavioral responses to sound was observed for LE and RF.

Intraventricular injection of kynurenines in doses of 0.05–50 μg did not modify audiogenic excitement (Table 3). Highest doses of the most active convulsive kynurenines (DL- and L-kynurenine—25 and 50 μg, quinolinic acid—2.5 μg) produced motor excitement prior to the sound chamber (Table 3). Doses tested intraventricularly produced about the same hypothermia (data are not presented in Table 3) as the highest doses of kynurenines administered intraperitoneally. Intraventricular injection of two convulsants, pentylenetetrazol and strychnine, in up to lethal dosages did not change audiogenic excitement (Table 3).

In C_{57}BL/6 and CC_{57}BR mice intraventricular injection of DL-kynurenine (1–25 μg) or quinolinic acid (0.1–5 μg) did not induce audiogenic excitement.

Repeated exposure to sound immediately after the first session in a chamber did not induce excitement, the so called "offset-induced reaction" [3]—in either control SHR, C_{57}BL/6 and CC_{57}BR mice or in animals of all strains treated intraventricularly with kynurenines.

Pretreatment with imipramine or haloperidol which did not change audiogenic excitement in controls diminished the hypothermia produced by nicotinic acid (taken as an example of kynurenines) but did not modify the decrease of LE (Table 4).

An adrenergic drug AW 151129 prevented hypothermia produced by apomorphine but did not modify the decrease of LE produced by this drug (Table 5). AW 151129 diminished hypothermia produced by a benzoquinolizine Ro 4-1284 and did not change audiogenic excitement (Table 5).

In a series of experiments apomorphine diminished audiogenic excitement only when used at hypothermic doses (1 mg/kg and higher).

Exposure of mice for 1 hr to room temperatures of 14, 20, and 28°C did not change their body temperature, but mice kept at 28°C responded in a sound chamber kept at 15°C by more frequent LE and RF than the other two groups (Table 6). Exposure for 1 hr at 13° and 20°C did not lower body temperature in either grouped or isolated mice (Table 6) and they, therefore, were not tested in a chamber. Exposure for 20 hr at 13°C lowered body temperature as compared with mice kept at 20°C. However, after 2 hr at a room temperature of 20°, the "cooled" mice became more "warm" than the

TABLE 3

EFFECT OF INTRAVENTRICULAR INJECTION OF KYNURENINES ON AUDIOGENIC EXCITEMENT

Kynurenines	Dose mcg	Mice total	Audiogenic excitement (number of mice) LE	RF	CJ	CC	TE	L	Effect prior to sound
Saline	—	24	16	7	6	3	3	0	
NA	5	11	4	2	2	1	1	0	
	50	12	4	1	1	0	0	0	LE=RF=CC=2
PA	5	12	5	1	0	0	0	0	
	50	12	6	3	2	1	1	0	LE=RF=3
AA	5	12	7	4	2	0	0	0	
	50	12	5	3	0	0	0	0	
Saline	—	12	5	2	2	2	1	0	
DL-K	25	12	9	5	5	2	1	1	LE=1
QA	2.5	12	7	3	2	1	0	0	LE=RF=6
Saline	—	24	15	7	6	4	4	4	
DL-K	1	12	5	2	1	1	1	1	
QA	1	12	7	2	1	1	0	0	
Saline	—	24	12	1	1	1	1	1	
3-HAA	5	12	5	2	2	2	2	1	LE=3
	50	12	6	1	1	0	0	0	
XA	5	12	9	0	0	0	0	0	LE=RF=3
	50	12	7	3	0	1	1	1	LE=RF=2
Saline	—	12	7	5	4	4	4	4	
L-K	5	12	7	3	2	2	2	2	LE=RF=2
	50	10	2	1	0	1	1	1	LE=RF=4; CC=3
Saline	—	24	16	6	3	3	2	1	
NAM	0.5	24	21	13*	10*	7	4	3	
	5	12	9	4	4	3	2	0	
	50	12	10	6	4	1	1	1	
	125	12	10	6	2	2	2	2	
Saline	—	24	19	9	6	3	2	1	
NAM	0.05	12	9	3	3	2	1	1	
	0.5	12	7	3	2	1	1	1	
Saline	—	12	8	3	2	1	1	1	
NAM	0.05	12	7	2	1	1	1	1	
	0.5	24	18	8	5	2	1	1	
Saline	—	24	12	6	4	2	2	2	
NAM	0.05	12	8	2	2	1	1	0	
	0.5	12	6	1	1	1	1	1	
			convulsants						
Saline	—	24	14	8	3	3	1	0	
Pentylenetetrazol	25	12	4	0	0	0	0	0	
	125	12	6	4	3	2	0	0	
	250	7	5	3	2	2	2	2	L=5/12
Strychnine	2.5	12	4	1	0	0	0	0	
	5	10	7	4	4	2	2	2	L=2/12

Abbreviations: see Tables 1 and 2.
*$p<0.05$.

