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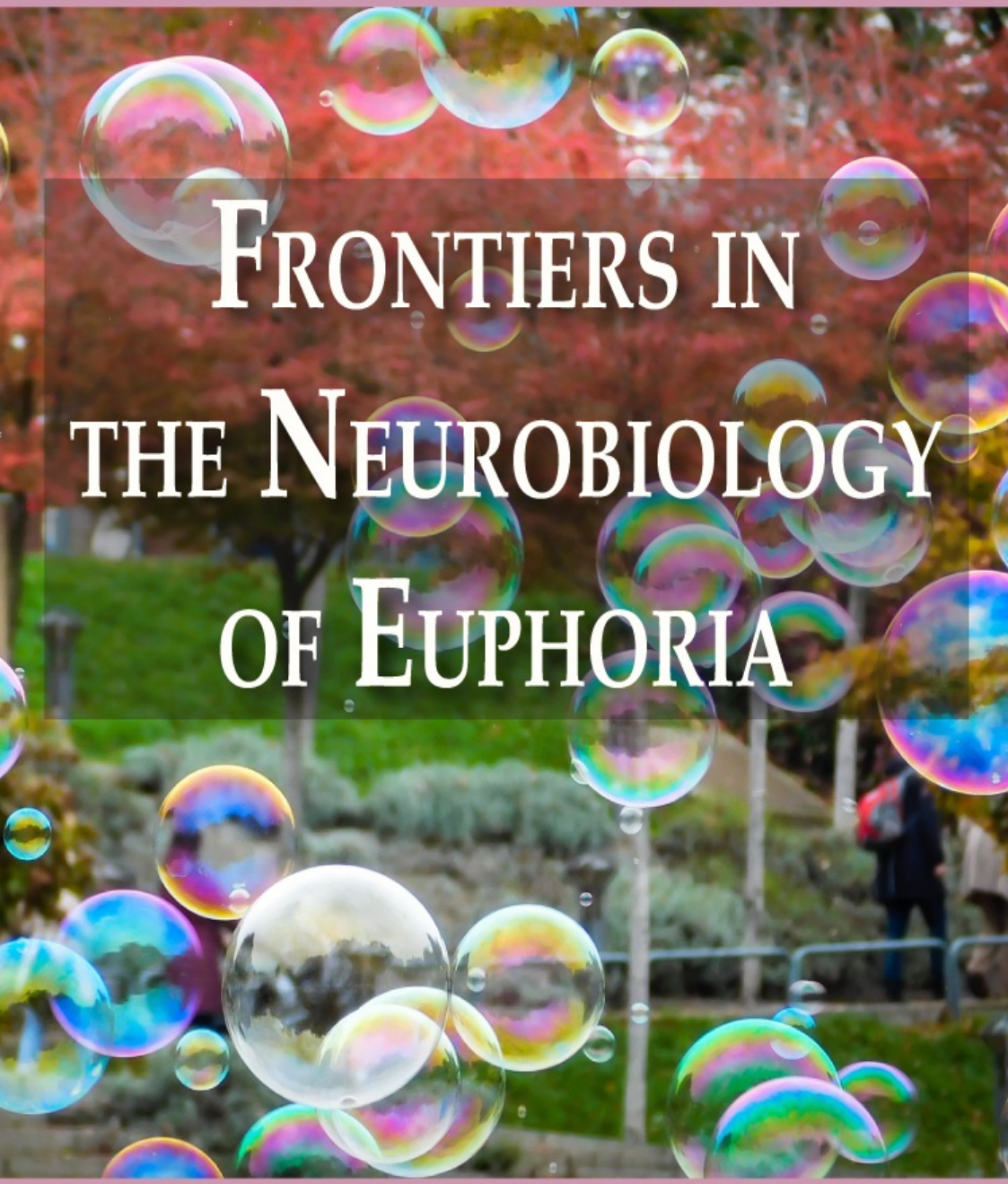

Frontiers in the Neurobiology of Euphoria

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FRONTIERS IN THE NEUROBIOLOGY OF EUPHORIA [1]

Introduction

The recognition and then the evaluation of a particular human affect state by a culture at a time and place in history are indeed very complex. Those of us working in an area that is in the interface between sociocultural and psychobiological variables intuitively know that there are affect states which, due to our culture's lack of focus on them, go without a name. As an example, multivariate behavioral analyses frequently generate emotive factors that have no common name and researchers must assign them numbers or invent words to describe them. The role of cultural factors in the definition of affect states relates also to changes in the values people assign to particular states. For example, we are aware of the interesting shift in features seen as highly valent in an excited young person of the Roaring Twenties compared to what was considered ideal in the cool, apparently relaxed, unresponsive young person of the Sixties. Yesterday's "flapper" is today's "up-tight;" yesterday's "schizo" is today's "cool" one. A dramatic example of this shift was clear to me when a recent freshman medical school class totally rejected a 1956 movie about a teenage borderline patient; in no way could they see his object relations and affect state as psychopathological.

