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32 PHARMACOLOGICAL THERAPY

"We must recollect that all our provisional ideas in psychology will some day be based on an organic substructure. This makes it probable that special substances and special chemical processes control the operation..."

Sigmund Freud

For the treatment of the major disturbances of personality—the psychoses—the psychotropic drugs to be described are the primary therapeutic agents. Certain of these drugs are useful in providing symptomatic relief in the psychoneuroses and physiological disturbances, while others act specifically in relation to certain symptoms, or are useful as enhancers for the effects of the neuroleptic.

The agents now well recognized as modifying pathological behavior may be classified into the neuroleptics, the antidepressants, the anxiolytic sedatives, the psychostimulants, and the somnifacients. The classification in Table 32–1 is based on the recommendation of the Special Committee of the World Health Organization.

The neuroleptics modify psychotic behavior in general and have become the major therapeutic agents, particularly in the treatment of the schizophrenias. The neuroleptics have the capacity to modify affective states without seriously impairing cognitive functions. In this respect, they differ from the somnifacient drugs. In addition to their reaction upon the central nervous system in modifying behavior, they affect the functioning of the extrapyramidal nervous system and the autonomic system. Generally, they act as dopamine-blocking agents. Included in the group are the phenothiazines, the butyrophenones, the dihydroindolines, the dibenzoxazepines, and the rauwolfia alkaloids.

The antidepressants are complex agents, with pharmacological effects in particular on the biogenic amines norepinephrine and serotonin. They include the tricyclic compounds and the hydroxide and nonhydroxide monoamine inhibitors.

The cerebral stimulants include the dextroamphetamines and methylphenidate. These agents tend to produce a transient increase in psychomotor activity, must be considered as stimulants, and are not effectively antidepressant. However, they enhance the activity of certain of the antidepressants.

The anxiolytic agents are sedative hypnotics that generally depress brain function. Pharmacologically, they do not affect the extrapyramidal or the autonomic nervous systems, as do the neuroleptics. In general, whether taken with or without a prescription, over a period of time the individuals receiving

these agents develop a tolerance and may become habituated or addicted or both. Because of the possibility of addiction, they have been classified in many countries as controlled substances.

The somnifacients include the well-known barbiturates, chlorohydrate, ethchlorvynol, glutethimide, methyprylon, methaqualone, and flurazepam. Pharmacological effects are generally shorter but more intense than in the anxiolytic drugs.

The anticholinergic agents are significant as they are effective in the treatment of drug-induced parkinsonism, so common in administration of the neuroleptics.

Since it is expected that the able psychiatrist comes to practice fully knowledgeable from his previous medical studies of the well-known properties and clinical indications of the long-known central nervous depressants such as the narcotics, anesthetics, hypnotics, and intoxicants, as well as the stimulants, consideration is not given to these drugs in this text. Their skillful prescription, often in conjunction with that of the neuroleptics, still is demanded in practice.

PHARMACOLOGICAL ACTION AND BRAIN FUNCTION

The active psychotropic drugs exert complex actions upon various neural systems and the neuron itself. These actions have been demonstrated through changes brought about in animal behavior (particularly through analysis of responses obtained by classical and instrumental conditioning), through depth electroencephalography, through electrophysiological and biochemical studies of synaptic transmission, and through studies of drug metabolism within bodily tissues and changes in endocrine functions.

It is well known now that the psychotropic drugs have a long half-life in bodily fluids. The drugs and their metabolites accumulate in bodily tissues as administration is continued over time. This accumulation ceases when the saturation level is achieved. With cessation of administration, the tissues slowly release the accumulated drugs. Thus, traces may be found in the urine for two or three months after discontinuance. The psychopharmacological properties are generally manifest days to weeks later than the early effects on the other segments of the central nervous system. Thus, the side effects frequently precede the therapeutic response. These well-recognized pharmacodynamic properties are most important, particularly in relation to the modes of administration, prescription, and assessment of therapeutic response, as will be described in a later section.

Much of the variation in effect produced by the differing agents is thought to depend upon their differing actions at the synaptic junctions within the brain. It is considered that the passage of a nerve impulse from activated neurons takes place across the synaptic junction by discharge into the synaptic cleft of the stimulating biogenic amines. These substances then activate the effector site of the postsynaptic neuron.

