in our laboratory (Symchowicz & Wong, 1966a, b), that in rat urine both 4-DM and DM were present as the major metabolites. The rate of urinary drug excretion in rat was also similar to that of the mouse. Therefore, the mouse and the rat appear to have a similar metabolic pattern for griseofulvin. The unidentified metabolite with an R_F value of 0·12 observed in mouse urine was probably also present in rat urine but in a much smaller amount.

Department of Biochemistry,
Schering Corp.,
Bloomfield, New Jersey 04503 U.S.A.

C. LIN
R. CHANG
J. MAGAT
S. SYMCHOWICZ

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REFERENCES

BARICH, L. L., SCHWARTZ, J., BARICH, D. J. and HOROWITZ, M. G. (1961). *Antibiot. Chemotherapy*, **11**, 566–571.

BARNES, M. J. & BOOTHROYD, B. (1961). *Biochem. J.*, **78**, 41–43.

DEMATTEIS, F., DONNELLY, A. J. & RUNGE, W. J. (1966). *Can. Res.*, **26**, 721–726.

DEMATTEIS, F. & RIMINGTON, C. (1963). *Brit. J. Dermatol.*, **75**, 91–104.

HARRIS, P. A. & RIEGELMAN, S. (1969). *J. pharm. Sci.*, **58**, 93–96.

HURST, E. W. & PAGE, G. E. (1963). *Br. J. Dermatol.*, **75**, 105–112.

KAPLAN, S. A., RIEGELMAN, S. & LEE, K. H. (1960). *J. pharm. Sci.*, **55**, 14–18.

KELLY, R. G., PEETS, E. A., GORDON, S. & BUYSKE, D. A. (1961). *Analyt. Biochem.*, **2**, 267–273.

MCNALL, E. G. (1960). *Arch. Dermatol.*, **81**, 657–661.

RIEGELMAN, S., EPSTEIN, W. L. & DAYAN, R. J. (1962) presented at the Scientific Section, Am. Pharm. Asso. Meet. Las Vegas, Nevada, March 1962.

SYMCHOWICZ, S. & WONG, K. K. (1966a). *Biochem. Pharmac.*, **15**, 1601–1606.

SYMCHOWICZ, S, & WONG, K. K. (1966b). *Ibid.*, **15**, 1595–1600.

WOELLER, F. H. (1961). *Anal. Biochem.*, **2**, 508–511.

Enhancement of audiogenic seizure by 6-hydroxydopamine

Recently investigations of the relation between changes in brain biogenic amines and changes in convulsive seizures were reported by Azzaro, Wenger & others (1972) and by Jobe, Picchioni & Chin (1972). The former group of workers showed that the ability of reserpine to lower electroshock seizure threshold is related to reduction in brain catecholamines and 5-hydroxytryptamine (5-HT). The latter group of workers concluded that endogeneous noradrenaline is a modulator of audiogenic convulsions. The present communication presents additional evidence to support the contention that catecholamines exert a modulation effect on sound-induced convulsions. The study involves the use of 6-hydroxydopamine, an agent which has the ability to cause selective degeneration of catecholamine-containing neurons (Bloom, 1971; Ungerstedt, 1971) and has been reported to lower minimal electroshock seizure threshold (Browning & Maynert, 1970).

Male rats, 280 to 320 g, from the University of Arizona colony of audiogenic seizure-susceptible rats, were used. Indwelling cannulae fashioned from 23 gauge stainless steel hypodermic needles were permanently implanted into the right lateral ventricle of the rats according to Grunden & Linburn (1969). One week after surgery, each rat in the test group was injected intracerebroventricularly with 6-hydroxydopamine, 200 μg in 20 μl of normal saline stabilized with 0·01 % ascorbic acid. Two such injections were given to each rat at an interval of 48 h. The control group of rats was similarly injected with the ascorbic acid-saline vehicle. A time-course study of audiogenic seizure response was conducted for 12-days. On the 13th day all the animals were killed and their brains compared for catecholamine content by means of he histochemical fluorescence technique of Falck, Hillarp & others (1962). The

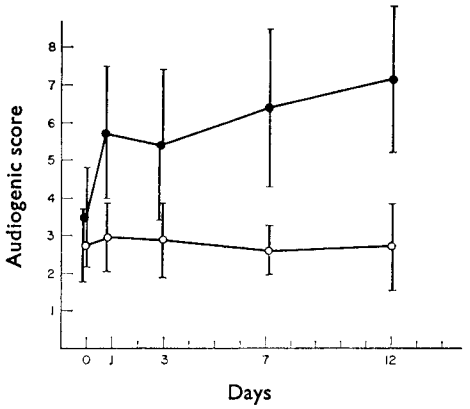

FIG. 1. Time-course study of audiogenic response. Open circles represent controls (8 rats). Closed circles represent 6-hydroxydopamine-treated animals (11 rats). Vertical lines represent 95% fiducial limits. On day 0 there was no significant difference between test animals and controls On days 1 and 3, the two groups were different at $P < 0.05$. On days 7 and 12, the groups were different at $P < 0.01$.

paraventricular nucleus of the hypothalamus was selected for histochemical analysis because this area of the brain is rich in noradrenaline and can be used to indicate the effect of 6-hydroxydopamine on brain catecholamine-containing neurons.

The severity of audiogenic response is ranked from 1 to 9 according to Jobe & others (1972). Intracerebroventricular injection of 6-hydroxydopamine caused an increase in severity of audiogenic seizure response which became apparent one day after treatment and persisted throughout the experiment (Fig. 1). The audiogenic seizure response score of the control rats was constant during the 12-day period.

The histochemical studies revealed that intracerebroventricularly injected 6-hydroxydopamine causes degeneration of catecholamine-containing neurons because the fluorescence of nerve terminals seen in the control animals was absent in the 6-hydroxydopamine-treated animals. It therefore seems likely that enhancement of audiogenic convulsions caused by 6-hydroxydopamine is related to depletion of brain catecholamines.

These observations lend further support to the belief that endogenous noradrenaline modulates audiogenic convulsions (Jobe & others, 1972).

Department of Pharmacology,
College of Pharmacy,
University of Arizona,
Tucson, Arizona 85721, U.S.A.

WILLIAM M. BOURN
LINCOLN CHIN
ALBERT L. PICCHIONI

July 27, 1972

REFERENCES

AZZARO, A. J., WENGER, G. R., CRAIG, C. R. & STITZEL, R. E. (1972). *J. Pharmac. exp. Ther.*, **180**, 558–568.

BLOOM, F. E. (1971). *6-Hydroxydopamine and Catecholamine Neurons*, pp. 135–155. Editors: Malmfors, T. & Thoenen, H. Amsterdam: North-Holland.

BROWNING, R. A. & MAYNERT, E. W. (1970). *Fedn Proc. Fedn Am. Socs exp. Biol.*, **29**, 417.

FALCK, B., HILLARP, N. A., THIEME, G. & TORP, A. (1962). *J. Histochem. Cytochem.*, **10**, 348–354.

GRUNDEN, L. R. & LINBURN, G. E. (1969). *J. pharm. Sci.*, **58**, 1147–1148.

JOBE, P. C., PICCHIONI, A. L. & CHIN, L. (1972). *J. Pharmac. exp. Ther.* In the press.

UNGERSTEDT, U. (1971). *6-Hydroxydopamine and Catecholamine Neurons*, pp. 101–127. Editors: Malmfors, T. & Thoenen, H. Amsterdam: North-Holland.