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NEUROCHEMICAL EFFECTS OF IMIPRAMINE AND AMPHETAMINE IN AGGRESSIVE MOUSE-KILLING (MURICIDAL) RATS*

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Abstract—Mouse killing (muricidal) rats have been shown to have higher forebrain levels of norepinephrine than control non-killer rats. In addition, they elicit higher rate constants for the decline of ^{3}H-norepinephrine given intraventricularly into the brain and, consequently, much higher turnover rates for norepinephrine than controls (non-killers). These differences have not been obtained in the hindbrain region. No differences in the levels or rate of turnover of serotonin have been observed in either brain region studied. Furthermore, the elevated rate constant seen in forebrain norepinephrine turnover studies using the isotopic procedure has not been observed in non-isotopic turnover studies in which α-methyl-*p*-tyrosine was used to inhibit tyrosine hydroxylase. Differences between the two methods may be attributable to the inhibitory action of muricidal behavior by α-methyl-*p*-tyrosine. The effects of imipramine and amphetamine on norepinephrine turnover in the forebrain of killer rats have been compared with those of drug-treated, non-killer rats as well as with untreated rats. Both agents, given at doses which inhibit mouse-killing behavior, accelerate the turnover rate of brain norepinephrine in non-killer rats; however, they do not influence the previously elevated levels of norepinephrine nor the elevated rate constants and turnover rate for this amine in killer rats. Suggestions involving altered reuptake mechanisms, as well as divergent effects of the antidepressants in muricidal rats, have been offered to explain these differences.

RECENTLY Valzelli[1] has reviewed the various methods for producing aggressive behavior in the laboratory animal. In humans, it has been shown that "sensory deprivation," a condition similar to isolation, results in a schizophrenic-like syndrome.[2–4] By analogy, a common laboratory model to study aggressive behavior has been the isolated fighting mouse.[5, 6] Pharmacologists have used this model to evaluate the effects of drugs, with the aim of finding selective anti-aggressive agents and, also, to gain further knowledge of biochemical changes in the central nervous system of aggressive animals.[1, 6, 7]

Another commonly used model of aggressive behavior is the mouse-killing or muricidal rat, as described by Horovitz *et al.*,[8, 9] which can be obtained by genetic selection. These rats, which show a spontaneous interspecific aggressiveness toward mice, a behavior which was found to be independent from hunger, were first described by Karli *et al.*[10, 11] Horovitz has shown that this behavior could be selectively

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blocked by certain classes of drugs, such as antidepressants, antihistaminics and stimulants.[9]

It has been shown that lesions of the amygdala or interruption of the amygdala-hypothalamic tract block the muricidal response, while lesions of the septal area, although not an inducer of this type of behavior in non-killer rats, intensify the voracious attack upon mice by killer rats.[9, 12] Horovitz[13] has correlated the relationship of the amygdala to the symptoms of depression and has postulated the implication of this region to the mechanism of tricyclic antidepressant agents. Several reports have shown that emotional changes induce alterations in brain monoamines.[14–16] In addition, mice subjected to prolonged isolation become more sensitive to drugs such as fencamfamine and amphetamine.[17–19] Neurochemical studies in male mice made aggressive by isolation have shown that serotonin turnover occurs at a lower rate.[20] On the other hand, Welch and Welch[21] have reported that noradrenergic neurons of mice living in groups seem to be adapted to a higher synthesis rate of norepinephrine and that the rate of synthesis of this amine diminishes slowly when mice are removed from the stimulus of grouping and placed in isolation.

In a recent communication from this laboratory, we reported an increased level of forebrain norepinephrine in the muricidal rat, with a concomitant increase in the turnover rate of this amine.[22] The purposes of this paper are to report the kinetics of brain norepinephrine and serotonin in the mouse-killing rat and the influence of imipramine and amphetamine on norepinephrine turnover in this model of aggression. These representative agents have been reported to block selectively the muricidal response and are both used clinically in certain types of depression.

