PHARMACOLOGICAL REVIEWS Vol. 24, No. 2
 Printed in U.S.A.

Report on the Discussion of the Second Session

SOLOMON H. SNYDER

Departments of Pharmacology and Experimental Therapeutics and Psychiatry and the Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland

New sensitive and efficient techniques of measurement are frequent keys to new advances in much of science, a notion well exemplified by Dr. Axelrod's opening address. In his laboratory during the past 2 years, Molinoff, Weinshilboum and Coyle have developed extraordinarily sensitive, specific and fundamentally simple methods for assay of dopamine-β-hydroxylase (DBH), which has led to findings in several areas. By showing a 6-hydroxydopamine-induced enhancement of DBH and tyrosine hydroxylase in the adrenal gland, Axelrod laid the groundwork for de Champlain's work which suggested that adrenal medullary hyperactivity maintains blood pressure despite widespread destruction of sympathetic nerves by 6-hydroxydopamine.

Axelrod's group also employed the DBH assay to provide evidence for an exocytic mechanism of transmitter release from sympathetic nerves. He linked mechanisms of sympathetic transmitter release to release of hormones such as insulin and thyroxine by showing similar effects of colchicine, implicating a microtubular role, and cytochalasin B, suggesting that the contractile neurofilaments play a part in the release process.

These studies progressed rapidly from basic transmitter release mechanisms to clinical implications. A subgroup of patients with familial dysautonomia appear to be devoid of plasma DBH activity and their parents have low activity. These findings, together with Lovenberg's (NIH, Bethesda) report of a subgroup of black male hypertensives deficient in plasma DBH, emphasize the potential of such assays for defining biochemically differentiable disease entities. Clearly broad, symptomatically derived diagnostic entities such as essential hypertension and the psychiatric syndromes of schizophrenia and depression will succumb to scientific scrutiny only with the identification of biochemically specified subgroups.

Lampert (NIH, Bethesda), in a screen of normotensive subjects, failed to find any clustering of serum DBH values or any differences between black and white subjects. Several discussants reported elevated serum DBH activity in a variety of types of hypertensive rats, which may relate somehow to Wooton's (NIMH, Bethesda) report (from Axelrod's group) of increased plasma DBH in cold stressed rats.

Kopin's presentation extended the new techniques of enzyme assay to an impressive evaluation of the dynamics of growth and development of catechol-

aminergic neurons. From experiments with nerve ligation and colchicine, he concluded that the axoplasmic transports of DBH and tyrosine hydroxylase are respectively fast and slow. Sympathetic ganglia in organ culture sprout axons which contain large rather than small dense core vesicles, yet are capable of depolarization-induced release of norepinephrine. This is consistent with a model in which large vesicles are the source of readily released transmitter, after whose release they are converted into small dense core "storage" vesicles. After much discussion of predictions afforded by Kopin's theory, Udenfriend noted that, like psychoanalytic theory, it could explain any and all data.

Thoenen's lecture focused on the influences of nerve growth factor and decentralization upon developmental alterations in catecholamine-linked enzymes in sympathetic ganglia. The limited retardation of developmental increases in these enzymes in sympathetic ganglia after decentralization de-emphasizes the importance of presynaptic input upon postsynaptic neuronal development.

Rall (Case Western Reserve, Cleveland) pointed out the importance of ascertaining whether nicotinic or muscarinic receptors mediate trophic effects of cholinergic transmission on sympathetic neuronal development. Goldstein (New York University, New York) questioned whether observed effects of nerve growth factor might be due to proteolytic enzymatic contaminants.

Dairman's presentation dealt with mechanisms whereby dihydroxyphenylalanine (dopa) treatment of animals may depress activities of tyrosine hydroxylase, DBH and dopa decarboxylase. Though effects on all three enzymes appear to be mediated by catecholamines formed from dopa, it is likely that mechanisms for dopa decarboxylase decrements differ from those for tyrosine hydroxylase and DBH. Thus the "non-neural" dopa decarboxylase activity of the liver falls after dopa treatment, whereas changes in DBH and tyrosine hydroxylase in the adrenal gland are thought to result from feedback effects of catecholamines within "neural" elements of the adrenal medulla.

Dairman speculated that the lowering by dopa of hepatic dopa decarboxylase may explain the enhanced therapeutic efficacy and fewer cardiovascular side-effects of L-dopa in parkinsonian patients after chronic therapy. Vogel (Jefferson Medical College, Philadelphia) disagreed, maintaining that dopa metabolism is accelerated, rather than slowed after chronic treatment with dopa. In contrast, Gyse (Mayo Clinic, Rochester, Minnesota) reported decreased dopa metabolism in her patients after prolonged treatment. Pletscher (Hoffman La Roche, Basel) suggested that increased formation of 3-O-methyl-dopa might be responsible for improved therapeutic responses to dopa with chronic therapy.