TABLE 4

EFFECT OF IMIPRAMINE AND HALOPERIDOL ON NICOTINIC ACID INDUCED HYPOTHERMIA AND PROTECTION AGAINST AUDIOGENIC EXCITEMENT

Pretreatments					Number of mice					
1		2		Hypothermia $-\Delta t°$ 60 min						
Drug	mg/kg	Drug	mg/kg	mean ± SE	Total	LE	RF	CC	TE	L
1. Dist. water	—	Dist. water	—	0.4 ± 0.1	16	8	4	3	3	1
2. Dist. water	—	NA	200	4.5 ± 0.4‡	8	1*	1	1	1	0
3. Imipramine	5	NA	200	2.5 ± 0.2‡	8	2	2	1	1	0
4. Haloperidol	0.05	NA	200	1.8 ± 0.3‡	8	2	0	0	0	0
1. Dist. water	—	Dist. water	—	0.4 ± 0.05	16	10	2	1	1	1
2. Dist. water	—	NA	200	4.2 ± 0.7‡	8	0*	0	0	0	0
3. Imipramine	5	NA	200	2.3 ± 0.5*	8	0	0	0	0	0
4. Haloperidol	0.05	NA	200	3.5 ± 0.2	8	1	1	0	0	0

Abbreviations: see Tables 1 and 2.

Results of two experiments (July 13 and 20, 1978) are presented. Comparisons made: group 2 with group 1, groups 3 and 4 with group 2. Statistical significance of a difference—see Table 2.

TABLE 5

EFFECT OF AN ADRENERGIC DRUG AW 151129 ON HYPOTHERMIA INDUCED BY APOMORPHINE AND Ro 4-1284 IN RELATION TO RESPONSE TO SOUND

Pretreatments					Number of mice					
1		2		Hypothermia $-\Delta t°$ 60 min						
Drug	mg/kg	Drug	mg/kg	mean ± SE	Total	LE	RF	CC	TE	L
1. Dist. water	—	Dist. water	—	0.1 ± 0.04	16	8	2	0	0	0
2. AW 151129	5	Dist. water	—	0.9 ± 0.2	8	7	4	0	0	0
3. Dist. water	—	Apomorphine	5	3.5 ± 0.5	8	1*	0	0	0	0
4. AW 151129	5	Apomorphine	5	1.6 ± 0.3*	8	1*	0	0	0	0
5. Dist. water	—	Ro 4-1284	20	5.3 ± 0.6	8	4	3	2	2	2
6. AW 151129	5	Ro 4-1284	20	2.1 ± 0.4†	8	5	4	4	4	3

Abbreviations: see Tables 1 and 2. Statistical significance of a difference—see Table 2.

compared group which maintained constant body temperature. Mice with higher body temperatures had higher rates of all responses to sound except L (Table 6). Lowering of body temperature in mice treated with chlorpromazine was associated with decreased rate of LE and RF (Table 6).

DISCUSSION

The decrease of audiogenic excitement after intraperitoneal administration of kynurenines raises the following questions: (1) is this effect central or peripheral (or both), (2) is it specific or nonspecific, (3) is it related to hypothermia or not.

DL-kynurenine penetrates into the brain in mice after intraperitoneal injection of doses of 0.5 and 5 mg/kg increasing brain concentrations of this metabolite by 94 and 86% respectively [7]. This has been observed in male Br/W mice. We do not know whether the same is true for SHR mice. Moreover, we do not know anything about penetration of other kynurenines tested. If, indeed, they penetrate into the brain, an expected increase of their brain levels after doses of 200 and 400 mg/kg would be expected to be much higher than that reported for doses of 0.5 and 5 mg/kg. Hypothermia produced by intraperitoneally administered kynurenines suggests their central action because a lowering of body temperature was observed after intraventricular injection of their doses (25 and 50 μg) which did not alter body temperature when injected intraperitoneally or subcutaneously. It remains puzzling why kynurenines, even in doses of 200–400 mg/kg (the present study) or 800–1000 mg/kg [17] which presumably penetrate into the mouse brain in high amounts, do not produce excitement or seizures, effects which are observed after intraventricular injection [17]. Perhaps the increase in concentrations of kynurenines in brain structures which are involved in seizures after intraperitoneal injection is smaller than that following intraventricular injection.

One can not exclude the possibility that some peripheral effects of intraperitoneally injected kynurenines may counteract their central stimulant or/and convulsive effect.

