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MINIREVIEW

PHARMACOLOGIC IMPLICATIONS OF HEMISPHERIC ASYMMETRY

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SUMMARY

The hemispheric asymmetry of brain activity is well established, and there is increasing evidence of a relationship between phenomena of asymmetry and personality, arousal status, and the existence of mental and emotional disease.

Differences in individual sensitivity to drugs may relate to hemispheric asymmetric patterns. Several mechanisms may contribute to the unequal influence of systemically administered drugs on each hemisphere, including effect of hemispheric activity status on 1) speed and degree of local uptake of drug; 2) differential in synaptic sensitivity; 3) degree of competition with local endogenous neurohumors.

Adequate knowledge concerning normal and abnormal hemispheric asymmetry, and the effects of spontaneous or manipulative changes in the activity of each hemisphere should lead to more rational and effective choices and patterns of administration of therapeutic agents.

There have been many major advances in recent years in the understanding of factors which influence drug disposition and mechanisms of action. Nevertheless, the clinician continues to be confounded by individual differences in patient response to a great many drugs, and often must resort to empirical trial and error in arriving at optimal doses and even a choice of drug for each patient. The clinician now knows that he must take an interest not only in how much of what drug he prescribes, but where that drug subsequently goes, what happens to it, and what it does to what organs. An obviously important variable which must help determine the nature of the response to the drug, but which has received relatively little attention, is the dynamic state, i.e., the state of activity, of the target organ at the time the drug arrives there.

In considering this factor in relation to centrally active drugs, one well recognized but poorly understood variable is the pattern of activity of those parts of the brain which determine the underlying personality and behavior of the subject. Since the personality of each subject, normal or disturbed, reflects the physiologic state of the brain, personality can be expected to be a contributing determinant of the response to centrally active drugs (1,2,3, 4,5). Similarly, the response to drugs can vary with cyclic alterations, such

as day-night and other periodic or induced variations in degree of alertness, etc. These variations within and between individuals demand the individualization of therapy which is so burdensome to the practitioner. His impatient hope for the day when chemists and pharmacologists will develop uniformly effective drugs for a given disturbance is not likely to be realized until the interplay between the underlying mental (brain activity) state and the drug is better understood.

An initial consideration in attacking this problem is to identify "target" structures which drugs must influence in order to correct the disturbance being treated in mental illness. Anatomical (reticular, thalamic, hypothalamic, cortical, etc.) concepts are often utilized in considering the mechanisms responsible for personality or specific types of behavior. Nevertheless, theories based on premises of selective drug action at specific structures have been treated with suspicion. Dews (6), for example, wrote: "If the effect of the drug is stated in categorical terms to be on certain gross anatomical regions of the brain, the reader would almost always have the right to be skeptical in the past. He will probably continue to be right a very large proportion of the time in the foreseeable future if he maintains the same strategy."

Drugs do penetrate different areas at different rates and to different concentrations. It is not unusual to seek clues as to the nature of a drug's action by determining its sites of localization. Certainly, the accumulation of systemically administered iodine in the thyroid correlates with the nature of the prime therapeutic utility of that agent. Specific receptors, critical to activity, have been detected at specific sites by the localization of appropriate labeled compounds (7,8). The state of development and activity of the organ can be expected to influence the degree to which these receptors are in a position to interact with an appropriate drug. Even though very few, if any, drugs are restricted to a single area (9), the ultimate effect of a drug is bound to be the consequence of its concentration at its "sites of action", rather than its general distribution.

This review is concerned primarily with recent evidence that the two hemispheres of the human brain exhibit fundamental differences in activity which play a role in personality and mental disease. These differences can no longer be ignored in considering differences in drug-response patterns (10). A better understanding of hemispheric differences, integrated with information concerning the pharmacokinetics and mechanism of action of centrally active drugs, may help to better understand and manage the plethora of individual responses to centrally active drugs and perhaps give clues as to a better selection and timing of drug therapy.

"Hemisphericity" may be a Critical Determinant of Personality

The phenomenon of right or left handedness in humans has long been correlated with the observation that hemiplegia of the dominant side is associated with asphasia, leading to the concept that the subdominant hemisphere (right hemisphere for right-handed people) is "mute", with the implication that not only the control of speech, but thought and personality as well, reside in the "dominant" left hemisphere.