METHODS

Male Long–Evans rats (Blue Spruce Farms, Altamont, N.Y.) weighing between 200 and 240 g were used throughout these studies. After arrival, all animals were housed individually for 6 weeks in cages measuring 6 × 12 in. They were permitted water *ad lib.* and were kept on a restricted food intake of approximately 15 g a day of solid food. During this period, the animals were tested periodically for their ability to kill mice as described by Horovitz *et al.*[8, 9] From such a colony, rats were selected which had shown a positive mouse-killing response within 2 min of challenge for 3 consecutive days prior to use, while those which failed to show a response were used for control purposes. We have designated such animals as killer and non-killer rats respectively. This method of treatment historically resulted in the selection of approximately 40 per cent of the colony as killer rats. In some experiments reported in the Results section, we have used the term "normal rats"; these were non-killer rats who were kept in a grouped environment for the 6-week interval.

In each experiment, animals were sacrificed approximately 24 hr after the last presentation of mice. Rats were killed by decapitation and the whole brain was removed. The brainstem, including the cerebellum (hindbrain), was separated from the forebrain by a cut above the corpora quadrigemina, and both regions were immediately frozen until ready for analysis.

Norepinephrine turnover was calculated from the decline of specific activity after the administration of tritiated norepinephrine (^{3}H-NE), as described by Brodie *et al.*[23] In these studies DL-[7-^{3}H-NE] hydrochloride (5 μc/kg; specific activity, 6·7 c/m-mole; New England Nuclear Corp.) was injected into the lateral ventricle as described by

Noble *et al.*[24] For these studies, brief halothane (Ayerst Laboratories) anesthesia was used, and all rats recovered 2–3 min after ^{3}H-NE injection. ^{3}H-NE was diluted with an appropriate volume of Merle's solution* such that each animal received approximately 1 μc in a volume of 20 μl. At different time intervals, the animals were sacrificed and the brain was removed and dissected as described above. Norepinephrine (NE) was adsorbed on alumina according to the method of Neff and Costa,[25] and assayed fluorimetrically by the method of McGear and McGear.[26] ^{3}H-NE was added to Bray's solution and counted in a Packard TriCarb scintillation spectrometer.

Serotonin (5HT) turnover studies were performed using the non-isotopic concepts of Tozer *et al.*[27] In these experiments the rate of 5HT accumulation was measured at various times after the intraperitoneal administration of pargyline (100 mg/kg). 5HT was extracted and assayed according to the method of Mead and Finger.[28]

Doses of imipramine hydrochloride and *d*-amphetamine sulfate were selected from pharmacologic studies in which near maximal inhibition of the muricidal response was obtained without serious motor impairment. In the turnover experiments, the drugs were administered 30 min prior to the intraventricular injection of ^{3}H-NE and sacrificed 1, 2 and 4 hr thereafter. The doses of each agent used refer to the amount of salt given. In order to avoid any diurnal changes in brain amines, all studies were conducted between 10 a.m. and 2 p.m.

RESULTS

Norepinephrine steady state levels in the two regions of brain studied in both killer and non-killer rats are shown in Table 1. There is a 27 per cent increase of NE in the forebrain region of the killer rat compared to that of its control (non-killer). No apparent differences were obtained in the hindbrain region. When rats were given an

TABLE 1. BRAIN NOREPINEPHRINE TURNOVER IN NON-KILLER AND KILLER RATS*

Source	Type of animal	Steady state level (μg/g $\pm$ S.E.)	Rate constant (k[hr^{-1}] $\pm$ S.E.)	Turnover rate (μg/g/hr)
Forebrain	Non-killer	0·55 $\pm$ 0·01 (6)	0·15 $\pm$ 0·02 (18)	0·08
	Killer	0·70 $\pm$ 0·02 (12)†	0·28 $\pm$ 0·03 (36)†	0·20
Hindbrain	Non-killer	0·50 $\pm$ 0·01 (6)	0·27 $\pm$ 0·05 (18)	0·14
	Killer	0·53 $\pm$ 0·02 (12)	0·34 $\pm$ 0·03 (36)	0·17

* Rats were given an intraventricular injection of ^{3}H-NE (5 μc/kg) and were sacrificed at various times later. Rate constant and turnover rate were computed as described in Methods. Numbers in parentheses represent the number of animals.