A more common (and perhaps professionally exploited) shift relates to

the current cultural view of anxiety. No longer is anxiety seen as a concomitant of living; in almost all forms it is seen as a treatable symptom. The recommended treatment for anxiety in the first several decades of this century was psychotherapy or psychoanalysis, and during the current era, it seems to be the use of an ever-burgeoning group of mild psychotropic drugs.

These cultural views of affect states have wide ramifications. For example, a person whose tendency is to be alert and to cope hyperactively in new, ambiguous circumstances may be made to feel abnormal. The hyperactivity may be seen as requiring some type of medical, pharmacological, or interpersonal intervention. In contrast, a person who withdraws emotionally may be seen as having a sense of mastery. This kind of issue has been of particular interest with respect to the drug treatment of some hyperactive children. In the case of a person manifesting features of the devalued affect state, the interpretation of this natural-for-him affect state as psychopathological may become in itself a stimulus for anxiety. Culturally determined positive and negative evaluations of various human affect states may be facilitated (at least within the diagnostic priesthood of medicine) by the advertising programs of pharmaceutical houses. It seems as though the effects of cultural consciousness, media management, and psychopharmacological discovery have and will lead to the birth and rationalization of many new dimensions of diagnosis and treatment in psychiatry.

This chapter focuses on an affect state that is emerging as important in the current era. Only very recently have even relatively sophisticated psychopharmacologists come to realize that euphoria can be chemically induced independent of the reduction of pain or anxiety or of hallucinatory propensity. In addition to the increasing professional awareness of this potential for affecting human mood, there is a growing pressure from patients who insist that doctors help them with a new kind of depression, an existential crisis of meaning, an individually felt, but perhaps culturally determined, sense of anomie. Rather than serve as signals for change, renewal, re-evaluation, or creative solutions, mild dysphoric states, categorized under the rubric of depression, sieve now as indications for treatment. Beyond the emergence of the chemical tools and increased cultural awareness, the vast American folk pharmacology and a new era of self-medication by both patients and younger doctors are making euphoria an acceptable state, a desirable state. Our studies have shown that young people are living through a period of poly-psychotropic drug experimentation in which the drug family with the consistently unsaturated market is the euphorigen-hallucinogen class. Younger doctors and residents are sensitized to the dimensions of dysphoria and anhedonia and ask why these states are not treated specifically with the agents that they learned about through their folk pharmacology experiences.

The physician in his usual daily practice seldom sees euphoria apart

from other drug actions like pain relief or antidepressant action. Some neurological syndromes that manifest aspects of euphoria have been described, however. The most dramatic would be the relaxed carefreeness of the middle and late stages of multiple sclerosis. Patients are described as being relatively happy while experiencing progressively crippling symptoms. In terms of clinical phenomena there isn't a more dramatic demonstration of the potential usefulness of this state in medicine. When discussing euphorigens, their method of action, and their potential uses in man, one encounters resistance to the topic even among scientists and medical men until the discussion is directed toward patients who have paid or soon will pay "their dues." It may be that the initial discussions of the development of drugs to produce primary euphoria (without attendant pain relief or antidepressant action) should be within the context of the clinical management of dying patients or their close relatives. Perhaps one should talk about these drugs as having the potential for the prevention or treatment of severe psychosomatic disorders attendant on the stressful experiences of life, such as the loss of a mate or child.

This paper will deal with four areas of the neurobiology of euphoria. The first section will be a brief discussion of some aspects of the physical chemistry of euphorigens in relation to naturally occurring neurotransmitters and their physiological and behavioral effects.

Second, there will be a description of some of the evidence that the brain may have the potential for the synthesis of euphorigens that could play some role in the normal regulation of subjective states in man. The third section will describe some of the barriers to developing euphorigens having long-term efficacy, i.e., the kinds of neurobiological adaptations that the brain can make to agents that alter normal synaptic function. The last section will suggest theoretical and experimental approaches for future research designed to deal with these adaptational processes.

Euphorigens—Some Structures and Effects

In 1931, in a fascinatingly farsighted book, Lewin created a useful typology of psychoactive drugs that focuses on five major effects: hypnotica, euphorica, phantastica, excitantia, and inebriantia. Increasing experience with human use of psychoactive agents suggests that, depending on the person and the dose, each drug can be euphorigenic, with the effect of higher doses depending upon drug class. Table 22-1 summarizes this concept with some examples. The euphorigenic properties of many drugs are not frequently acknowledged. For example, hypnotic drugs such as the barbiturates can produce a kind of "paradoxical" excitement early in the time course of their onset of action or at low doses. The "hit" that many barbiturate takers experience is described as euphoric. Mild to moderately depressed people especially frequently report euphoric relief from stimulants like the

amphetamines.

An operational definition of euphoria for use in experimental work is most difficult. Using a wide variety of behavioral items and a relatively non-euphorigenic control drug that mimics such phenomena as central activation and autonomic effects (e.g. amphetamines) we can study the euphoric effect. The studies of Snyder, Faillace, and Weingartner on the methoxy-amphetamine derivatives, and that of Szara on the N-methylated indoleamines are good examples. We have summarized the clinical aspects of the effects of the euphorigen-hallucinogen family of drugs elsewhere.

