Perspectives in Neuro Pharmacology

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Contents

1. Julius Axelrod: A Triumph for Creative Research, 3
SEYMOUR S. KETY

2. Isolation of Cholinergic Receptor Proteins, 9
L. T. POTTER AND P. B. MOLINOFF

Introduction, 9
Recognition of Isolated Receptors, 13
Isolation of the Cholinergic Receptor of Torpedo Electric Tissue, 21
References, 39

3. Histamine in the Brain: A Neurotransmitter?, 43
SOLOMON H. SNYDER AND KENNETH M. TAYLOR

Histamine Estimation in Brain Tissue, 44
Regional Localization of Histamine in Mammalian Brain, 49
The Subcellular Localization of Histamine and Histamine Methyltransferase in Rat Brain, 51
Nuclear Localization of Histamine in Neonatal Rat Brain, 57
Histamine Turnover in Rat Brain, 61
Acceleration of Brain Histamine Turnover and Partial Depletion by Stress, 66
Histamine Release by Depolarization of Brain Tissue, 69
Unanswered Questions, 70
References, 72

4. The Uptake, Storage, Release, and Metabolism of GABA in Inhibitory Nerves, 75
LESLIE L. IVERSEN

GABA as an Inhibitory Neurotransmitter Substance, 76
Biochemistry and Pharmacology of GABA Synapses, 83
References, 108

5. Interaction of Estrogens, Progestational Agents, and Androgens with Brain and Pituitary and Their Role in the Control of Ovulation, 113
ARNOLD JOEL EISENFELD

Radioactive Estrogen Interaction with the Brain, 114
Radioactive Progesterone Interaction with the Brain, 129
Radioactive Androgen Interaction with the Brain, 130
Mechanism of Action, 131
Regulation of Ovulation, 133
Role of Estrogens and Progestational Agents in the Regulation of Ovulation, 135

6. L-Tryptophan, L-Tyrosine, and the Control of Brain Monoamine Biosynthesis, 143
RICHARD J. WURTMAN AND JOHN D. FERNSTROM

Biosynthesis of Brain Monoamines, 145
Control of Brain Levels of L-Tyrosine and L-Tryptophan, 156
Experimental Evidence Relating the Availability of L-Tyrosine and L-Tryptophan to Brain Monoamine Synthesis, 169
References, 189

7. The Sympathetic Neuro-Humoral System and White Adipose Tissue, 195
SUNE ROSELL

Cholinergic Innervation of Adipose Tissue, 195
Adrenergic Innervation of Adipose Tissue, 196
Responses to Sympathetic Nerve Activity, 197
Responses to Circulating Catecholamines, 207
Fate of the Adrenergic Transmitter Substance in Subcutaneous Adipose Tissue, 207
Adipose Tissue and Hemorrhagic Shock, 209
References, 211

8. Hypertension and the Sympathetic Nervous System, 215
JACQUES DE CHAMPLAIN

The Autonomic Nervous System and the Control of Blood Pressure, 216
Vascular Reactivity in Hypertension, 218
The Sympathetic Nervous System in Experimental Hypertension, 221
The Sympathetic Nervous System in Human Hypertension, 253
References, 260

9. Influence of Neuronal and Extraneuronal Uptake on Disposition, Metabolism, and Potency of Catecholamines, 267
GEORG HERTTING AND JOSEF SUKO

Historical Remarks, 268
Properties of the Sympathetic Neuron, 270
Experiments with the Isolated Spleen, 273
Fate of ^{3}H-Dopamine Taken Up into the Rat Heart, 289
The Influence of Different Perfusion Concentration on the Metabolism of ^{3}H-DA, 290
References, 297

10. Chemical Sympathectomy: A New Tool in the Investigation of the Physiology and Pharmacology of Peripheral and Central Adrenergic Neurons, 301
H. THOENEN

