the adrenal weight is not altered. Furthermore, glycyrrhizin was found effective as an anti-inflammatory agent in adrenalectomized animals.[14] Thus, it may be concluded that the anti-inflammatory action of β-glycyrrhetinic acid is independent of the pituitary adrenal axis.

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REFERENCES

1. H. V. COUWENBERG, *Lancet* ii, 374 (1954).
2. G. C. FEENEY, P. E. CARLS and K. P. SMITH, *J. Pharmac. exp. Ther.* **114**, 99 (1955).
3. A. K. DONE, R. S. FLY and V. C. KELLEY, *Metabolism* **7**, 52 (1958).
4. C. A. WINTER, E. A. RISLEY and G. W. NUSS, *J. Pharmac. exp. Ther.* **141**, 369 (1963).
5. R. DOMENJOZ, *Ann. N.Y. Acad. Sci.* **86**, 253 (1960).
6. J. J. BURN, T. F. YU, P. G. DAYTON, A. B. GUTMAN and B. A. BRODIE, *Ann. N.Y. Acad. Sci.* **86**, 259 (1960).
7. R. S. H. FINNEY and G. F. SOMER, *J. Pharm. Pharmac.* **10**, 613 (1948).
8. M. L. GUJRAL, K. N. SAREEN, K. K. TANGRI, A. K. ROY, G. P. GUPTA and M. K. P. AMMA, *Ind. J. Physiol. Pharmac.* **3**, 39 (1959).
9. N. ZENKER and D. E. BERNSTEIN, *J. biol. Chem.* **231**, 695 (1958).
10. H. SILBER and C. C. PORTER, *J. biol. Chem.* **210**, 923 (1954).
11. M. L. SWEAT, *Analyt. Chem.* **26**, 773 (1954).
12. R. MEIER, W. SCHULER and P. DESANLLES, *Experientia* **6**, 965 (1963).
13. F. D. HART and P. L. BOARDMAN, *Br. Med. J.* **2**, 965 (1963).
14. M. L. GUJRAL, K. N. SAREEN, D. P. PHUKAN and M. K. P. AMMA, *Ind. J. Med. Sci.* **15**, 625 (1961).

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Norepinephrine turnover and brain monoamine levels in aggressive mouse-killing rats

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KARLI[1] and Karli and Vergnes[2] reported that some laboratory rats will spontaneously attack and kill a mouse when presented. Horovitz *et al.*[3,4] showed that this response, which they called "muricide," could be selectively blocked by certain classes of drugs such as antidepressants and stimulants. Karli[1] reported that the muricidal response could be exacerbated by lesioning of the septal area, but that it could not be induced in normal nonkilling rats. Additionally, Horovitz *et al.*[4] reported that lesions of the amygdala blocked this response, as did interruption of the amygdala-hypothalamic routes.[5] Since the initial report of Yen *et al.*,[6] several investigators have studied the aggressive behavior in mice induced by prolonged isolation. Valzelli[7] showed that serotonin synthesis occurs at a slower rate in aggressive mice. In his recent review on drugs in various aggressive states, Valzelli[8] reported that blockade of catecholamine synthesis results in a faster decline in brain norepinephrine levels in aggressive than in normal mice.

This communication reports our findings on the levels of brain serotonin and norepinephrine and the turnover rate of norepinephrine in aggressive mouse-killing rats. Male Long–Evans rats weighing

between 200 and 240 g were used in these studies. All animals were housed individually for several weeks and were kept on a restricted food intake of approximately 15 g/day of solid food. The subjects were tested periodically for their ability to kill mice as described by Horovitz *et al.*[3,4] From the colony, 35 killer rats were selected which had shown a positive response for 3 consecutive days prior to use, while 39 nonkiller rats were used for control purposes. Both killer and nonkiller rats were sacrificed 24 hr after the last challenge. For baseline levels of each, animals were randomly selected and sacrificed. The remainder were given 250 mg/kg i.p. of an aqueous suspension of L-α-methyl-*p*-tyrosine and were divided into groups which were sacrificed at periodic intervals thereafter. Norepinephrine and serotonin brain levels were determined by the method of Shore and Olin[9] as modified by Mead and Finger.[10] Norepinephrine turnover was calculated by using the steady state concepts of Neff and Costa.[11] Levels of L-α-methyl-*p*-tyrosine in brain were determined as described by Spector *et al.*[12] Each brain was sectioned into forebrain and hindbrain including cerebellum.

The results of the studies on the levels of monoamines are given in Table 1. There was no significant difference between killer and nonkiller rats on the levels of serotonin in forebrain or hindbrain as well

TABLE 1. BRAIN NOREPINEPHRINE AND SEROTONIN LEVELS IN KILLER AND NONKILLER RATS

Source	Type and (No.) of animals		Norepinephrine (μg/g ± S.E.)	Serotonin (μg/g ± S.E.)
Forebrain	Killer	(8)	0·69 ± 0·01*	0·38 ± 0·02
	Nonkiller	(10)	0·55 ± 0·01	0·32 ± 0·02
Hindbrain	Killer	(7)	0·53 ± 0·04	0·37 ± 0·01
	Nonkiller	(8)	0·54 ± 0·03	0·43 ± 0·04

* Significantly different from nonkiller rats ($P < 0·01$).