A most fascinating approach to the analysis of personality was discovered 25 years ago when Bogen split the brain of an epileptic patient for the purpose of controlling the interhemispheric spread of epileptic discharges. Further research (11,12,13) revealed that commissurotomy totally disrupted the interhemispheric exchange of information, so that the function of each hemisphere could be evaluated separately. Investigations of commissurotomized patients

with a variety of brain lesions and ingenious designs for the study of hemisphere function in normal subjects resulted in the conclusion that the presumably "mute", "subdominant" right hemisphere has its own type of reasoning. While the left hemisphere is involved in the elaboration of language, the right appeared to be superior in spatial skills (11). Further distinctions between the left and right hemispheres have been defined in terms which contrast the 2nd vs. 1st signalling system (14), serial vs. parallel (15,16), analytic vs. gestalt (11), propositional vs. appositional (11) responsibility for the general vs. local orienting response (17), etc. On the basis of experimental evidence, Bogen (18) has hypothesized that the right hemisphere is "more kinesthetic than visual and more visual than auditory, and possibly more intero- than extroceptive." It is believed that the two hemispheres have different "modes" of cognition and emotionality.

Most of the limited data on the emotional asymmetry of the cerebral hemispheres have been reviewed by Schwartz et al. (19). Carmon and Nachshon (20) report that non-verbal emotional human voices were perceived better by the right (non-dominant) hemisphere. According to Schwartz et al. (19), even verbal material is processed by the non-dominant hemisphere if it has affective meaning. Nevertheless, the nature of the "emotional specialization" of the two hemispheres is still a mystery.

Emotional reactions paired with disturbances of speech may offer clues to the mechanism of centrally active drugs. Unfortunately, "'speech researchers' have not been particularly interested in drugs, and 'drug researchers' have not been much more interested in speech ..." (21).

By recording auditory evoked potentials to words and syllables, Molfese et al. (22) demonstrated that there is asymmetry of responsiveness even in preverbal infants. Potentials were lateralized in most of them in the left hemisphere. Non-speech, sound stimuli produced larger evoked potentials in the right hemisphere.

It would be an erroneous over-simplification to infer that one hemisphere is totally unable to do the work of the other (14). People are unequally lateralized, i.e., have different degrees of verbal ability and visuo-spatial skills in the left and right hemispheres, respectively. "Lateral specialization, including language functions ... would appear to be subject to a considerable range of individual variations" (12). People tend to preferentially utilize one hemisphere over the other in the solution of different problems, i.e., their behavior is biased by their "hemisphericity" (18). In this respect, it is safe to assume that certain aspects of behavior are preformed.

"Hemisphericity" is Changed During Slow-Wave Sleep

To date, the functional asymmetry of the human brain has been inferred exclusively from studies conducted in the waking state. There is limited evidence indicating that the differences in hemispheric activity observed in the waking brain might be considerably altered in sleep. Asynchronous sleep patterns have been considered normal up to five months of age while interhemispheric asymmetry of EEG thereafter was presumed to be abnormal (23). However, the definite waking EEG asymmetry associated with specific hemispheric functions in adults leads one to expect that the peculiar type of mentation, perception, learning and responding which occurs in sleep would also involve interhemispheric functional differences.

It has been demonstrated (24) that loss of consciousness followed intracarotid amobarbital injection into the speech dominant hemisphere, while with similar injection of the non-dominant hemisphere loss of consciousness was rare and of

short duration. These observers concluded that "consciousness is generally linked with the function of the hemisphere dominant for speech" (24).

Myslobodsky et al. (25) measured the interhemispheric asymmetry of sleep spindles in EEG and averaged visual evoked potentials across slow-waves in sleeping normal volunteers. A consistent prevalence of spindles over the right hemisphere and more pronounced slow-wave activity over the left were demonstrated. Asymmetry in the slow-wave activity was confirmed by an analysis of the secondary components of the visual evoked potentials (25,26). The data indicate that the hemisphere generally considered to be "subdominant" during the awake state is subject to less intense non-REM sleep, suggesting a reversal in the "dominance" of the hemispheres in sleep.

It may be premature to speculate on the nature of this day-night interchange of dominance. There is the possibility of asymmetry of serotoninergic or GABA mechanisms or the receptivity of telencephalic mechanisms in slow-wave sleep. Fink (27), in correlating the therapeutic nature of a drug with the effect of single modest doses on the EEG of normal volunteers, noted that the characteristic EEG alterations which he identified with drug action required the subject to be relaxed but awake. The EEG strips recorded when the subject dozed off were not applicable to the criteria he had established for drug evaluation.