Two general categories of compounds are similar to naturally occurring neurotransmitters in the brain and relevant to the neurobiological issues addressed here. The first group consists of the indoleamines, exemplified in Figure 22-1. Note the indoleamine structure of serotonin and its obvious derivation from tryptophan via the 5-hydroxylation pathway. The dimethylation of the nitrogen group in serotonin produces a centrally active stimulant, N,N-dimethylserotonin (bufotenin). Because this compound will not cross the blood-brain barrier, it has not been demonstrated to have central action in man. However, when the 5-hydroxy position is made less polar by methylation, 5-methoxy-N, N-dimethyltryptamine is formed, which is an extremely potent compound, active in doses of 3 to 5 μg/kg in man. The other major group of euphorigens that resemble neurotransmitters are noted

in Figure 22-2, compounds structurally related to the brain catecholamines norepinephrine and dopamine. A well-known parent compound in this family is mescaline (3,4,5-trimethoxyphenylethylamine), and the relationship between this agent and dopamine is relatively clear. Another parent compound is one in which the aliphatic side chain is a-methylated, as in amphetamine. These two parent compounds can yield a wide variety of potentially euphorigenic derivatives, which have been reviewed by Shulgin and his associates. The derivatives, such as 2,5-dimethoxy-4-methylamphetamine (STP) or 2,5-dimethoxy-4-4ethylamphetamine (DOET), are euphorigenic at lower doses and have varying degrees of hallucinogenic activity at higher doses.

Table 22-1 Typology of Psychoactive Drugs

	EFFECT	
DRUG CLASS	LOW DOSE	INTERMEDIATE DOSE
Stimulant	Euphoria	Excitement
Sedative	Euphoria	Sedation
Alcohol	Euphoria	Inebriation
Euphorigen, potent	Euphoria	Euphoria-hallucinosis
Euphorigen, mild	Euphoria	Euphoria

After L. Lewin. Relative doses represent multiples of minimum psychoactive doses.

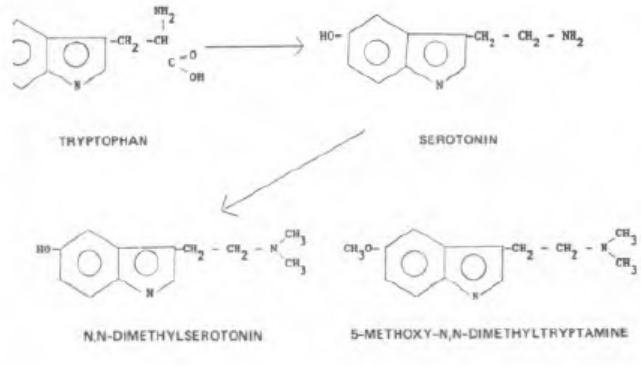

Figure 22-1.
The metabolic derivation of indole (ethyl)amine euphorigens from the amino acit tryptophan.

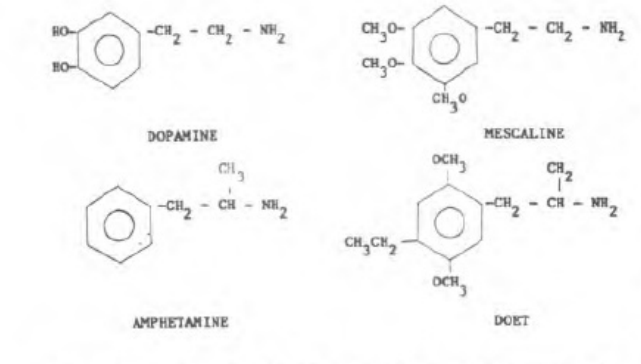

Figure 22-2.
Molecular similarities between exogenous euphorigens and an endogenous phenylethylamine neurotransmitter, dopamine.

Structure-activity considerations involving these compounds have been theoretically elaborate, but Shulgin has perhaps the most simple and

straightforward formulation about the structure and electronic requirements for the euphorigen family. He suggests that at least three elements are necessary for central activity: (1) an aromatic system with potentially high molecular orbital energy, (2) an aliphatic carbon chain of optimal length separating the aromatic system from a (3) terminal nitrogen site. This scheme for euphorigenic activity is applicable to the indoleamines when we note that the five-membered pyrrole part of the indole ring donates electrons to the substituted benzene ring. Electron donor groups on the nitrogen may increase basicity, thereby increasing the potency of the compound. If we view the pyrrole ring as a methoxy group we can associate most psychoactive indoleamine compounds with the derivatives of mescaline or amphetamine. N-methylation apparently increases potency in the indoleamine series more effectively than in the phenylethylamine series. Alpha-methyl substitution may increase potency by hindering an enzymatic attack on the nitrogen of the amino group.

Various theories of action of these agents have been reviewed elsewhere, but the general assumption is that they interact with their analogous neurotransmitters and in so doing stimulate or inhibit receptor activity in an abnormal way or to an abnormal extent. Considerable evidence is accruing, from microelectrode studies in cell body and nerve ending regions of known biogenic amine pathways, that these agents result in abnormal activity associated with electrical evidence of various attempts at

feedback compensation. Such evidence is available for the noradrenergic, dopaminergic, and serotonergic systems.

