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MECHANISM OF ACTION OF PSYCHOTROPIC DRUGS

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YEARS ago W. R. Hess of Zurich[1] formulated bold and comprehensive concepts of brain function which have not been fully appreciated. Today, however, we find that his views are of paramount importance in bridging the gaps between biochemical and anatomic aspects of brain function and in explaining the mechanism of psychotropic agents.

Hess stimulated electrically a great number of brain stem areas in unanesthetized cats. From the responses he postulated that two opposing systems in the brain stem integrate autonomic, somatic, and psychic functions, thereby coordinating physiologic responses to endogenous and exogenous stimuli. Stimulation of one system (ergotropic) elicited increased sympathetic responses, psychomotor activity, and alertness, and evoked marked emotional responses. In contrast, stimulation of the opposing system (trophotropic) elicited opposite effects: increased parasympathetic effects, decreased psychomotor activity, lowered responsiveness to stimuli, quietude and sleep, and decreased emotional responses.

Reserpine induces a syndrome that is strikingly like that of trophotropic stimulation, suggesting that the drug activates this system. Conversely, LSD induces responses similar to those of ergotropic stimulation, suggesting that it activates this system. It is logical to consider that these psychotropic agents may affect the relative excitability of the subcortical systems by influencing transmission at synapses. Diametrically opposing neuronal systems, closely interwoven in the same area of the brain, should require different neurohormonal transmitters. There is now con-

siderable evidence that norepinephrine may be the ergotropic neurohormone and serotonin the trophotropic neurohormone.[2]

The mechanism of action of a number of psychotropic agents may be described according to their effects on the two neuronal systems. Bearing in mind that the subcortical brain systems are mutually antagonistic, it should be possible to elicit the same syndrome by stimulating one system or by depressing the other.

Drugs that Produce the Trophotropic Syndrome

A drug may produce trophotropic predominance either by stimulating the trophotropic system or blocking the ergotropic system (thus unmasking the trophotropic). Thus, reserpine appears to stimulate the trophotropic system, perhaps through free serotonin, whereas chlorpromazine elicits similar results by blocking the ergotropic system through interfering with the action of norepinephrine.

Action of reserpine-type drugs

The action of reserpine is an indirect one, as indicated by the observation that its action persists long after the drug has disappeared from the brain. The alkaloid interferes with the mechanism that stores serotonin in cells without interfering with the rapid biosynthesis of brain serotonin.[3] Consequently, the serotonin that forms and leaves the cells in a continuous stream may stimulate synapses of the trophotropic system. The action of reserpine is similar in a number of respects to that of free serotonin in brain. The parenteral administration of serotonin in mice induces ptosis, sedation, and potentiation of hypnotics.[3] In rats it decreases motor activity and depresses a specific partial block in a conditioned response.[4] It has been shown to induce EEG sleeplike patterns.[5] In cats, small doses of 5-hydroxytryptophan, which enters the brain and is decarboxylated to serotonin, also produces sedation and EEG sleep patterns.[6]

The capacity of brain cells to store norepinephrine is also impaired by reserpine;[7, 8] and the catechol amine, like serotonin, may also be formed and leave the cells continuously. Reserpine may be depicted, therefore, as inducing the stimulation of both trophotropic and ergotropic systems with the major effect that of trophotropic stimulation, perhaps because of a faster biosynthesis of serotonin.

Certain pharmacologic actions of reserpine illustrate this dual action. For example, the miosis induced in rabbits by large doses of reserpine is much more pronounced than that seen after section of the cervical sympathetic fibers. This effect apparently results from central parasympathetic (trophotropic) stimulation.[6] On the other hand, the centrally

mediated release of catechol amines from the adrenal medulla, which lasts for many hours following reserpine administration,[8,9] may be considered to reflect ergotropic stimulation, since the adrenal medulla is innervated only by the sympathetic division of the autonomic nervous system.

The central action of reserpine has also been considered to result from the depletion of serotonin or of norepinephrine in the brain. But this possibility is based on animal experiments in which large doses of the drug completely deplete the depots of brain amines. But studies using small doses of reserpine provide evidence that the brain depots are only partly depleted. It seems simpler to assume that the central effects are due, not to a shortage of stored neurohormones, but rather to the amines which are being continuously made and released to receptor sites.

It has been usual to consider that reserpine acts as an antimetabolite of serotonin. But Pletscher[10] has reported that a series of non-indole derivatives of benzoquinolizine also release serotonin and elicit reserpine-like effects. Studies of the action of one of these drugs (tetrabenazine) revealed that it releases norepinephrine[11] as well as serotonin. This new drug differs from reserpine in a number of ways. It is much less potent pharmacologically than reserpine, and a dose of 25 to 50 mg./kg. releases only part of the brain norepinephrine and serotonin. In addition it acts more rapidly than reserpine and appears to act reversibly in that the amine content and the behavior of the animal return to normal in a much shorter time after this drug than after reserpine. This type of drug is potentially important since its pharmacologic effects rapidly disappear after therapy is discontinued.

Tetrabenazine appears to act on the same receptor sites as does reserpine. This was shown by experiments in rabbits given tetrabenazine a few minutes before reserpine. Animals were sedated for only a few hours, whereas animals given reserpine alone were sedated two to three days.[11] These results suggest that tetrabenazine occupies the sites on which reserpine acts and thus prevents its action. By the time the action of the tetrabenazine is terminated the reserpine has been metabolized and can no longer exert its "irreversible" effect.