In Chapter 3 (The Brain and Behavior) and Chapter 19 (Schizophrenic Psychoses), respectively, the synaptic action of the various biogenic amines and the "dopamine hypothesis" as it relates to schizophrenia were described. Norepinephrine, dopamine, the indoleamine serotonin, gamma-aminobutyric acid or acetylcholine are differentially disposed through the brain stem. Certain pathways have been identified as principally containing and thereby activated by dopamine and noradrenaline (Fig. 32–1).

As the storage, release, action, and later re-uptake of norepinephrine, believed significant particularly in the affective disorders, is now well worked

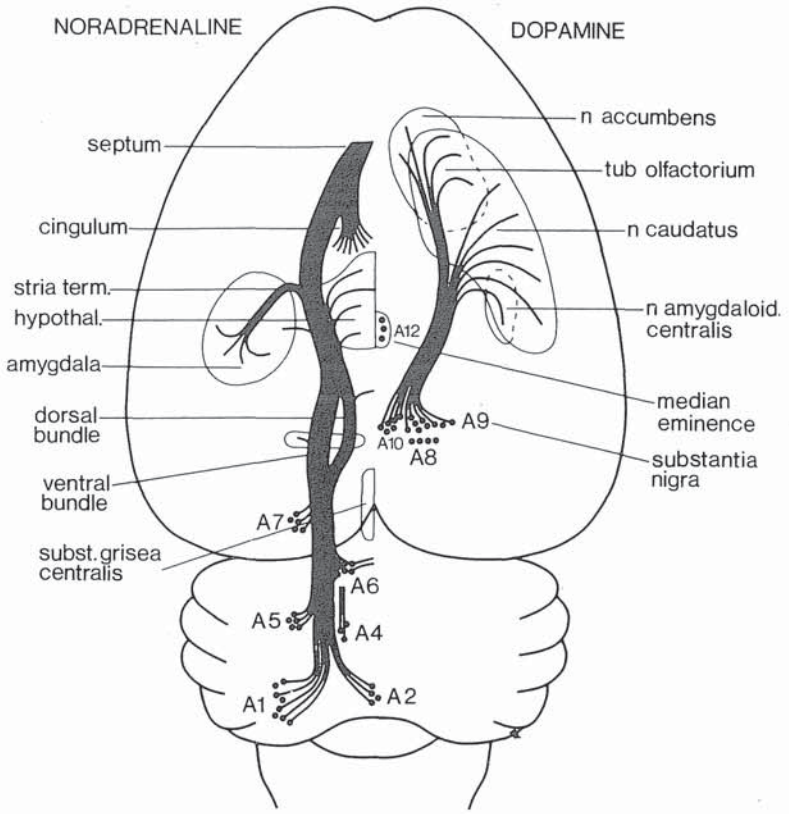

Figure 32–1 Horizontal projection of the ascending NA and DA pathways. A1 and A2, cells in medulla oblongata; A4, cells sending axons to locus ceruleus; A5 and A7, cells in pons; A6, cells in locus ceruleus; A8, cell bodies caudal to substantia nigra; A9 and A10, cells in substantia nigra; A12, cells in N. arcuatus. (From Ungerstedt, U.: Stereotaxic mapping of the monoamine pathways in the rat brain. Acta Physiol. Scand. (Suppl.)*367*:1–48, 1971.)

out, norepinephrine is used here as a model to indicate what are considered the sites of pharmacological action of the drugs used in treatment. Figure 32–1 illustrates the events described hereafter in the text. In Chapter 19, where the dopamine hypothesis in schizophrenia was outlined, it was suggested that this hypothesis alone was insufficient to explain the effective action of the neuroleptics and an alternative was described implicating as well the noradrenergic system.

In the neuron, norepinephrine exists in two forms: the labile form, capable of release by stimulation or by sympathomimetic drugs such as amphetamine, and that form contained in storage granules and released by reserpine. When released from the interneuronal structure, the norepinephrine flows into the synaptic cleft and then is returned to the cell, where it is stored or oxidized by the enzyme monoamine oxidase. The monoamine oxidase inhibitors, such as iproniazid, increase the amount of intraneuronal norepinephrine, making more available. Reserpine depletes the intraneuronal amines, thus diminishing the amount available for activation.

Both the phenothiazines and the iminodibenzyls, such as imipramine, diminish cellular permeability. For this reason, the released norepinephrine is partially prevented from returning to the neuron and its concentration in the synaptic cleft is prolonged over time.

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