The long-term effects of these agents present far more formidable challenges for mechanistic explanation. The post-hallucinatory glow that has been reported by a number of workers can last several weeks. It could be viewed as either some sort of adaptation by the brain to the action of the drug or the continuing action of the drug stored in nerve endings. In our laboratory we are considerably more impressed with the first concept, i.e. the potential importance of the behavioral expression of dramatically fast adaptation to these agents by the brain. Figure 22-3 summarizes data indicating very fast behavioral adaptation to a powerful hallucinogen when it was administered in such a way that hepatic mechanisms could not account for the tolerance. Note that within half an hour there was marked diminution in the behaviorally activating effects of both 5-methoxy-N,N-dimethyl-tryptamine and bufotenin. Work to be reviewed below demonstrates that these adaptations can last several hours, days, or weeks. Thus, in addition to the immediate neurophysiological compensation manifested by changes in action potentials and/or unit firing rates there appear to be longer-term macromolecular changes that could change either the turnover of the neurotransmitter or the effectiveness of its receptor, or both.

Following the administration of an hallucinogen, a cell system's unit

firing rate changes in a direction indicating an attempt by the brain to compensate in the system whose transmitter the euphorigen resembles. This suggests that the euphorigen fools the brain not only in terms of producing immediate alterations in receptor stimulation but also into making an internally oriented systematic adaptation unrelated to environmental conditions. This evidence is consistent with the rather simple idea that euphorigens masquerade as transmitters and alter the function of synaptic systems both immediately *and* on long term bases.

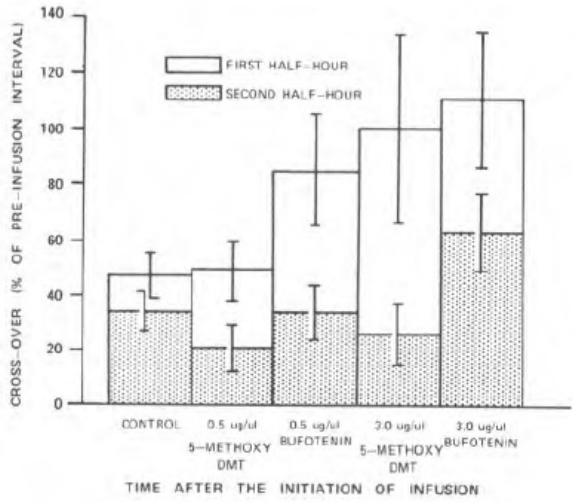

Figure 22-3.
Effects of intraventricular infusion of 5-methoxy-dimethyltryptamine (DMT) and bufotenin on the gross motor activity of freely moving rats. The potency of these two compounds is comparable when they are administered directly to the brain. N = 6. Rate of infusion = 1 ^1 per 3 minutes.

A Naturally Occurring Euphorigen

For a number of years evidence has been accruing that mammalian cells may be able to convert neurotransmitter biogenic amines into compounds in the euphorigen-hallucinogen category. The most common source of interest was the potential of such a transformation to cause various kinds of psychopathology, particularly the schizophrenias. One of the best known

speculations about conversion of a transmitter to a euphorigen was first reported by Friedhoff and Van Winkle. They found a compound resembling dimethoxyphenylethylamine more frequently in the urine of schizophrenic patients than in that of a nonschizophrenic control group. This was confirmed as well as denied by other investigators. The theory is that dopamine is converted from a normal neurotransmitter to a euphorigen-hallucinogen via an abnormal 4-0-methylation. The involvement of dopamine and/or its products and of the striate area in the brain has been suggested by others because of evidence concerning the site of action of psychotomimetic doses of amphetamine and the high-potency antipsychotic agents such as haloperidol.

A similar conversion, the dimethylation of serotonin, has occupied our attention for a number of years. There has been considerable interest in the methylated indoleamines since it was found that a psychic-energizing effect associated with euphoria and/or the precipitation of an acute attack of schizophrenia can result when an indoleamine source, such as tryptophan, is combined with a methyl source, such as betaine or methionine, and administered with a monoamine oxidase inhibitor. In small doses exogenous tryptophan produces behavioral activation and an increased sense of well-being; in larger doses it activates latent psychotic symptoms.

When we administered 5-hydroxytryptophan and a monoamine oxidase inhibitor to newborn white Leghorn chicks, the result was behavioral

activation and abnormal posture that resembled patterns we had seen when we administered hallucinogens. The stereotypic response of these animals to psychotropic drugs made such comparisons possible. The speculation followed that the monoamine oxidase inhibitor blocked the normal metabolic degradation of serotonin and shunted the transmitter to a methylation reaction. This scheme is diagrammed in Figure 22-4. A major reservation attendant on this theory was that there had been no demonstration of a specific indoleamine N-methyltransferase in brain that could make such a conversion.

