effects. In ecology there is a commonly accepted principle which is worthy of serious consideration in this situation: If conditions are less than optimum for an organism with respect to one ecological factor, the sensitivity of the organism to other factors may be increased. There is ample evidence that some environmental "stress" factors, especially suboptimum amounts of oxygen and abnormal temperatures, increase the sensitivity of plants to radioactivity (see *2*). Therefore, at the present time the most tenable hypothesis appears to be that background radioactivity, acting in conjunction with other suboptimum environmental factors, is responsible for the greater incidence of anomalous morphological forms (*3*).

WILLIAM S. OSBURN, JR.
Institute of Arctic and Alpine Research, University of Colorado, Boulder

References and Notes

1. G. Phair, *Radioactive Tertiary Porphyries in the Central City District, Colorado (TEI-247)* (Technical Information Service, Atomic Energy Commission, Oak Ridge, Tenn., 1952).
2. A. H. Sparrow, J. P. Binnington, V. Pond, *Bibliography on the Effects of Ionizing Radiation on Plants, 1896–1955* (Brookhaven National Laboratory, Upton, N.Y., 1958), subject index.
3. Full financial support for this study was received from the U.S. Atomic Energy Commission under contract No. AT(11-1)435.

13 April 1961

Enzymatic Formation of Psychotomimetic Metabolites from Normally Occurring Compounds

Abstract. An enzyme has been found that N-methylates serotonin and tryptamine to psychotomimetic metabolites, bufotenine and N,N-dimethyltryptamine. This enzyme is highly localized in the rabbit lung and also N-methylates phenylethylamine derivatives such as tyramine, phenylethylamine, mescaline, and dopamine.

In recent years, there has been an active search for a biochemical cause of mental disease. Several compounds have been reported to be present in the body which produce abnormal behavior, but in rigorously controlled studies none of these findings have been confirmed (*1*). Cohoba, a snuff obtained from *Piptadenia peregrina,* has been used by Indian tribes of Haiti to enable them to communicate with unseen powers. Recently, bufotenine (N,N-dimethylserotonin) and N,N-dimethyltryptamine have been found to be present in *Piptadenia peregrina* (*2*), and both of these compounds have been shown to produce psychotomimetic effects in man (*3*). I wish to report that an enzyme has been found in the rabbit lung that can convert the normally occurring compounds, serotonin and tryptamine, to the psychotomimetic metabolites, bufotenine and N,N-dimethyltryptamine.

Table 1. Enzymatic N-methylation of indoleamines. Rabbit lung was homogenized with three volumes of isotonic potassium chloride and centrifuged at 80,000 *g* for 30 min. Soluble supernatant fraction obtained from 15 mg of rabbit lung was incubated at 37°C with 10 mμmole of S-adenosylmethionine-methyl-C^{14}, 100 μmole of phosphate buffer at *p*H 7.9, and 0.5 μmole of substrate. After 90 min of incubation, the methyl-C^{14} indoleamine was determined in the incubation mixture (*4*).

Substrate added	Product formed	
	Name	Amount (μg/g of tissue)
Serotonin	N-Methylserotonin	80
N-Methylserotonin	Bufotenine	56
Tryptamine	N-Methyltryptamine	71
N-Methyltryptamine	N,N-Dimethyltryptamine	20

When the methyl donor S-adenosylmethionine-methyl-C^{14} (C^{14}AMe) was incubated with the soluble supernatant fraction of rabbit lung, a normally occurring compound present in this tissue became radioactive. In trying to characterize this substance, it was found that, when serotonin was incubated with the soluble supernatant fraction of rabbit lung and C^{14}AMe, considerable amounts of a radioactive compound were formed. This derivative could be extracted into isoamyl alcohol at *p*H 10. After chromatography with three solvent systems—butanol, ethanol, and ammonia (8:2:1), *n*-propanol and ammonia (1*N*) (5:1); and isopropanol, ammonia, and water (16:1:3)—the radioactive compound formed from serotonin and C^{14} AMe had the same R_F values as authentic N-methylserotonin. When N-methylserotonin was incubated with C^{14}AMe and the rabbit lung enzyme preparation, a compound was formed having the same R_F values as bufotenine in several solvent systems. In addition, typtamine and N-methyltryptamine, when incubated with C^{14}AMe and the enzyme from rabbit lung, formed radioactive metabolites having the same R_F values as N-methyltryptamine and N,N-dimethyltryptamine, respectively, when chromatographed on Whatman No. 1 paper buffered at *p*H 8.0, with *n*-butanol or isoamyl alcohol saturated with water as the solvent systems. These compounds were isolated from the enzymatic reaction mixture by extraction into isoamyl alcohol at *p*H 10. The relative rates of enzymatic formation of the N-methylated derivatives are shown in Table 1. These observations were taken as evidence that serotonin and tryptamine are converted to their corresponding N-dimethyl derivatives by an enzyme present in the soluble supernatant fraction of the rabbit lung in two steps as follows:

$$\text{serotonin} \xrightarrow{\text{AMe}} \text{N-methylserotonin} \xrightarrow{\text{AMe}} \text{bufotenine}$$

$$\text{tryptamine} \xrightarrow{\text{AMe}} \text{N-methyltryptamine} \xrightarrow{\text{AMe}} \text{N,N-dimethyltryptamine.}$$

This enzyme was also found to N-methylate other phenylethylamine derivatives such as phenylethylamine, tryamine, mescaline, and dopamine (*4*); and it appeared to differ from other N- and O-methyltransferases with regard to substrate specificity and distribution (*5*).

Recently, Pollin *et al.* (6) found that the repeated oral administration of large amounts of *l*-methionine and *l*-tryptophan caused marked alterations of behavior in schizophrenic patients. Both of these amino acids can serve as precursors for the psychotomimetic compounds, bufotenine and N,N-dimethyltryptamine.

JULIUS AXELROD
Laboratory of Clinical Science, National Institute of Mental Health, National Institutes of Health, Bethesda, Maryland

References and Notes

→ S. S. Kety, *Science* **129**, 1528 (1958).
→ V. L. Stromberg, *J. Am. Chem. Soc.* **76**, 1707 (195→ M. S. Fish, N. M. Johnson, E. C. Horning, *J. Am. Chem. Soc.* **77**, 5892 (1955).
3. H. D. Fabing and J. R. Hawkins, *Science* **123**, (195 → S. Szara, *Experientia* **12**, 441 (1956); A. Sai-Halasz, G. Brunecker, S. Szara, *Psychiat. Neurol.* **135**, 285 (1958).
4. A report on the assay, purification, properties, and distribution of this enzyme is in preparation.
5. J. Axelrod and R. Tomchick, *J. Biol. Chem.* **233**, 702 (1958); D. D. Brown, R. Tomchick, J. Axelrod, *J. Biol. Chem.* **234**, 2948 (1959); J. Axelrod and H. Weissbach, *J. Biol. Chem.* **236**, 211 (1961); J. Axelrod, *Federation Proc.* **20**, 236 (1961).
6. W. Pollin, P. V. Cardon, Jr., S. S. Kety, *Science* **133**, 104 (1961).

6 April 1961