NEUROPHARMACOLOGY AND AGING

A. Horita

Department of Pharmacology, University of Washington
School of Medicine, Seattle, Washington 98195

It is difficult to discuss the subject of the neuropharmacology of aging when it is well known that we presently have very few agents which can be classified as such. Many psychotropic drugs are used in the elderly, either to treat specific neuropsychiatric disorders, or in an attempt to treat the signs and symptoms associated with the "organic brain syndromes." In the former cases the therapeutic approach is straightforward provided appropriate precautions and hazards specific to the elderly be recognized (1-3). It is in the latter cases, the "organic brain syndromes," where pharmacological intervention has met essentially without success, and where the greatest need exists for the development of newer therapeutic agents.

The status of geriatric neuropharmacology may be likened to that of the neuropharmacology of mental disorders some 25 years ago. At that time drugs for the treatment of schizophrenia and affective disorders were unknown. Yet, through careful observations and much serendipity, the phenothiazines, rauwolfia alkaloids, monoamine oxidase (MAO) inhibitors, and tricyclic anti-depressants emerged. As a result, drug therapy has become the most important approach to the treatment of mental disorders. Although little was known in the 1950's as to how these drugs were exerting their therapeutic effects, it was enough that they were effective and relatively safe. During the past 25 years we have come to understand a great deal about their mechanisms of action, but this came about only as we began to understand some of the neurobiological and neurochemical properties of the normal and abnormal brain. Toward this end many
of these therapeutic agents, as well as non-therapeutic chemical agents, have been extremely useful research tools, as we shall find in this discussion. Although the etiology of schizophrenia or affective disorders is still not understood, based on the known actions of drugs employed for these disorders, it has become possible to formulate working hypotheses around which further research may be directed.

Geriatric neuropsychopharmacology will undoubtedly undergo a similar series of unexpected and serendipitous events before effective drugs are found. Once a truly useful drug materializes, many new ones will be developed, and an understanding of their mechanisms of action will eventually follow. That is the way with new drug development, because the synthesis of new chemicals is much easier than the unraveling of the neurochemical substrates upon which they act. This is especially true for central nervous system (CNS) drugs, since brain research poses much greater problems of appropriate models, species differences, functional endpoints and, above all, its neuroanatomical and neurophysiological complexities. The many problems associated with geriatric neurochemistry have been emphasized by various investigators (4-7). Nevertheless, all would agree that fundamental to an understanding of geriatric drug mechanisms is the differentiation between the normal and abnormal neurochemistry of the aging brain. Our current knowledge of these differences is minimal, and the future of rational geriatric drug development will depend on progress in this area.

However, we have a good start because of the advances made in our knowledge of the neurochemistry and neuropharmacology of the non-aged brain. Our current understanding of psychotropic drug mechanisms may provide us with the clues necessary to embark into research of geriatric agents. This paper will briefly review the current ideas of the mechanisms of those drugs used in neuropsychiatric disorders and will attempt to relate them with known neurotransmitter alterations in the aged. It will not be a comprehensive review of the literature on neurotransmitter metabolism or neurochemistry of the aging brain which has been done ably by various authors (5-10).

NEUROTRANSMISSION AND DRUG ACTION

As Weiner has indicated there are at least a half dozen chemicals in the brain which fulfill the criteria of a neurotransmitter (10). These include acetylcholine (ACh), norepinephrine (NE), dopamine (DA), 5-hydroxytryptamine (5HT), D-aminobutyric (GABA), and glycine. In addition, the recent breakthroughs in neuropeptide research indicate that peptides such as the hypothalamic releasing factors, substance P and the endorphins, may represent a whole new