Using isotopic loads of tryptophan, however, and S-adenosylmethionine as a methyl donor, we were able to demonstrate the presence of both monomethyl and dimethylserotonin in brain extracts. Previous reports of a nonspecific lung enzyme that could methylate a variety of biogenic aromatic amines complicated the conclusion that the methylation of the indoleamines was occurring in the brain. Because of the decreased blood-brain barrier in the newborn chick it was impossible to determine whether the radioactive bufotenin came from the lungs or the brain.

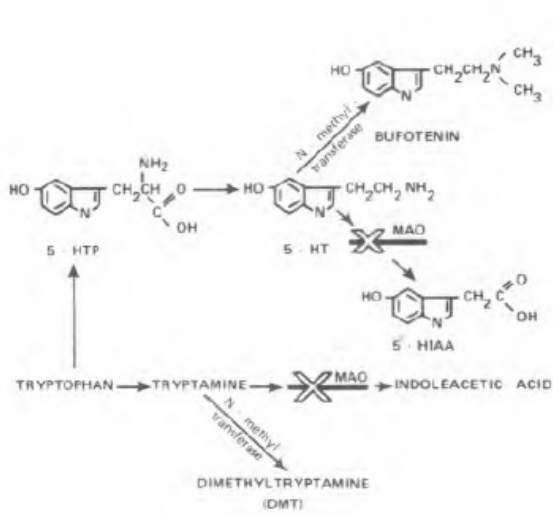

Figure 22-4.
A hypothetical indole (ethyl) amine shunt that may be activated when the normal degradation of serotonin by oxidative deamination is blocked by a monoamine oxidase inhibitor (or a high dose of amphetamine).

We then began to investigate whether the brain itself had an N-methylating enzyme for indoleamines. Our initial studies demonstrated that a chick brain homogenate could catalyze the production of radioactivity extractable in isoamyl alcohol when S-adenosylmethionine and either serotonin or tryptamine were used as substrates. The enzymatic production of radioactivity was linear with time and protein concentration, and the protein fraction capable of catalyzing this reaction could be enriched over tenfold by ammonium sulfate precipitation and Sephadex G-200 column chromatography. The monomethyl and dimethyl products of this reaction

were isographic with known standards on chromatograms in several solvent systems. This enzymatic activity was also demonstrated in the human brain. We have since enhanced this indole (ethyl)amine N-methyltransferase (IENMT) activity twenty-five fold by progressive purification, including dialysis (Table 22-2). Table 22-3 summarizes experiments demonstrating the substrate specificity of the enzyme. Note that the imidazoleamine histamine and the catecholamines were not methylated by the enriched protein fraction. Saavedra and Axelrod have confirmed our findings in temporal lobe material from the brains of non-psychotic subjects. In addition, Frohman has reported identification of dimethylated tryptamine from the human brain by the use of gas chromatography and mass spectroscopy.

The functional significance of brain indoleamine N-methyltransferase activity is far from settled. Its Km for indoleamine substrates is about 50 μM. This suggests that under usual circumstances brain monoamine oxidase, which has higher specific activity and greater affinity for substrate, would probably degrade the indoleamines before methylation could occur unless compartmental variables prevented contact between the substrate and the oxidase. The other known inactivation mechanism for serotonin in the synapse is reuptake. The reuptake mechanism too has a higher affinity for the substrate than the methylation enzyme does. It thus appears that IENMT might function only under conditions of impaired presynaptic uptake or monoamine oxidase inhibition.

Table 22-2. Specific Activity of Indole (ethyl) amine N-Methyltransferase in Homogenate from Sheep Brain

FRACTION		ACTIVITY *pmoles tryptamine methylated per mg. protein per hour*
8,000 X *g* supernate		14.8
100,000 X *g* supernate		28.2
$(NH_4)_2SO_4$ precipitate	0-25%	8.9
	25-35%	33.9
	35-45%	71.5
	45-55%	99.3
	55-65%	24.4
	65-80%	10.0
Sephadex G-200 fraction of 35-55% $(NH_4)_2SO_4$ precipitates		460.1

IENMT from sheep brain was progressively purified by centrifugation, ammonium sulfate precipitation and Sephadex column chromatography. The 35-55% ammonium sulfate precipitate was fractionated on a column equilibrated with potassium-phosphate buffer. Some portion of the 30-fold increase in activity probably reflects the removal of an inhibitor of the enzyme.

Table 22-3. Substrate Specificity and Purification of Indole (ethyl) amine N-Methyltransferase from Sheep Brain

	SPECIFIC ACTIVITY *nmoles of substrate methylated/ mg. of protein per/hour*		
SUBSTRATE	100,000 X *g* supernate	35-45% (NH4)2S04 precipitate	Sephadex G-200 fraction

Tryptamine	0.22	0.86	2.13
Histamine	7-13	1.23	0.17
Normetanephrine	0.04		
Norepinephrine			

Values below 0.02 were disregarded.