† Significantly different from non-killer rats ($P < 0·01$).

intraventricular injection of ^{3}H-NE and the rate of its decline in brain was followed as a function of time (1, 2 and 4 hr), the rate constant (k) in the forebrain of the killer rat was found to be about twice that of the non-killer rat (Table 1). No such effects were observed in the hindbrain region. Due to an increase both in NE steady state levels in forebrain and in the rate constant, the turnover rate of killer rats was calculated to be 0·20 μg/g/hr as compared with 0·08 μg/g/hr in non-killer rats.

* Merle's solution can be made by dissolving NaCl, 8·98 g, KCl, 0·25 g, $CaCl_2$, 0·14 g, $MgCl_2$, 0·11 g, NaH_2PO_4, 0·07 g, urea, 0·13 g, and glucose, 0·61 g, in 1 l. of water.

TABLE 2. BRAIN SEROTONIN TURNOVER IN NON-KILLER AND KILLER RATS*

Source	Type of animal	Steady state level (μg/g $\pm$ S.E.)	Rate constant ($k[h^{-1}] \pm$ S.E.)	Turnover rate (μg/g/hr)
Forebrain	Non-killer	0·53 $\pm$ 0·01 (6)	0·40 $\pm$ 0·01 (24)	0·21
	Killer	0·53 $\pm$ 0·01 (6)	0·39 $\pm$ 0·01 (20)	0·21
Hindbrain	Non-killer	0·40 $\pm$ 0·02 (6)	0·40 $\pm$ 0·01 (24)	0·16
	Killer	0·40 $\pm$ 0·02 (6)	0·36 $\pm$ 0·01 (20)	0·14

* Rats were given 100 mg/kg i.p. of pargyline and sacrificed at various times later. Rate constant and turnover rate were calculated as described in Methods. Numbers in parentheses refer to the number of animals used.

The steady state levels of serotonin in the two regions of the brain studied reflect no significant alteration of this amine in killer rats. When animals were given 100 mg/kg of pargyline and the rate of serotonin accumulation was followed, there were no significant differences in either the rate constant or turnover rates (Table 2).

In order to select the proper pharmacologic conditions in which to study the biochemical effects of imipramine, it was given intraperitoneally to a colony of muricidal rats. The dose and time–response effects for this agent are shown in Fig. 1. An ED_{50} at the time of maximal effect of 13·4 mg/kg was obtained, which compares favorably with that obtained by earlier workers.[8] Based on these results, we selected 25 mg/kg of imipramine for the turnover studies, a dose capable of producing near maximal inhibition within a half hour, with a duration of about 4–5 hr. During the turnover experiments, animals were sacrificed at a maximum time of 4·5 hr after administration of imipramine; at this time, approximately 20 per cent of the group still demonstrated muricidal blockade.

The effect of a single dose of imipramine on forebrain NE turnover in normal (non-isolated) rats is given in Table 3. From the table, it can be concluded that this dose does not change the steady state level of forebrain NE, but does cause a greater than 2-fold increase in both the rate constant of ^{3}H-NE efflux and turnover rate.