Individual Responses to Drugs may be Associated with their Differential Action on the Right and Left Hemispheres

Goldstein and Stoltzfas (28) compared changes of integrated EEG amplitudes from the two hemispheres (occipital areas) in awake human subjects under the influence of various psychoactive drugs. Interhemispheric EEG relationships were definitely affected by some drugs. D-amphetamine decreased interhemispheric EEG differences. An experimental analgesic, (D-675 N-isopropyl-N-methyl-3-formamido-1-pyrazole-carboxamide), which was found to produce hallucinations in man reversed the right to left EEG amplitude ratio. Chlorpromazine did not affect interhemispheric EEG differences.

Rossi and Rosadini (29) have demonstrated that intracarotid amobarbital injections elicited different emotional reactions depending on the side of injection in many of their subjects. In most cases, left-side injection produced depressive reactions, while right-side injections were followed by euphoria. However, in some subjects the reverse response was observed, and in several instances emotional reactions to right-sided injection were quite complex, with manifestations of both depression and euphoria. The results of these studies show a correlation of hemispheric dominance with the observed "emotional specialization of hemispheres", as determined by reaction to intracarotid amobarbital, but with enough dominance/emotion dissociation for the authors to conclude that "the hemispheric specialization for mood and emotion appears to be independent of a dominance of one hemisphere over the other."

Essentially nothing is known about the asymmetry of neurochemical mechanisms associated with hemispheric specialization. Some authors believe that the affective states of the two hemispheres are quite similar (18) on the basis of both animal studies and observations in patients with a split brain. There is some evidence, however, that affective charges of the two hemispheres are different even in the subhuman primate (30).

Drugs may Act by Uncovering or Potentiating a Pre-existing State of Hemispheric Activity

There are numerous examples in which the emotional state at the time of

exposure to a drug influences the nature of the response. Evarts, in his comment on the report of Rossi and Rosadini (29), mentioned that emotional reactions to LSD in normal subjects depend upon the situation in which the drug is taken. When subjects are busy with psychological or psychomotor tests, they display little or no emotional reaction to the drug. Reports about hostile feelings brought on by LSD have been linked to the fact that the subjects were prisoners with feelings of hostility prior to LSD administration. These feelings were potentiated, rather than caused by the drug (21). Some phenothiazines decrease anxiety scores only in those patients who score high on this measure in a placebo period (31). Even in animals, the apparent response to a "stimulant" such as pipradrol is not simply "stimulation". It depends largely upon the conditioning status of the animal at the time the drug is given (32). In more active rats, modification of locomotor activity by stimulants and depressants is more readily apparent (33).

Individual differences in responses to barbiturates and alcohol are well known. Most users become euphoric, but some become depressed and hostile. The degree to which some phenothiazines and other drugs affect speech depend upon the pretreatment verbal activity (21). Morphine in the same dose may evoke euphoria in some patients and mild anxiety or fear in others. It is remarkable that euphoria was observed in patients with initial anxiety and tension, while fear was induced in optimistic, pain-free individuals (34).

Since all these pretreatment states may be reflecting functional hemispheric asymmetry, drugs may influence each hemisphere differently, yielding resultant patterns of behavior which are highly individualized.

The response to electrical stimulation may also be a function of the underlying activity state of the brain. Valenstein (35) observed that some rats electrically stimulated at several different sites within a given anatomical region exhibit a particular pattern of behavioral response, while other animals stimulated at comparable sites exhibit a different response or no detectable response. Valenstein concluded that "The behavior produced by brain stimulation is, in part, the concomitant of the responses that tend to be dominant as a result of the interaction of such factors as environmental conditions, the presence of compelling stimuli and a particular aroused animal." These determinants of behavior were defined as the "prepotent response". For instance, natural mouse killing behavior in rats was a good predictor of the effectiveness of hypothalamic stimulation to elicit mouse killing (36). Penfield and Perot (37) were able to evoke dreams and memories by stimulation of the temporal lobe only in patients who had had such experiences as a feature of an underlying epileptic status.

Brain Pathology may Selectively Change Reactivity of the Hemispheres to Drugs

In depressed patients, intracarotid amytal injections lead to elevation of mood for both dominant and non-dominant hemispheric injections, as if in depression "both hemispheres appear to have the organizational structure of the non-dominant hemisphere" (38). An interesting set of data, consistent with this interpretation, are the observations that a) visuo-spatial skills (39) and some aspects of verbal processing (40) are less lateralized in females than in males, b) depression is twice as frequent in women than in men, and c) women benefit more than men from antidepressant drugs (41).