Table 22-4. Regional Distribution of Indole (ethyl) amine N-Methyltransferase (IENMT) and Two Forms of Tryptophan Hydroxylase (TRYP-OH) in Rat Brain

	ENZYME ACTIVITY *pmoles per mg. of protein per hour*		
BRAIN REGION	synaptosomal TRYP-OH	IENMT	soluble TRYP-OH
Caudate	100.6	83-5	0
Cortex	41.6	34-6	0
Medulla	29.8	36-4	3-7
Hypothalamus	29.3	36.1	29.8
Spinal cord	26.0	37-4	10.0
Midbrain	14.4	25.8	87.1
Whole brain	10.8	23.6	18.4

Table 22-4 demonstrates the relationship between IENMT and the nerve ending serotonin biosynthetic unit; note that the enzyme is present in nerve endings in more significant amounts. We have demonstrated adaptive changes in tryptophan hydroxylase, the rate-limiting enzyme in the

biosynthesis of serotonin, after drug treatment or environmental manipulation. Such changes could increase serotonin biosynthesis and, in turn, the probability that IENMT would function. So could exaggerated neural activity and the extra-neuronal release of serotonin. Tryptophan loads increase the uptake of tryptophan into serotonergic nerve endings, and the combination of tryptophan loads and monoamine oxidase inhibitors at lower doses elevates mood and promotes a sense of well-being, suggesting to us that serotonin may have become available to IENMT. The potency of bufotenin, once the blood-brain barrier has been overcome, is at least as great as that of 5-methoxy-N,N-dimethyltryptamine, which suggests that serotonin in the brain could be converted into a powerful euphorigen.

Since “proof” of relationships between behavioral and neurobiological variables is so difficult, theorists talk about possibilities rather than probabilities. It can be said now only that the brain is capable of making an euphorigen that had been discussed previously only in pharmacological studies. Whether this capacity can be realized except under experimental circumstances has not been demonstrated.

The functional significance of a central euphorigen is obscured by myriad synaptic neurobiological compensatory mechanisms that would prevent prolongation of its action. This is particularly true of the drugs in the euphorigen class. It is clear that, in addition to agents that can induce

euphoric feelings in man, the human brain may be able to produce such feelings with the biotransformation of a neurotransmitter. A major technical barrier to understanding how man can mobilize his own euphorigenic mechanisms and how we might be able to use drugs of this sort in the management of long-term clinical problems appears to be the dramatic adaptation to the presence of such substances in the brain.

Some Neurobiological Adaptive Mechanisms

The amount of neurotransmitter active at the synapse is thought to be determined by the release and reuptake of the transmitter, mediated by the activity of the neural system involved. Another component in the regulatory process seems to be the amount and/or the activity of the enzymes involved in transmitter degradation. In the case of the catecholamines, for example, the latter would involve O-methylation and/or oxidative deamination. The third factor in the regulation of the functional transmitter level in the brain is a sequence of biosynthetic enzymes. An active neural system releases into the synapse newly synthesized transmitter in preference to stored transmitter. Until very recently the only known regulatory mechanisms for tyrosine hydroxylase, the rate-limiting enzyme in the biosynthesis of catecholamines, appeared to be product-feedback inhibition.' Norepinephrine or its immediate precursor, the transmitter dopamine, as products of this pathway, can compete with tyrosine hydroxylase for its pteridine cofactor. Dopamine is

ten times more effective as an inhibitor of the enzyme than norepinephrine is. When more transmitter product is released, less product remains in the nerve ending to inhibit the enzyme activity, so more product is synthesized. When less product is released there is more remaining to inhibit the enzyme, and less transmitter is synthesized. This scheme is clearest for catecholamine biosynthesis in the adrenal where the amine is released into the general circulation and acts, as endocrine products do, on a distant target organ. The importance of product-feedback regulation compared to other regulatory mechanisms in nerve endings is less clear in both peripheral sympathetic systems and the brain. The cell's task is to convey information to the next cell in the system by affecting the receptor, and thus *effect* appears to be more critical than the amount of transmitter released. The regulatory significance of informational feedback from the receptor cell in activating mechanisms other than product-feedback inhibition is becoming prominent in experimental work on the brain.

Work from our laboratory has suggested that substrate supply, regulated by an energy-dependent, stereospecific uptake mechanisms, may account for some regulatory changes in transmitter synthesis. For example, whereas morphine inhibits serotonin synthesis in the nerve ending by inhibiting tryptophan hydroxylase activity, cocaine accomplishes the same thing by the noncompetitive inhibition of the uptake of the substrate tryptophan. Too, changes in the physical state of an enzyme can alter synaptic

transmission by allosteric activation or occlusion of the enzyme.'- Tyrosine hydroxylase, when bound to nerve-ending membranes or altered from a tetramer to a monomer, gains affinity for its cofactor as well as its inhibiting products. This kind of change is represented schematically in Figure 22-5. A conformational alteration can be induced in the rate-limiting biosynthetic enzyme to "tune" it. We have shown that stimulants, like amphetamines, rapidly change the physical state of some of the enzyme tyrosine hydroxylase in the nerve ending from soluble to membrane-bound, and so does the acute administration of reserpine or the β-receptor blocker propranolol, with an apparent activation of the enzyme.