Peripheral Sympathetic Nervous System, 302
Central Nervous System, 318
Reversible and Irreversible Chemical Sympathectomy: Comparison with Surgical and Immunological Methods, 326
Compensatory Mechanisms, 329
Mechanism of Action, 330
References, 335

11. False Aminergic Transmitters, 339
IRWIN J. KOPIN

Origin of the Concept of "False" Transmitters, 339
Nonspecificity of Synthesis, Storage, and Release of Amines, 340
Selective Release of Newly Synthesized Neurotransmitters, 342
Serotonin Storage in Catecholaminergic Neurons, 344
Catecholamines in Serotonin Storage Sites, 345
References, 347

12. Some New Facts About Synthesis, Storage, and Release Processes of Monoamines in the Central Nervous System, 349
J. GLOWINSKI

Introduction, 349
Noradrenergic Neurons, 350
Dopaminergic Neurons, 365
Serotoninergic Neurons, 383
References, 400

Perspectives in Neuropharmacology

A TRIBUTE TO JULIUS AXELROD

EDITED BY

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1

Julius Axelrod: A Triumph for Creative Research

SEYMOUR S. KETY

Scientists, like journalists, are sometimes "scooped" by their colleagues, and it is not unusual, especially among those who work in the field of the catecholamines, to learn that one's very exciting finding has been anticipated by a group in Goteborg or Stockholm. We didn't realize, however, until quite recently, into what high circles in Sweden that tendency had penetrated.

More than a year ago, in January 1970, several former fellows of Julius Axelrod—Sol Snyder, Jacques Glowinski, Leslie Iversen, Hans Thoenen, and Linc Potter—met at a neurotransmitter conference in Paris, and decided to honor their mentor by arranging a grand reunion of all the fellows and associates with whom Axelrod had shared his genius, to be followed by the publication of a *Festschrift.* There was not the usual occasion for this since Julie was not about to reach some convenient chronological milestone and hadn't the remotest idea of retiring. It was simply a spontaneous expression of their affection and admiration for him and a recognition of his contributions to science. I was given the privilege of writing this introduction to the *Festschrift*—the only contribution which was to be personal.

It was decided to wait until the Federation meeting of 1971 and—the rest is history. On October 15, 1970, while he was sitting in a dentist's chair with his mouth full of cotton sponges, Julie learned that the Committee in Stockholm had awarded the Nobel Prize in Physiology and Medicine jointly to him, von Euler, and Katz. (It is rumored that there has been a sharp rise in the number of scientists coming for dental checkups since that time.)

Sol Snyder wrote me that day, exultant, but also concerned about how that affected the plans for the *Festschrift.* It was soon agreed, however, that the plans for this tribute were not to be altered, since the action of the Nobel Committee simply confirmed the conviction that we were on the right track!

It is clearly difficult to avoid the "halo" effect (that term has never seemed more appropriate) and to speak of Julie as we would have done last April. Yet the feelings we want to express are those which have been shared for a long time by all who were associated with him. His scientific contributions gained him international recognition but it is his human qualities which have so endeared him to his colleagues.

It is not necessary to do more than briefly summarize Axelrod's scientific contributions. A major segment of neuropharmacology and experimental psychiatry depends upon his elucidation of the biochemical and physiological processes involved in the storage, release, and inactivation of norepinephrine at the adrenergic synapse, which has made possible an understanding of the role of that amine in neurotransmission and a clarification of the mechanism of action of numerous drugs and hormones that affect adrenergic activity peripherally and centrally.

In 1957 he described the O-methylation pathway in the metabolism of catecholamines, and shortly thereafter demonstrated its importance in the inactivation of epinephrine in animals and man, characterizing the enzyme involved and its distribution in the mammalian organism. Within a few years and based largely upon his work, knowledge of the metabolism of catecholamines advanced from almost total ignorance to characterization of their major and minor pathways and metabolites. With Glowinski and Kopin he extended this knowledge to the metabolism of catecholamines in the brain.