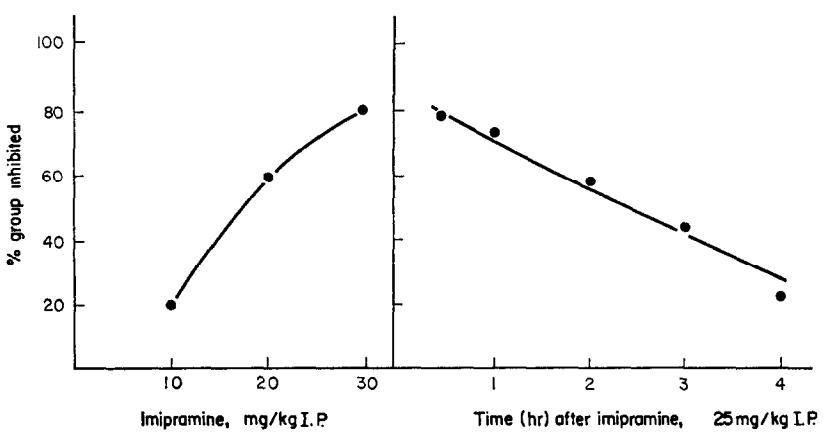

FIG. 1. Effect of imipramine on mouse-killing behavior in rats. There were ten rats in each group. Prior to drug administration, each rat had a muricidal latency of less than 2 min. Animals were considered inhibited if a mouse was not attacked during 5 min after presentation.

The effect of imipramine on forebrain NE levels and turnover in the killer rat is shown in Table 4. In addition, the rate of disappearance of ^{3}H-NE in killer and non-killer rats given saline or imipramine is graphically represented in Fig. 2. In these studies, non-killer rats were given saline or imipramine prior to the intraventricular injection of ^{3}H-NE, while killer rats were given a similar dose of imipramine. Representative animals from each group were sacrificed at 1, 2 and 4 hr after ^{3}H-NE. As determined in the non-isolated rat (Table 3), imipramine does not alter the norepinephrine levels in the forebrain of non-killer rats, but does markedly elevate the rate constant and turnover rate of this amine. Killer rats given imipramine do show an

TABLE 3. EFFECT OF IMIPRAMINE ON FOREBRAIN NOREPINEPHRINE TURNOVER IN NORMAL GROUPED RATS*

Treatment	Steady state level (μg/g $\pm$ S.E.)	Rate constant (k[hr^{-1}] $\pm$ S.E.)	Turnover rate (μg/g/hr)
Saline	0·61 $\pm$ 0·02 (6)	0·20 $\pm$ 0·04 (24)	0·12
Imipramine	0·64 $\pm$ 0·01 (6)	0·42 $\pm$ 0·03 (24)†	0·32

* Rats were given an intraventricular injection of ^{3}H-NE (5 μc/kg) 30 min after saline or imipramine (25 mg/kg i.p.) injection and were sacrificed at various times later. Rate constant and turnover rate were calculated as described in Methods. Numbers in parentheses represent the number of animals.
† Significantly different from saline-treated rats ($P < 0·01$).

TABLE 4. EFFECT OF IMIPRAMINE ON FOREBRAIN NOREPINEPHRINE TURNOVER IN NON-KILLER AND KILLER RATS*

Treatment	Type of animal	Steady state level (μg/g $\pm$ S.E.)	Rate constant (k[hr^{-1}] $\pm$ S.E.)	Turnover rate (μg/g/hr)
Saline	Non-killer	0·56 $\pm$ 0·01 (6)	0·15 $\pm$ 0·02 (18)	0·08
Imipramine	Non-killer	0·55 $\pm$ 0·01 (10)	0·39 $\pm$ 0·01 (30)†	0·22
Imipramine	Killer	0·70 $\pm$ 0·02 (12)†	0·24 $\pm$ 0·02 (30)†	0·17

* Rats were given an intraventricular injection of ^{3}H-NE (5 μc/kg) 30 min after saline or imipramine (25 mg/kg, i.p.) injection and were sacrificed at various times later. Rate constant and turnover rate were calculated as described in Methods. Numbers in parentheses represent the number of animals.
† Significantly different from non-killer (saline-treated) rats ($P < 0·01$).

increase in the levels of NE; however, the magnitude of this increase is identical to that observed earlier in untreated killer rats when compared with non-killers[23] (Table 1). In addition, the rate constant of ^{3}H-NE efflux and turnover rate in the forebrain of the killer rats after imipramine is also elevated when compared to saline-treated, non-killer rats; but this increase appears to be somewhat lower than that obtained after imipramine in the non-killer rat. The turnover rate after imipramine in non-killer and killer rats appears, however, to be equal in magnitude, despite the elevated steady state levels in the killer rats.