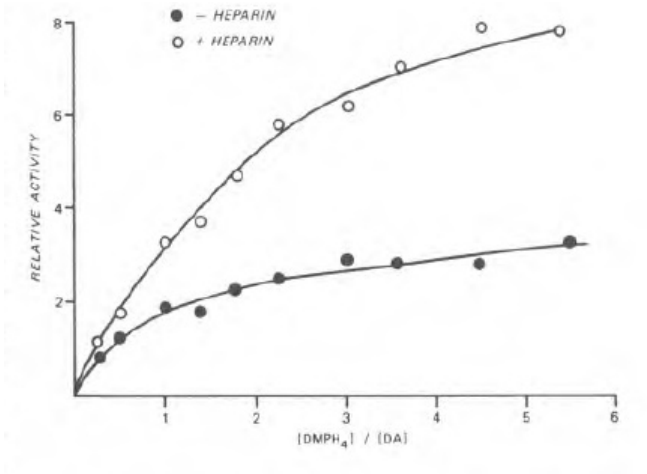

Figure 22-5.
The sulfated mucopolysaccharides heparin activates native soluble tyrosine hydroxylase from the striatum of the rat. If the relative activity of the enzyme in the presence and in the absence of heparin is plotted as a function of various concentrations of artificial pteridine cofactor (DMPH4) or catecholamine product (DA), it appears that activation by heparin sensitizes ("tunes") the enzyme to changes in the concentration of cofactor and/or end-product inhibitor.

Other adaptive mechanisms are associated with changes in the total amount of enzyme available in the nerve ending for synthesizing transmitter. Using various environmental, hormonal, and drug-induced changes in behavior as markers, we have demonstrated that some systems can be regulated by alterations in the amount of enzyme available, which in turn are affected by changes in the rate of synthesis or degradation of the enzyme. A good example of such regulation comes from our studies of antidepressant drugs like the tricyclics, the monoamine oxidase inhibitors, or the

amphetamines. Most of these drugs produce a systematic decrease in measurable tyrosine hydroxylase in the midbrain if they are administered over several days. Figure 22-6 summarizes the effects of the chronic administration of various drugs on midbrain tyrosine hydroxylase in the rat. Note that those that are generally antidepressant decrease the specific activity of the midbrain enzyme; those that are depressant increase it. The time course of these changes (which are, of course, dose-dependent) is several days. The time course of the functional or behavioral correlates of these enzymatic effects may reflect either the latency in enzyme turnover or the transport of the additional or reduced amounts of enzyme from the cell body to the nerve ending—a process called axoplasmic flow. The rate for this transport in our studies of tyrosine hydroxylase and tryptophan hydroxylase is on the order of 1 to 2 mm. per day.

The receptor, too, is sensitive to alterations in synaptic function, and it may play an important role in neurobiological adaptation. We have shown that thyroid hormone sensitizes central receptors to norepinephrine. Preliminary experiments show a similar phenomenon in the brain after the intraventricular administration of 6-hydroxydopamine, a drug that selectively destroys catecholamine nerve endings.

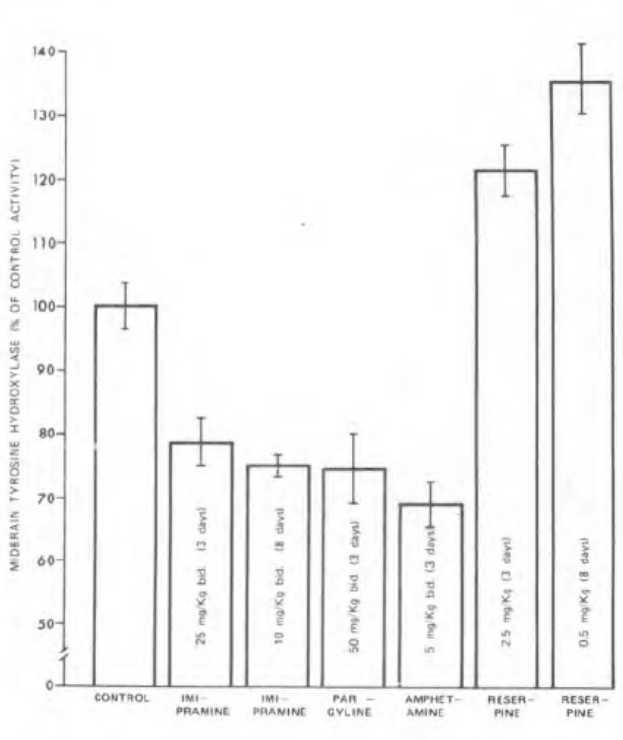

Figure 23- 6.
The effects of chronic drug treatment on the activity of tyrosine hydroxylase in the midbrain of the rat.

So, neurochemical changes that apparently can regulate the amount or effect of neurotransmitter in a synapse in the brain include: (1) the amount of neurotransmitter released into the synapse; (2) the state of the neurotransmitter reuptake mechanism in the presynaptic nerve ending; (3) the amount, availability, and affinity of neurotransmitter-metabolizing enzymes; (4) the amount of product available in proximity to the rate-limiting

enzyme to function as a feedback inhibitor; (5) the state of the supply and transport of precursors into the cell; (6) the physical state and/or conformation of the enzyme molecule as a regulator of activity or affinity for substrates; (7) increases or decreases in the amount of synthesizing enzyme in the nerve ending, regulated by its own synthesis, degradation, and the axoplasmic transport of enzyme protein; and (8) alterations in the sensitivity of the receptor.