On the basis of the analysis of psychotic symptoms in temporal lobe epilepsy, Flor-Henry (42) related schizophrenia and psychopathy to dominant lobe temporal-limbic dysfunction and manic-depressive symptoms to the non-dominant temporal involvement. Observations on lateral asymmetry of electrodermal activity in schizophrenic and depressive patients seem to be in accord with

this model (43,44). However, others have come to the conclusion that the dominant rather than non-dominant hemisphere is more deeply disturbed in depression (45).

Recent unpublished studies (Myslobodsky and Horesch) showed that in depressed patients the skin conduction response was significantly greater in the left (non-dominant) hand. Similarly, by the technique reported by Schwartz et al. in normal subjects (19), depressed patients were mostly "left movers" in terms of the eye deflection response to questions of all types (emotional, neutral, analytical and spatial). Thus, both skin conductance and eye deflection studies strongly suggest a higher arousal of the right hemisphere in depressed patients. The phenomenon may be due to right hemispheric primary hyperactivity, or a left hemisphere derangement which releases activity of the right, or both. Our understanding of the problem is too limited to allow definite conclusions. Nevertheless, the evidence indicates that hemisphericity is deranged in psychotics, suggesting that a rational therapeutic goal and a possible technique for assessing the success of therapy could be the restoration of normal patterns of hemispheric asymmetry, or normal balance of arousal of the two hemispheres (26).

Several Mechanisms may Contribute to the Selective Effects of Systemically Administered Drugs on Hemispheric Activity

Before reviewing the possible mechanisms of asymmetric action of systemically administered centrally active drugs, it may be worth noting some characteristics of non-drug therapeutic modalities, such as electroshock and REM sleep deprivation for comparison with drug effects. There is a tendency for the same depressed patients who are responsive to imipramine also to be responsive to REM sleep deprivation (46). This capacity to respond to such apparently totally different modalities of therapy suggests that responsiveness may be a predictable phenomenon if one can properly evaluate the underlying status. One index to be considered is responsiveness to placebo, since valid therapeutic efficacy is often built upon the potential for placebo response (47). These facts are not inconsistent with the hypothesis that the nature of the underlying disturbances in asymmetry may determine the success of drug or non-drug treatment. The electrophysiologic and biochemical consequences of both the introduction of a drug or interruption of REM activity may predominate in that hemisphere which is functionally disturbed.

Amytal has long been used to make withdrawn patients more communicative. It shifts the emotional state along the depression-elation scale in the direction of elation. Systemic (intravenous) amytal administration mimics the effect of the right (non-dominant) hemisphere barbiturization via the carotid artery. Amphetamine increases performance in numerical and reading tasks, and is also euphoric, i.e., consistent with activation of what are considered left hemispheric functions. These differences in hemispheric activity may be reflecting corresponding differences in neurohumoral receptors in terms of a selective capacity to pick up different drugs, resulting in what is recognized as different drug actions. The addicts' preference to use amphetamine-type stimulants when in the company of others might be the consequence of a more effective drug uptake or enhanced sensitivity of the active hemisphere when it is in a behaviorally more active state. Perhaps the common technique of anesthesiologists to ask patients to count backwards during pentothal induction serves more purpose than is realized.

Alcohol is similar to amphetamine in several respects. It is a powerful catecholamine releaser. In modest doses it mimics centrally antidepressant drugs, i.e., activation of speech and elation, which are predominantly left hemisphere functions. With large doses, alcohol could mimic the effect of

the left hemisphere barbiturization. Asymmetry of alcohol action was demonstrated recently with the analysis of evoked brain potentials. Rhodes et al. (48), report that alcohol selectively depressed the reactivity of the right hemisphere (components P90-N120 of the visual evoked potential) to a significantly greater extent than left hemispheric reactivity. The dose of alcohol used yielded a blood level of 90-100 mg.% and produced drowsiness, motor and visuo-spatial difficulties, i.e., impairment of functions controlled predominantly by the right hemisphere. However, this result is subject to other explanations, and more data are needed with different doses of alcohol for more definite conclusions.

The following is a theoretical review of several possible mechanisms by which systemic drug therapy may be hemispherically selective:

I. Differences in hemispheric activity create an opportunity for hemispheric differences in degree and rate of drug uptake: The penetration of substances into the brain is governed by many factors. The classical concept of a blood-brain barrier, penetration of which depends on lipid-water partition coefficient and pKa of the compound, explains why many drugs fail to get into the brain (49). But many which do penetrate are found unequally distributed within the brain tissue. Autoradiographs frequently demonstrate such unequal distribution. As may be expected, lateralization of distribution is not seen in such studies which are generally performed in young animals. However, they leave little doubt that all drugs do not distribute homogeneously in the brain.