His studies, with Whitby and Hertting, of the effects of psychotropic drugs on the uptake of ^{3}H-norepinephrine by sympathetically innervated tissues led to his recognition of the most important mechanism for the inactivation of norepinephrine at the adrenergic synapse and initiated a major area of current research activity on the anatomical, physiological, and pharmacological aspects of this process.

With Wurtman and Snyder he adduced evidence for the regulation of biogenic amine synthesis under environmental variations throughout the body but especially in the pineal gland, an organ resurrected by Wurtman and himself from historic neglect. Steroid hormones of the adrenal cortex

were shown to regulate epinephrine formation in the adrenal gland. More recently, with Mueller and Thoenen, he has demonstrated what appears to be an induction of tyrosine hydroxylase following increased sympathetic activity. And currently, together with Weinshilbaum, Molinoff, and Coyle, he has explored the regulation of dopamine hydroxylase and its "exocytic" release by nerve impulses.

His scientific talents are so unusual that one senses them early in one's association with him. Ten years ago they impressed me in this way: "In all of his contributions success has been much less attributable to good fortune and much more to a unique ability to develop imaginative new concepts, to select and perform crucial experiments and to stimulate the activity and productivity of others in the field." These are some of the qualities which contribute to Axelrod's creativeness, but there are many more.

Sol Snyder describes the experience of many of the research associates who have come under his influence: "Perhaps the greatest lesson Julie taught was that science is fun and exciting . . . I was struck by his intense involvement in experiments he was doing. He would lean over the scintillation counter urging it on to higher and higher counts with impatient 'body English' (a trait I inherited, and a tradition that the new computerized machines sadly have laid to rest) . . . What was quite evident then . . . was his scientific vision. He saw (and still perceives) the farthest reaching implications of apparently trivial data. And he would put forth important ideas in such deceptively simple ways that, at first glance, they seemed incredibly naive."

The excitement which Julie derived from his experiments and his ability to read what apparently mundane results were saying are certainly two of his outstanding characteristics as a scientist, and they have played a crucial role in his most important discoveries. When he saw the abstract by Armstrong and McMillan in the Federation Proceedings reporting the presence of 3-methoxy-4-hydroxymandelic acid in the urine of patients with pheochromocytoma, he immediately recognized the importance of the possible direct O-methylation of catechols and carried out his first experiment that very afternoon. Incubating epinephrine with the soluble supernatant fraction of liver, ATP, and methionine, he saw the catecholamine disappear—"right before my eyes"—to be replaced by a new compound which appeared to be the methylated derivative. He communicated his excitement to Witkop, who with Senoh synthesized the authentic O-methyl-

epinephrine in short order, providing Axelrod with a means of proving the identity of his new metabolite.

Another flash of insight led to the discovery of the reuptake mechanism as the major means by which the synaptic action of catecholamines is terminated. When he, Weil-Malherbe, and Tomchick examined the fate of tritiated epinephrine and, a little later, with Whitby, the disposition of norepinephrine, they found high concentrations of the labelled amines in certain tissues. I remember Julie excitedly telling me that the labelled catecholamines were concentrated in the tissues with the richest sympathetic innervation, convinced even then that they were taken up by the sympathetic nerve endings. Within a year Hertting and he had the evidence to permit their conclusion that reuptake of norepinephrine at sympathetic nerve endings occurred.

Perhaps the most remarkable thing about Julie is his ability to maintain an indomitable scientific conviction without losing his humility and warmth in human relationships. One of his associates wrote about him thus: "I would like to try to describe the personality of Julie from the point of view of a younger European scientist who has worked (and suffered) in the atmosphere of the 'Herr Professor and Geheimrat.' What a tremendous contrast to Julie's lab!" Hans Thoenen describes his human side in a way which needs no embellishing: "Besides his extraordinary scientific qualities Julie showed the ability to create a highly stimulating but at the same time pleasant atmosphere in his laboratory, determined by his kindness, tolerance, and great modesty. It certainly would be possible to find people with either the scientific or the human qualities of Julie, but the combination of both is unique in him."