The burgeoning vocabulary of central synaptic regulatory mechanisms that we have examined with the use of drugs and environmental manipulations has pointed toward one major principle of functional organization: the tendency of the adaptive mechanism to return the net function of the transmitter-receptor interaction to a baseline state. In addition, since even drugs with multiple actions do not impair all these mechanisms simultaneously, there appear to be some mechanisms always intact to carry through a serious attempt at compensation. Treatment with depressant drugs tends to lead to enzyme activation and/or increases in amount of enzyme, receptor sensitivity, or substrate supply. Stimulant or antidepressant drugs tend to decrease the excitability of the synapse though the opposite trend in the mechanisms. This rule of compensatory adaptation holds for the stimulant, narcotic, psychotropic, autonomic, and hallucinatory drugs that we have studied, and for environmental and genetic manipulations as well. For example, prolonged isolation appears to increase the activity of

tyrosine hydroxylase, the rate-limiting enzyme in the synthesis of catecholamines, which activate behavior. Genetic differentiation of six strains of rats on the basis of their levels of spontaneous motor activity shows a systematic inverse relationship between activity level and midbrain tyrosine hydroxylase activity.

When we look for clinical evidence for adaptive changes to psychoactive drugs we do not have far to go. It is well known that tolerance develops very quickly to the potent euphorigen-hallucinogen lysergic acid diethylamide (LSD). A dose of 150 μg would be euphorigenic on Monday, mildly stimulating on Tuesday, and almost without effect on Wednesday, if the drug were taken daily. Furthermore, any one of a number of other euphorigens taken in an average dose on Thursday would have a markedly reduced effect because of cross-tolerance. The rapidity with which tolerance develops to amphetamines is another example of these adaptive mechanisms at work.

Thus, from both neurobiological and clinical points of view, it is clear that the extension of central euphorigen action over time has reached a technical barrier in the form of these acute and chronic mechanisms of adaptation. The acute responses may make a bad matter worse, or, the effects of the euphorigen may be modified or eliminated by the brain itself.

New Frontiers

If the major impediment to the use of euphorigens for the long-term management of patients is the brain's capacity to adapt, there are still at least two useful ways to look ahead. The first and most straightforward is to consider the possibility that since most of the adaptations are macromolecular and subject to a prolonged time base, it may be possible to configure a management strategy to produce an end-state that *is* the adaptation, e.g. the tolerant state would be the treated state of the brain. Of course, further adaptations to induced tolerance could occur, but, at least superficially, this strategy is promising. We are speculating that some of the major psychotropic drugs, such as the tricyclic antidepressants, may actually work by the creation of the tolerant state rather than by their primary effect. The delay of days to weeks for their behavioral effects to appear is similar to the time course of the macromolecular mechanisms described above. Mania, for example, has been thought to be a psychodynamic defense mechanism, but it is seductive to speculate that mania could represent an overdose of endogenous euphorigen in an effort to overcome a dysphoric state.

It might be useful to be able to modify the rate of development of these adaptive changes. Because new protein is probably involved with some presynaptic alterations of enzymatic activity and with postsynaptic alterations in receptor function, we are examining specific inhibitors of protein synthesis in an effort to find agents that may counteract adaptation. Parachlorophenylalanine is such an inhibitor for tryptophan hydroxylase. It

could also be useful to sensitize adrenergic receptors by means of the administration of thyroid hormone.

Concluding Remarks

Society currently acknowledges euphoria as a desired and sought-after affect state in man. Certain drugs that produce euphoria bear remarkable resemblance to two major, naturally occurring, neurotransmitter families. At least one of these compounds can be synthesized in the brain via N-methylation. A major obstacle to the use of euphorigens in the management of chronic diseases or disease relates to the brain's metabolic adaptive processes. Adaptive mechanisms can be looked at in two ways. We might be able someday to induce these adaptations to achieve their ultimate behavioral and subjective consequences, or we might learn to alter or inhibit the rate of adaptation the brain makes to new treatments.

It appears that the age of euphorigens is upon us, and we are coming to it with far greater understanding of the biology of the brain than men have in earlier eras. Exciting times are ahead for those in the brain sciences. It wouldn't be surprising if over the next few years a wide variety of drugs that produce euphoria were available for use. The question of who will be in charge of them or how they will be used is, I think, beyond the legitimate purview of a brain scientist or a psychiatrist. Whether they can ever be used

effectively, except on a periodic basis, awaits further research. It is perhaps philosophically important that drug-induced pleasure is habituated too quickly. It calls to mind a recent statement Heinz Lehmann made after hearing about some of this work: "It seems to me that puritanical attitudes toward pleasure must have as part of their bases these neurobiological mechanisms of adaptation." Perhaps pleasure can only be experienced against the background of its absence.

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Notes

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