The concept of asymmetric "activity directed drug disposition" has several possible mechanisms:

a) Asymmetric blood flow rates: The obvious increase in blood flow to an actively functioning peripheral organ, such as a muscle or gastric mucosa, has its counterpart in the brain. Metabolic events (as measured by uptake of radioactive substances, local blood flow, changes in brain temperature, pO_2, pCO_2, etc.) are related to electrophysiological activity and their behavioral expressions. General seizures are accompanied by a marked increase of the metabolic rate of the brain (50). The increase is considerable during grand mal and minimal during petit mal (51).

Activation of the visual system results in local blood flow acceleration and increase in Ach release in the visual cortex (52). Photic stimulation results in selective increases in the level of labeled (S^{35}) sulphate in the visual cortex and lateral geniculate body, while auditory stimulation produces corresponding increases in the penetration of S^{35}-sulfate into the inferior colliculus in the brain (53). In anesthetized cats, light stimulation at frequency 2-12 cps produced temperature increase, while frequencies from 52 to 62 cps produced temperature decrease in the lateral geniculate. Auditory stimuli increased temperature in the inferior colliculus (54). It is believed that evoked thermal response is the result of local neural metabolic heat production and increases in local blood flow (54).

Regional blood flow appeared to be markedly different in the waking state, REM, and slow-wave sleep. During REM sleep in unrestrained cats, there was a marked increase in local flow in all regions measured in the study. In slow-wave sleep, 10 of 25 regions showed a small but significant increase in flow (55). In man, frontal cortical blood flow measured by different methods was also increased during REM sleep. It differed from local flow increases in slow-wave sleep by a

disappearance of fluctuations which correlated with slow-wave patterns (56).

Recently, asymmetry of cerebral circulation was found during sleep with rheoencephalographic techniques. An inflow angle and amplitude of rheoencephalographic wave appeared to be greater in the right hemisphere (57).

Olesen (58) demonstrated that vigorous hand exercises can affect regional cerebral blood flow and metabolism in the area corresponding to cortical representation of the hand. During work with the ipsilateral hand, focal changes were absent or minimal.

Ingvar and Risberg (59) measured regional blood flow in four circumscribed hemispheric regions in human subjects at resting state and during the performance of an analytic task. The mental task elicited an increase in grey matter flow in the suprasilvian region, showing that augmentation of such flow "reflects more or less regional functional (metabolic) accompaniments to mentation." Similar results were obtained for another group of patients, again indicating that the grey matter of the brain does not work at a uniform functional level, but that "islands" of activity can be identified by techniques which are sensitive enough to measure blood flow regionally (60).

Recently, Risberg et al. (61) used ^{133}-Xe inhalation techniques for studies of regional cerebral blood flow during mental activities chosen to engage the hemispheres selectively (verbal test vs. spatial test). The verbal test altered the flow more in the left hemisphere, while the spatial test increased the flow in the right hemisphere. The hemispheric differences were more apparent and statistically significant in the "motivated group" of subjects who were promised more pay for a successful performance.

Such increased flow means more drug-containing blood bathes the tissue per minute. Since the concentration of drug in the blood brought to all regions is the same, one might argue that a change in flow rate would not alter the tissue exposure to the drug. This argument does not take into account the kinetics of water-to-lipid partition for agents with a very high partition coefficient in favor of lipids. In such instances, which are almost universal for drugs which pass the blood-brain barrier, the amount of drug per unit time available for lipid tissue uptake may be as much or more of a determinant of drug uptake than just the concentration of the drug in the circulating aqueous phase. An analogous situation which illustrates this phenomenon is the toxicity of drugs to fish. The sedating effect achieved with a barbiturate in a fish tank is a function of the total amount rather than concentration of drug in the tank. The amount of drug the "lipid" fish picks up from the water per unit time is a function of the amount of drug brought to its gills in that time, i.e., the product of concentration times flow rate. In tanks of finite size, the fish will pick up essentially all the barbiturate in the tank, regardless of concentration.

b) Altered neurohumoral turnover as a function of activity: For drugs which exert their effect by becoming incorporated in the cycle of neurohumoral release and re-uptake, the more active the cycle the more extensively is a drug likely to be incorporated into the cycle within a given time and concentration framework. Thus, with the same exposure to drug at a site of action, more drug may become localized at that

site of action if it is more active at the time of exposure.