TABLE 2. BRAIN NOREPINEPHRINE TURNOVER IN KILLER AND NONKILLER RATS*

Source	Type and (No.) of animals		Steady state level (μg/g ± S.E.)	$k(h^{-1})$ ± S.E.	Synthesis rate (μg/g/hr)
Forebrain	Killer	(26)	0·66 ± 0·01†	0·12 ± 0·01	0·079
	Nonkiller	(30)	0·52 ± 0·01	0·10 ± 0·01	0·052
Hindbrain	Killer	(22)	0·48 ± 0·04	0·12 ± 0·01	0·058
	Nonkiller	(23)	0·51 ± 0·03	0·14 ± 0·05	0·071

* Rats were given 250 mg/kg i.p. of L-α-methyl-*p*-tyrosine and were sacrificed at various times later. The rate constant (k) was calculated by the method of least squares.
† Significantly different from nonkiller rats ($P < 0·01$).

as in norepinephrine levels in hindbrain. However, there was a 25·5 per cent increase in norepinephrine content in the forebrain of the aggressive animals. The results of brain norepinephrine turnover studies are given in Table 2 and, in addition, the decline in forebrain norepinephrine levels following inhibition of tyrosine hydroxylase is shown in Fig. 1. Since the norepinephrine levels in the forebrain of killer rats as well as the derived steady state levels were higher than in controls and the rate constant of norepinephrine efflux did not vary significantly, it would appear that killer rats have a normally higher synthesis rate of this amine in forebrain (52 per cent higher) to maintain higher steady state levels. This difference was not attributable to the precursor, since tyrosine levels in the forebrain of killer and nonkiller rats did not vary significantly; nor were any differences obtained after L-α-methyl-*p*-tyrosine injection. It is entirely possible 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 must be conducted to investigate this possibility as well as to study the effects of tricyclic antidepressants in these animals since they have been reported to increase the

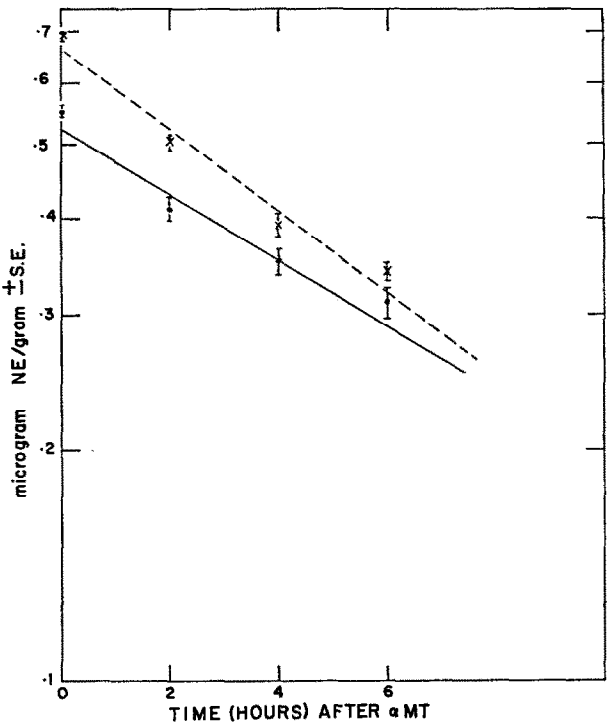

FIG. 1. The effect of L-α-methyl-*p*-tyrosine (α MT) on forebrain norepinephrine levels in killer and nonkiller rats. ●—●, Nonkiller; ×—×, Killer.

synthesis rate of brain norepinephrine.[11] It is premature to speculate whether the observed difference can explain the physiological basis for differentiating killer and nonkiller rats.

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REFERENCES

1. P. KARLI, *C. Seanc. Soc. Biol.* **154**, 1079 (1960).
2. P. KARLI and M. VERGNES, *J. Physiol, Paris* **56**, 384 (1964).
3. Z. P. HOROVITZ, P. W. RAGOZZINO and R. C. LEAF, *Life Sci.* **4**, 1909 (1965).
4. Z. P. HOROVITZ, J. J. PIALA, J. P. HIGH, J. C. BURKE and R. C. LEAF, *Int. J. Neuropharmac.* **5**, 405 (1966).
5. P. KARLI and M. VERGNES, *C. Seanc. Soc. Biol.* **159**, 754 (1965).
6. C. Y. YEN, R. L. STANGER and N. MILLMAN, *Archs int. pharmacodyn. Ther.* **123**, 179 (1959).
7. L. VALZELLI, *Neuro-Psycho-Pharmacology*, p. 781. Excerpta Medica Foundation, Amsterdam (1967).
8. L. VALZELLI, *Advances in Pharmacology*, p. 79. Academic Press, New York (1967).
9. P. A. SHORE and J. S. OLIN, *J. Pharmac. exp. Ther.* **122**, 295 (1958).
10. J. A. MEAD and K. F. FINGER, *Biochem. Pharmac.* **6**, 52 (1961).
11. N. H. NEFF and E. COSTA, *Antidepressant Drugs*, p. 28. Excerpta Medica Foundation, Amsterdam (1967).
12. S. SPECTOR, A. SJOERDSMA and S. UDENFRIEND, *J. Pharmac. exp. Ther.* **147**, 86 (1965).