To study the neurochemical effects of amphetamine in the muricidal rat, a dose and time-response study was performed similar to those described for imipramine. An ED_{50} of 1·8 mg/kg i.p. was obtained for blocking the muricidal response 30 min after

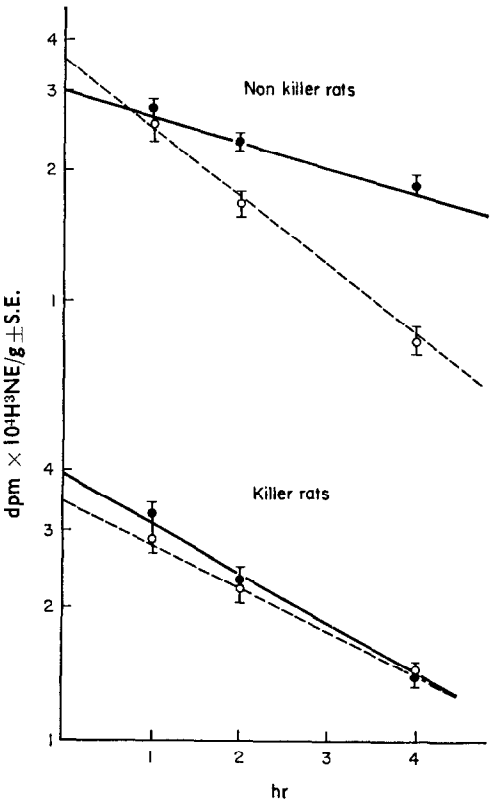

FIG. 2. Effect of imipramine on forebrain norepinephrine turnover in non-killer and killer rats. Rats were given an intraventricular injection of ^{3}H-NE (5 μc/kg) 30 min after saline (———) or imipramine, 25 mg/kg i.p., (- - - - -) injection and were sacrificed at the indicated time intervals. Rate constant and turnover rate were calculated as described in Methods.

TABLE 5. EFFECT OF AMPHETAMINE OF FOREBRAIN NOREPINEPHRINE TURNOVER IN NON-KILLER AND KILLER RATS*

Treatment	Type of animal	Steady state level (μg/g ± S.E.)	Rate constant (k[hr^{-1}] ± S.E.)	Turnover rate (μg/g/hr)
Saline	Non-killer	0·52 ± 0·01 (6)	0·18 ± 0·03 (18)	0·09
Amphetamine	Non-killer	0·60 ± 0·02 (6)	0·34 ± 0·04 (18)†	0·20
Saline	Killer	0·75 ± 0·02 (6)†	0·30 ± 0·04 (24)†	0·23
Amphetamine	Killer	0·79 ± 0·02 (6)†	0·28 ± 0·04 (18)†	0·22

* Rats were given intraventricular injection of ^{3}H-NE (5 μc/kg) 30 min after saline or amphetamine (5 mg/kg, i.p.) injection and were sacrificed at various times later. Rate constant and turnover rate were calculated as described in Methods. Numbers in parentheses represent the number of animals.
† Significantly different from non-killer (saline-treated) rats ($P < 0·01$).

injection. We selected 5 mg/kg i.p. of amphetamine, a dose which causes complete blockade initially and which blocks the muricidal response in 50 per cent of killer rats for at least 4 hr.

The effects of amphetamine on forebrain norepinephrine in killer and non-killer rats are shown in Table 5. After 5 mg/kg, amphetamine does not alter forebrain levels

of NE in non-killer rats. We have shown previously in these rats that doses of 8 mg/kg and above cause significant depletion of brain NE.[29] However, 5 mg/kg of the stimulant does cause a 2-fold increase in the rate constant of ^{3}H-NE efflux and a corresponding increase in the turnover rate of this amine. Killer rats treated with saline show their characteristic high level of NE as compared with non-killer rats. This increase is not altered by prior treatment with amphetamine. Similarly, elevated rate constants and turnover rates were obtained in killer rats; however, there was no further augmentation of these parameters in killer rats given amphetamine.