c) Altered availability of receptor sites: A variety of forms of tissue activity has been shown to change the quantity of specific receptors in various tissues (62). The presence of steroid receptors in the brain and the influence of steroids on emotional and other cerebral function have been correlated with drug and neurohumoral metabolizing enxymes (63). While this field of investigation is still embryonic, activity-induced changes in important hormonal receptors may have to be considered in evaluating the potential influence of hemispheric asymmetry on drug localization, especially with relatively long-term therapy.

d) "Active transport" mechanisms: Some drugs which penetrate the blood-brain barrier do not meet the partition coefficient-pK requirements for passive transfer, and seem to penetrate by active transport mechanisms such as those responsible for brain penetration by sugars and amino acids. Since the amount of these nutrients actively transported is a function of the overall rate of tissue activity and metabolism, the transport of some drugs may mimic metabolic asymmetry.

At this point, all of the above possible mechanisms of activity-directed disposition remain hypotheses, far from proved, but deserving consideration.

II. Differences in hemispheric activity may influence synaptic sensitivity: The phenomenon of sensitization to drugs by presynaptic denervation and desensitization by synaptic destruction are well recognized. The influence of more subtle changes in the presynaptic and synaptic state in the CNS as a correlate to activity could be expected to be reflected in altered responsiveness. Supersensitivity to certain substances may be created by partial denervation of the nervous center. In effect, sensory deprivation resembles such denervation (64). For centuries the trend of our culture has been to "underload" the right hemisphere, reinforcing mainly skills of the left hemisphere (16,18). As a consequence, the right hemisphere should be relatively supersensitive. On the other hand, some of the evidence cited above suggests that the left hemisphere is more responsive to drugs. Perhaps ultimate relative responsiveness is a balance between greater drug uptake in the more active left hemisphere, and a degree of synaptic hypersensitivity in the "underloaded" right hemisphere.

III. Activity related differences in concentration of neurohumoral mediators may influence the local response to drugs which are analogues of these mediators: The concentration and bound vs. free status of endogenous neurohumoral transmitters often reflects the activity state of the synapses. The activity of "false transmitters", "competitive inhibitors", "releasers", etc., are superimposed on this base of endogenous catechols, etc. The increased toxicity of amphetamine in grouped vs. isolated animals is not correlated with brain amphetamine levels, i.e., the same dose of amphetamine yields essentially the same brain levels of the drug in both groups (65). However, the endogenous catechol brain levels are higher in crowded animals. In fact, such endogenous stimulants can be released to the point of gross "toxicity" without any exogenous drug. The fatal response to otherwise modest doses of amphetamine given to grouped animals probably results from the summated effects of high endogenous catechol levels and the administered sympathomimetic drug, since such fatality correlates with motor activity and temperature with grouped, but not isolated animals (66).

In the context of hemispheric asymmetry, these concepts suggest one possible

mechanism by which a drug may have significantly different effects if given while the subject is engaged in spatial conceptual tasks vs. language or mathematical activity. Since there is definite and non-identical hemispheric day-night cycling, this represents another mechanism by which the timing of a therapeutic program may be important to the outcome. There may well be some advantage to knowing which hemisphere shows a functional abnormality at what time in selecting a drug and a time-dose pattern for its administration. Can depressed patients be diagnostically grouped as being a consequence of left hemisphere over-activity, right hemisphere under-activity, or possibly an inversion of the day-night pattern? If so, would such grouping correlate with responsiveness to different modalities and patterns of treatment?

Given the present state of the art, the subject deserves more attention than it is getting.

CONCLUSION

The activity of the brain is not uniform or symmetrical. It involves metabolic and other factors which can influence the localization of drugs and drug action. With adequate knowledge of normal and abnormal hemispheric asymmetry, selective manipulation of the functional states may be an effective means to achieve a more desirable drug disposition and reactivity. It might be preferable to administer some drugs only at night or only in the daytime, preferably during periods of controlled mental activity or against a background of accompanying external manipulations, ranging from formidable procedures such as electroshock, to selective sensory stimulation by such simple maneuvers as reading aloud or listening to Beethoven. To date, few studies of drug efficacy have considered these variables as deserving control. The data and concepts reviewed suggest that the asymmetric nature of cerebral function and metabolic events should no longer be ignored in evaluating the disposition and activity of centrally active drugs.

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