The protective effect of high doses of intraperitoneally injected kynurenines seems to be nonspecific because it is partially related to hypothermia, a nonspecific effect, and a similar and even much more successful protection can be achieved with a great variety of drugs [12,24] whose common

TABLE 6

RELATIONSHIP BETWEEN ROOM, CHAMBER AND BODY TEMPERATURE AND AUDIOGENIC EXCITEMENT

No. of experiment	Groups	Temperature °C				Number of mice						
		Room	Body mean 60 min	Body mean 120 min	Body mean 180 min	In a sound chamber	Total	LE	RF	CJ	CC	TE	L
		1 hr											
I	1	14	37.7	36.7	—	15	12	9	1	1	0	0	0
	2	20	37.6	36.6	—	15	12	6	0	0	0	0	0
	3	28	38.0	36.9	—	15	12	11*	7*	0	0	0	0
II	1	20	36.9	36.3	36.3		6 +g						
	2	20	37.0	36.5	36.3		6 i	not tested in a chamber					
	3	13	37.1	36.7	35.3		6 g						
	4	13	37.0	35.8	35.5		6 i						
		20 hr											
III	1	13	33.6 ±0.2	37.1 ±0.2	—	20	12	9	6	2	4	4	1
	2	20	35.2 ±0.3†	35.9 ±0.3†	—	20	12	4*	1*	0	0*	0*	0
IV	1++	20& 13	37.0 ±0.3	—	—	18	10	8	4	1	2	0	0
	2++	20& 13	34.8 ±0.5‡	—	—	18	8	0*	0*	0	0	0	0

+g—grouped.
i—isolated.
++Pretreated with chlorpromazine (0.5 mg/kg) 20 hr prior to first measurement of temperature. Mice (24 animals) were kept for 20 hr under room temperature 20°C. Then animals were kept for 1 hr under room temperature 13°C. Those who had body temperature higher than 36.8°C were gathered in a group 1 (10 mice). Those with body temperature below 35.8°C were taken in a group 2 (8 mice).

features are hypothermia and behavioral inhibition [1, 12, 23].

The probable role of hypothermia in the protective effect of kynurenines is puzzling. There are data which support both pro and con positions. Pros are as follows. (1) Kynurenines (IP) are active in doses which lower body temperature. (2) The same is true for apomorphine. The latter observation agrees with data reported in the literature [1]. All drugs which protected against audiogenic seizures in DBA/2 mice (apomorphine, ergot alkaloids) lowered body temperature, and the greatest decrease in temperature occurs at the time of maximal protection. (3) Lowering of body temperature by a treatment with chlorpromazine decreased audiogenic excitement and elevation of body temperature increased it. (4) In general, in cooled mice and rats at temperatures below 28–27°C epileptogenic acoustic stimulus becomes completely ineffective [2]. The following cons have to be taken into consideration. (1) The metabolite which produced the greatest hypothermia among kynurenines tested, picolinic acid, was not the most active in diminishing audiogenic excitement. (2) Kynurenines injected intraventricularly lowered body temperature similarly to those injected intraperitoneally but the former are not protecting. Perhaps the protective influence of the hypothermic effect of intraventricularly injected kynurenines is "neutralized" by their stimulating effects. (3) Diminution of apomorphine or nicotinic acid produced hypothermia by the preinjection of imipramine or AW 151129 did not decrease the protective effect against audiogenic excitement. This argument requires some comments. Principally, imipramine affects audiogenic excitement not only through diminishing hypothermia, but also through its proper protective action (presumably related to potentiation of brain noradrenaline). This latter action might explain why diminution of apomorphine hypothermia, a well known effect of imipramine [13, 19, 25], does not lead to a decrease of the protective effect of apomorphine. A dual effect on audiogenic excitement is evident for Ro 4-1284 as well. Due to depletion of brain monoamines it enhances audiogenic seizures ([9] and our observation in the present study) while its hypothermic effect has an opposite influence. Perhaps the observed diminution of the hypothermic effect of Ro 4-1284 by AW 151129 was not sufficient to enhance audiogenic excitement. A slight tendency of such enhancement was observed (Table 5). Weighing all pros and cons of the importance of hypothermia on the protective action of kynurenines one may suggest that this action is partially related to lowering of body temperature.

Lack of enhancement of audiogenic excitement after intraventricular injection of kynurenines was opposite to our expectations. However, typical convulsants, pentylenetetrazol and strychnine, appeared to be ineffective as well when injected both intraventricularly and intraperitoneally. Data in the literature on the effect of convulsants on audiogenic seizures are contradicting. Perhaps audiogenic excitement, including seizures, is not an appropriate model to study

genuine convulsions and convulsants. Similar skepticism has been expressed about audiogenic seizures in rats as a model for anticonvulsants [12]. Nevertheless the effect of kynurenines on audiogenic excitement has to be taken into consideration in studies on the role of tryptophan in audiogenic behavioral responses (e.g. [21]). Although intraventricularly injected kynurenines did not enhance audiogenic seizures, convulsive effects of these metabolites of tryptophan [8, 17, 18] suggest that increases in their concentrations in the brain may be involved in the genesis of seizures, e.g. so-called stress convulsions [4] where hormonal induction of brain tryptophan pyrrolase is probable.

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