DISCUSSION

Neurochemical correlates of aggressive behavior have been concentrated largely in two different models: (1) isolated fighting mice[1, 30] and (2) septal lesioned rats.[31] Although many biochemical studies have appeared during the past several years, there have been no common factors linking definite and consistent biochemical changes with the aggressive response. The isolated fighting mouse has received the greatest attention and, at the same time, has offered conflicting results from different laboratories. Welch and Welch[32] have demonstrated that, in mice isolated for 1 week, there was a significantly higher level of brain NE when compared with that of grouped animals, and after αMT injection, depletion of brain catecholamines was slower in isolated animals when compared to grouped animals.[21] Valzelli[1] has reported, on the other hand, that mice rendered aggressive by prolonged isolation appear to have normal brain levels of 5HT and NE, but demonstrate changes in the turnover rate of these amines, where 5HT synthesis appears to occur at a slower rate and NE synthesis occurs at a faster rate when compared to non-aggressive mice. To our knowledge, no previous reports on biogenic amine metabolism in the muricidal rat model of aggression have appeared prior to our preliminary communication.[22] It was the purpose of the present investigation to extend our earlier results and to study the effects of two agents which (1) were commonly used as antidepressants and (2) block selectively this type of behavior.

In our earlier communication,[22] we reported that there were no significant changes in brain serotonin levels in killer rats. After inhibition of monoamine oxidase (MAO) by pargyline, we were unable to detect any differences in the rate of accumulation of 5HT in killer and non-killer rats, in either the forebrain or hindbrain. Thus, unlike the evidence presented for a decrease in the synthesis rate of this amine in the isolated fighting mouse, this model of aggression does not appear to be related to alterations in serotonin metabolism. However, it should be mentioned that Horovitz *et al.*[8] have shown that iproniazid, another potent MAO inhibitor, had muricidal blocking properties. We have found that paragyline also has some inhibitory effect on this type of behavior. After 100 mg/kg of pargyline, the dose used in the serotonin turnover studies, we found that two of ten killer rats were blocked for several hours; a dose of 150 mg/kg resulted in muricidal inhibition in eight of ten rats. These doses are considerably higher than those needed to cause marked inhibition in brain MAO, and the results may not be attributed to enzyme inhibition or to the subsequent increase in brain biogenic amines or to both. On the other hand, Kulkarni[33] has shown recently that high doses of 5-hydroxytryptophan also cause inhibition of muricidal behavior in some rats. Before concluding that serotonin turnover is not implicated in this model

of aggression, it is felt that it should be studied by an isotopic procedure similar to that described below for norepinephrine.

In agreement with our earlier report,[22] we have found in these studies a similar increase of approximately 30 per cent in forebrain NE levels of the killer rat when compared directly to isolated non-killer rats (or indirectly to normal grouped non-killer rats). Horovitz *et al.*[9, 13] have observed that amygdaloid lesions blocked the muricidal response, and it is possible that this type of behavior may be related to an excited state of the amygdala in animals predisposed to aggressive tendencies. Unfortunately, in these studies, we were unable to measure directly NE levels of the amygdala. However, because of the substantial increase in NE levels in the forebrain of killer rats, it is reasonable to speculate that similar alterations occured in this region. In support of this speculation, we found no changes in NE content in the hindbrain of killer rats. A detailed study of different regional sites of the forebrain of the killer rat would be informative.