There are some special meanings for many of us in Julie's achievements and the world-wide recognition they have so eminently deserved. He returned from Stockholm last December by way of Israel, where he received a hero's welcome. He gave strength and confidence to the Research Institutes in Bethesda and to the philosophy they have represented. He reinforced the viability of pharmacology as a challenging and intellectually satisfying discipline. But what he has done at an especially crucial time has been to exemplify the importance and the productivity of research which is undirected and untargetted, except by scientific insight.

Our society is now laboring under a well-meaning but nevertheless false assumption that the great needs we have belatedly recognized in the provision and distribution of physical and mental health care must necessarily

compete with research and the acquisition of new knowledge. Arbitrary ceilings have thus been put on research funds and the training of new investigators. Moreover, like the goose that laid the golden eggs, even this commitment to research is being tampered with and operated on in the erroneous belief that by channeling them we can somehow accelerate the processes of creativity and scientific discovery. Axelrod is an emphatic refutation of that notion.

When I became chief of the Laboratory of Clinical Science in 1956, I felt that it would be worthwhile to test the hypothesis which was then current, that abnormal metabolites of epinephrine circulation in the blood were the cause of schizophrenia. If one could use a small dose of epinephrine with very high specific radioactivity, then, with the help of chromatography and the new liquid scintillation counters which were becoming available, one might hope to characterize some of the normal and abnormal metabolites. It wasn't a bad plan as targetted research goes, and I pursued it in the modest way it deserved so as not to disturb the ecology of the laboratory. Seymour Rothschild agreed to attempt the synthesis of tritium-labelled epinephrine of the required activity. In the year it took before the first successful batch arrived, Axelrod (who was not part of the plan) had discovered the O-methylation pathway and characterized the various metabolites of epinephrine. As a minor spin-off of his work, the search for abnormal metabolites of epinephrine in schizophrenia was greatly facilitated, but—much more important—his contributions have had implications for psychiatry which were simply undreamed of in 1956.

It is quite fortunate that there were no administrative or legislative directives to put the funds of the Laboratory into mission-oriented research at the expense of the individual creativity of its scientists, no cost-benefit analyses prematurely and inappropriately applied, no requirement to answer for duplication of effort.

Axelrod has courageously voiced his concerns regarding the dangers of constricting the funds, restricting the training of new investigators, and channeling research support into illusory hierarchies of relevance. We hope his advice is heeded, for no one knows better than he the ingredients of scientific discovery.

2

Isolation of Cholinergic Receptor Proteins

L. T. POTTER
P. B. MOLINOFF

Introduction

Scope and Definitions

Nerve cells have the ability to transmit information rapidly and precisely from one or a few cells to a limited number of other cells which are often far away. The mechanism developed for carrying impulses along nerve axons is electrical in nature and highly efficient for maintaining an unaltered message in hair-thin axons (Hodgkin, 1964). At almost all synapses in the central and peripheral nervous systems, each nerve terminal passes on a chemical messenger, or neurotransmitter, to special receptors on the next cell. Chemical transmission permits a marked amplification of the weak electrical signal in axons, and allows the nature of the message to be varied by changing the transmitter and/or the type of receptor. In addition, since the duration of action of neurotransmitters exceeds the duration of a nerve impulse, chemical transmission facilitates summation of the effects of many impulses.

Even before the first conclusive demonstration of a neurotransmitter (acetylcholine, ACh: Loewi, 1921), it was beginning to become apparent (Langley, 1906; cf. Dale, 1953) that chemical synaptic transmission requires a number of special adaptations: (a) synthesis of the transmitter; (b) a mechanism for coupling the arrival of impulses at a nerve terminal with rapid secretion of the transmitter (Katz, 1969); (c) a receptor for the transmitter on or in the postsynaptic cell; (d) a means of coupling an activated receptor to the required response; and (e) provision for removal of