THE BIOCHEMICAL PHARMACOLOGY OF THE LIMBIC SYSTEM:

NEUROLEPTIC DRUGS

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I. INTRODUCTION

Although neuroanatomical considerations of limbic circuits are approaching their centennial celebration (dated from Broca, 1878) and have been considered as the neuroanatomical substrate of emotion for 40 years (Papez, 1937), the neurochemical anatomy of these brain areas has been seriously considered for little more than a decade. This initial lag period was due mainly to inadequate methods for the assay of putative neurotransmitter substances in small discrete brain regions. However, commencing in the early 1960's with the fluorescent histochemical techniques for elucidation of neurons containing catecholamines or serotonin and continuing with the sensitive radioenzymatic assays for dopamine (DA), norepinephrine (NE), acetylcholine (ACh), gamma-aminobutyric acid (GABA) and their related enzymes, receptors and metabolites, the knowledge of the neurochemistry of limbic regions has literally exploded. Pharmacological considerations of limbic functions by definition include study of any drug which either alters emotionality, or which is used in clinical states where an emotional abnormality exists. To briefly categorize (in a non-inclusive manner) these drugs include hallucinogens, euphoriants, antidepressants, neuroleptics (antipsychotics) and tranquilizers. It would be the scope of a major text to review the biochemical pharmacology of these classes of drugs. In order to present a cohesive and to some extent thorough examination, the author has chosen to review the biochemical pharmacology of the neuroleptics, a class of drugs which are clinically effective against the schizophrenias and other major psychoses (e.g. manic-depressive psychosis).
It is virtually undisputed that neuroleptics ameliorate the schizophrenic condition and that they probably act against the core symptoms of this psychiatric illness (cf. Snyder, 1976; Byck, 1975). If the present theories on biological psychiatry are correct then the antipsychotic actions of these drugs are effected at a biochemical level on specific neurons. The present review will consider the biochemical pharmacology of the neuroleptics with respect to limbic areas and neurons which utilize DA, NE, ACh or GABA.

II. LIMBIC DA NEURONS AND NEUROLEPTIC DRUGS

A. Existence and Distribution of DA Neurons in the Mammalian Limbic System

The first definitive evidence that catecholamine neurons terminate in the limbic system was produced by the fluorescent histochemical technique (Andén et al, 1965; Dahlström & Fuxe, 1964 and 1965; Fuxe, 1965; Ungerstedt, 1971). These studies showed that in the rat, the limbic DA neurons originate in cell bodies medial to the substantia nigra and dorsal to the nucleus interpeduncularis and project to the olfactory tubercle, amygdala, accumbens, septum and limbic cortex. The areas of limbic cortex receiving DA terminals include the cingulate, entorhinal, piriform, and dorsal frontal cortex (Fuxe et al, 1974; Hokfelt et al, 1974; Lindvall et al, 1974). Similar mesolimbic projections have also been reported in the turtle (Parent & Olivier, 1970) and cat (Parent & Poirier, 1969).

In addition to the findings from histochemical fluorescence there is also extensive neurochemical evidence for the existence of limbic DA neurons. The distribution of DA and its metabolites (homovanillic acid, HVA and dihydroxyphenylacetic acid, DOPAC) in the limbic system is outlined in Tables 1 and 2 respectively. Within the limbic areas studied, the olfactory tubercle and nucleus accumbens show similar, high levels of DA, HVA and DOPAC. These levels of DA and DOPAC are of the same magnitude as those in the striatum, the area which has traditionally been considered to contain the highest density of DA terminals. DA turnover in the accumbens (26 nmol/g/h), is reportedly similar to that of the striatum (23 nmol/g/h) (Zivkovic et al, 1975). Similarly, the limbic system and striatum exhibit similar rates of turnover for DOPAC and HVA (Wilk et al, 1975a; Westerink & Korf, 1976). Thus, it appears that at least these limbic nuclei receive as dense a DA innervation as does the striatum. Other limbic cortical and subcortical areas examined contain much lower levels of DA. Of the latter regions internal nuclei within the septum or amygdala may contain high concentrations of DA. Even in the limbic regions containing the low levels of DA, this DA appears to be localized to specific neurons. Thus, lesion of the mesolimbic cell bodies lowers the limbic cortical DA levels.