In previous studies, we followed NE turnover by utilizing the method and concepts of Neff and Costa[34] in which the rate of decline of NE after the tyrosine hydroxylase inhibitor, αMT, was compared in killer and non-killer rats. During the present investigations, we noted that doses of αMT, which are needed to study turnover rate, block the muricidal response in most rats (unpublished observations). Thus, the use of this agent as a tool for studying synthesis rates of NE could have confounded the results and, thus, necessitated the isotopic method selected for these investigations. Furthermore, since we wanted to study the effects of amphetamine on NE turnover in the killer rats, we could not use the concepts of tyrosine hydroxylase blockade with αMT, since it has been reported that αMT antagonizes most pharmacologic effects of amphetamine.[35] It is of interest to mention that since αMT blocks the muricidal response and inhibits tyrosine hydroxylase, the rate-limiting enzyme in the biosynthesis of NE, there is a suggestion that the adrenergic system is implicated in the expression of muricidal behavior. Utilizing αMT to study NE turnover, we reported a 52 per cent increase in the synthesis rate of this amine in killer rats.[22] In the present studies we obtained increases of 150 per cent in forebrain norepinephrine synthesis rate. Thus, it appears that turnover results, using αMT, should not be considered absolute, possibly due to the inhibitory effect of the compound on this type of behavior. In addition, results obtained for the rate constant of NE efflux on the forebrain of killer rats using the isoptic procedure were different from those observed in the non-isotopic method. After blockade of tyrosine hydroxylase, the rate constants were similar in killer and non-killer rats, while in the isotopic studies we observed a 2-fold increase in efflux rate. Although the direction of the turnover rates is similar for the two methods, the magnitude of the increase for the isotopic method clearly results from differences in rate constants obtained.

The differences between the rate constants could well be attributed to the fact that in the isotopic method we are in a sense measuring the rate of efflux of DL-NE, while in the non-isotopic method, the rate of decline of the L-isomer of NE is being measured. Concomitant with unchanged norepinephrine levels in the hindbrain region, rate constants and turnover rate were similar in killer and non-killer rats. Thus, it appears that killer rats maintain normally higher steady state levels of NE by a compensatory increase in synthesis rate. These differences probably exist as a result of the innate aggressiveness of the animals and do not appear to be due to the isolation period

involved in their selection. This conclusion may be inferred by the comparison of steady state levels and turnover rate in non-killer rats (Table 1) and grouped control rats used in the initial imipramine study (Table 3). No apparent differences in these parameters were obtained. These results are in agreement with studies by Valzelli,[1] who has shown that increases in NE turnover rates in isolated fighting mice were due to aggressivity and not to isolation. Furthermore, the rate of NE utilization in the aggressive animals may be altered to explain the turnover results. It is also possible, however, that the stress induced in muricidal rats after a killing response could cause an activation of forebrain tyrosine hydroxylase, which could be responsible for these changes. Further studies are necessary to clarify these points. It would be of particular interest to study these animals at varying times after the last muricidal endeavor to determine the permanency of these changes.

The results obtained in the drug studies are difficult to interpret. Both imipramine and amphetamine have been reported to accelerate the turnover rate of NE in brain.[34,36] Glowinski[37] has reported that stress markedly accelerates the increase in NE turnover rate obtained after 5 mg/kg of amphetamine. Clearly, no such augmentation occurred in our studies when either drug was superimposed upon the already elevated turnover rate of NE in the forebrain of killer rats. Our results suggest that some type of "ceiling effect" exists between the factors involved. Several possibilities exist for the failure of imipramine and amphetamine to enhance further the increased turnover of NE in killer rats. (1) There could be a greater sensitivity of tyrosine hydroxylase to feedback inhibition by NE, particularly evident with the higher brain levels of this amine in killer rats. (2) There may be a difference in the dopamine turnover of imipramine-treated killer rats, leaving NE turnover unaltered, such as has been reported with chlorpromazine in normal animals.[34] (3) It is possible that the reuptake mechanism of NE in killer rats is different from that of non-killers, and that the inhibitory effect of imipramine and amphetamine on reuptake does not take place as completely in these impaired situations.[36, 38] Such changes could alter the homeostatic neuronal equilibrium. (4) Failure of imipramine and amphetamine to further augment apparent synthesis rates in killer rats could be attributable to divergent pharmacologic activities in which: (a) their antimuricidal effects would cause a tendency to diminish the elevated synthesis rate normally seen in killer rats (possible analogy to αMT-induced inhibition of muricide and decrease in catecholamine levels); and (b) their usual biochemical effects would result in a faster synthesis rate of norepinephrine. Thus, it is conceivable that the results reflect the balance of these actions.

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