Action of chlorpromazine-type drugs

Considerable evidence now indicates that chlorpromazine acts centrally by a different mechanism than reserpine, one not involving the release of serotonin or norepinephrine. Experiments showing clearly that chlorpromazine and reserpine act by different mechanisms involve administration of dihydroxyphenylalanine (DOPA), the amino-acid precursor of the catechol amines. This substance, administered intravenously to

rabbits, elicits typical ergotropic effects.[12] We have found that the amino-acid precursor passes into the brain and is there decarboxylated to dihydrophenylethylamine, which differs structurally from norepinephrine only by lacking the side chain hydroxyl group. We have also found that the effects of DOPA are actually potentiated in rabbits pre-treated with reserpine, and that the excitement and increased psychomotor activity can be blocked by chlorpromazine but not by additional amounts of reserpine.

Since chlorpromazine blocks the central actions of parenterally administered catechol amines and synthetic norepinephrine analogs such as mescaline and amphetamine, it may be considered to block the ergotropic system by interfering with the action of norepinephrine in brain.[13] In accord with this view chlorpromazine constricts the pupils by a central action to a lesser degree than does reserpine, and only to the extent observed on sectioning the cervical sympathetic ganglia. Many adrenergic blocking agents in high dosage produce sedation and decreased sympathetic activity, presumably by acting as central adrenergic blocking agents.[13] Chlorpromazine is unique in that it has little direct effect on the peripheral autonomic system; and sedation, miosis, and relaxation of the nictitating membrane are observed after the intraventricular injection of a dose too small to exert a direct peripheral action.[14]

Drugs that Produce the Ergotropic Syndrome

A drug may induce the ergotropic syndrome either by stimulating the ergotropic system or inhibiting the trophotropic system (thus unmasking the ergotropic).

Mescaline and a number of other compounds (amphetamine, ephedrine, desoxyephedrine), chemically related to norepinephrine, may stimulate the ergotropic system by mimicking the action of norepinephrine at ergotropic synapses. It is particularly noteworthy that in addition to eliciting the usual signs of ergotropic stimulation these compounds induce in man euphoria, and, in larger doses, psychotic behavior and illusions. The reversible psychoses produced by these agents may be regarded as exaggerated responses to stimuli produced by the hyperactive ergotropic system.

LSD, the most potent of the ergotropic agents, is an indole ethylamine and has been considered to exert its effects by interfering with the action of serotonin.[15] From this viewpoint it may be considered to block the trophotropic system, thereby unmasking the ergotropic. Bufotenine may also produce its ergotropic effects in the same way.

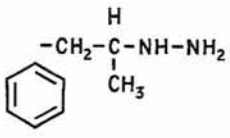
Ergotropic agents usually exert some direct action on the peripheral autonomic system in addition to their central ergotropic action. How-

ever, phenidylate (Ritalin), a phenylethylamine, is reported to have only minor peripheral effects and to be useful in treatment of the depressed patient.[16]

Drugs that Block Monoamine Oxidase

A large number of compounds inhibit monoamine oxidase, the enzyme mainly responsible for the inactivation of both serotonin and norepinephrine in the brain.[17] The best known of these inhibitors is iproniazid[18] (l-isonicotinyl-2-isopropylhydrazine (Marsilid)), which was originally introduced as a drug for the treatment of tuberculosis; but it was soon found that the drug caused effects of a central stimulatory nature. Recent observations by Kline and his associates[19] indicate that the central actions of this drug make it effective in treatment of depressed mental conditions.

Certain amine oxidase inhibitors have been shown to induce an increase in the level of norepinephrine and of serotonin in the brain.[20] Thus, the daily administration of 10 mg./kg. of iproniazid to rabbits induces excitement after four to five days, at which time the brain levels of both serotonin and norepinephrine have risen to approximately twice the normal values. Another compound, JB 516 (Lakeside Laboratories),



is an unusually potent monoamine oxidase inhibitor of a different chemical series. Given to rabbits in daily doses of 1 mg./kg., it induces, in three to five days, pharmacologic effects similar to those of iproniazid and raises the brain level of amines about twofold.

It is possible that the ergotropic (anti-depressive) effects of the monoamine oxidase inhibitors are causally related to the rise in brain norepinephrine, but additional studies are needed to establish the precise mechanism of action.

Discussion

Hess[1] postulated that the autonomic, somatic, and psychic functions in the body are balanced by two opposing systems in the brain stem, the trophotropic and the ergotropic. On the basis of evidence presently available the theory is proposed that these systems have receptor sites that are modulated by serotonin and norepinephrine. Rauwolfia alkaloids are

considered to elicit a trophotropic syndrome by stimulating the trophotropic system (through release of serotonin), whereas chlorpromazine and its analogs may act by depressing the ergotropic system by interfering with norepinephrine action. The resulting imbalance of the subcortical systems leads to sedation, decreased response to sensory impressions, a decline in skeletal muscle tone, and a decrease in sympathetic activity. In contrast, LSD and mescaline produce an imbalance by eliciting an ergotropic syndrome — LSD perhaps indirectly by blocking the trophotropic system through interfering with serotonin action; mescaline and other norepinephrine analogs by stimulating the ergotropic system, by mimicking the action of norepinephrine.

The question arises as to what psychotropic drugs do in subjects with mental disorders. Reserpine and chlorpromazine usually affect any of a number of mental disorders provided they are manifested by hyperactivity and exaggerated emotional responses. It is logical to presume, therefore, that they may influence the symptoms of the disease by changing the balance in the direction of trophotropic predominance, and thus blunting initiative by decreasing psychomotor activity and lowering the responsiveness to endogenous and exogenous stimuli. On the other hand, Ritalin and monoamine oxidase inhibitors are useful in the treatment of depressed patients by changing the balance in the direction of ergotropic predominance.

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