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Norepinephrine-Dopamine Interactions and Behavior

A new hypothesis of stress-related interactions between brain norepinephrine and dopamine is proposed.

Seymour M. Antelman and Anthony R. Caggiula

Of the many transmitter candidates known to exist in the central nervous system, the catecholamines dopamine (DA) and norepinephrine (NE) have been most often linked to the behavioral pathology of a number of neurological and psychiatric disorders. Among these disorders are Parkinson's disease (*1*), Huntington's and hyperthyroid chorea (*2*), Gilles de la Tourette's syndrome (*3*), and the schizophrenias (*4*). It has also been suggested that catecholamines may play a role in affective disorders (*5*).

Work with animals similarly suggests that NE- or DA-containing neural pathways, or both, may play critical roles in numerous basic survival-related activities such as eating (and food-oriented activities such as licking and gnawing) (*6–8*) as well as reproductive behavior (*9, 10*), stress-related aggression (*11, 12*), and electrical self-stimulation of the brain (*13, 14*). The seemingly ubiquitous nature of catecholamine involvement across a wide spectrum of behaviors and the remarkable adaptive capacity of catecholamines to maintain relatively normal function even in cases of severe damage (*1*), suggests that catecholamine systems may play a very fundamental role in mediating the interaction between the organism and its environment.

In recent years, there has been a considerable shift of opinion regarding the relative importance of NE and DA in the mediation of many behaviors. In stark contrast to the ever-growing number of activities in which DA appears to be implicated, the list of behaviors in which a role for NE is seriously considered appears to be declining. Indeed, in summarizing a recent symposium on monoamines, Lipton (*15*) was prompted to remark that "So much of the behavior previously attributed to NE now has been found to be mediated by DA that questions arise about the role of NE." We believe that these questions may be the unfortunate result of the traditional NE versus DA approach which has characterized catecholamine research in psychopharmacology for so long.

As an alternative to an either-or approach, it may be more profitable to study the possible interactions between these catecholamines. Although very little work has been deliberately devoted to examining possible interactions between NE and DA (*16*), there is substantial support for the existence of an important relationship between these amines. Moreover, the implications stemming from this relationship may help in the resolution of long-standing controversies dealing, for example, with the relative importance of brain NE and DA systems in reward behavior, and may have far-reaching importance for the better understanding of disorders such as Parkinson's disease and schizophrenia.

Statement of Hypothesis

There is much evidence that suggests that interference with brain NE-containing systems will, under some circumstances, potentiate a variety of behaviors while, under other conditions, the identical manipulations may depress the very same behaviors. We believe that these apparently contradictory findings can be explained or resolved by the consideration of three key factors: (i) the behaviors in question are critically dependent on the normal functioning of brain DA-containing systems, (ii) the potentiation or depression of an organism's behavior relates to the activational features of the environment, and (iii) the behavioral out-

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come reflects a functional interaction between NE and DA systems. The salient features of the NE-DA interaction hypothesis are conceived of as follows:

1) Under conditions of normal functioning (that is, in the absence of pharmacological intervention or gross pathology of brain NE systems), activity in NE-containing neurons exerts an indirect modulatory influence on DA systems and, in this way, regulates their function.

2) Under those circumstances (either experimental or naturally occurring) where functional activity of NE-containing neurons is diminished and the organism is in the presence of activating or stressful stimuli, a facilitation of DA-dependent behaviors is likely to occur.

3) Conversely, under conditions of minimal stress or activation, precisely the same interference with NE activity would be expected to produce either no change or perhaps an actual depression of DA-dependent behavior.

According to this hypothesis, the functions of NE- and DA-containing systems are dynamically interrelated. As would be expected, when such a relationship is upset by manipulating one component, the remaining component will act in a compensatory fashion to maintain normal function. In the hypothesis being proposed, compensation is most likely to occur during stressful circumstances.

In the sections which follow, we will first consider the effects of interfering with NE function on a wide variety of activated and stress-induced behaviors, ranging from stimulant-induced stereotypy to tail-pinch–induced feeding. These effects will be characterized by such terms as behavioral facilitation or depression. Our use of these terms will emphasize increases or decreases in amount or intensity of a given behavior without necessarily implying corresponding changes in the quality of that behavior. We will then contrast these data with those obtained when the effects of similar manipulations of NE activity are tested under relatively nonactivating conditions. With each behavior discussed, we will present evidence which suggests a key role for DA.

Next, we will consider evidence bearing on the exact nature of the NE-DA interaction; that is, whether NE systems facilitate or inhibit DA activity. Finally, some clinically relevant aspects of this hypothesis will be discussed.

Stereotypy

It seems appropriate to begin a consideration of our NE-DA interaction hypothesis by discussing stereotypy, since there seems to be a consensus that the expression of this type of behavior is markedly influenced by activity in central DA-containing systems (*17*). Moreover, there is also fairly general (though not universal) agreement that the particular DA pathway involved is the nigrostriatal bundle, a collection of DA-containing fibers originating in the substantia nigra of the midbrain and projecting to striated forebrain structures such as the caudate and putamen.

Stereotypy refers to a repetitious, relatively invariant (that is, stereotyped) feature of behavior. It may be characteristic of any one of a number of behaviors, for example, stereotyped locomotion, licking, or rearing, and can be induced by high doses of certain stimulants known to release DA from presynaptic neurons, such as amphetamine (*17*), or by mildly stressful circumstances (*18*). Manipulations of NE, when done in relation to this behavior, have typically involved the use of compounds which block the formation of NE by inhibiting the enzyme dopamine-β-hydroxylase (E.C. 1.14.17.1) (see Fig. 1). For instance, amphetamine-induced stereotypy has been markedly potentiated by the dopamine-β-hydroxylase inhibitor disulfiram [in cats (*19*)] and diethyldithiocarbamate, a disulfiram derivative [in mice (*20*)]. Similarly, FLA-63, which is thought to be a more potent and specific inhibitor of dopamine-β-hydroxylase, has also been shown to produce a significant increase in both L-dopa- and amphetamine-induced stereotypy in rats (*21*). In our view, the behavioral potentiation produced by interrupting NE activity is indirectly mediated by a functional increase in DA activity. This is supported by the finding that FLA-63 increases the synthesis of DA from a radioactively labeled precursor in the striatum (*22*), and also produces marked increases in 3-methoxytyramine, an *O*-methylated metabolite of DA (*23*) (see Fig. 1). At present, the mechanism underlying these changes, which is believed to reflect increased activity in DA-containing neurons (*23*) is unknown, and the question of whether other dopamine-β-hydroxylase inhibitors produce similar effects cannot yet be answered.

Despite this evidence for increased DA function being responsible for the potentiation of amphetamine-induced stereotypy by FLA-63, there is an alternative interpretation of the results. The common effect of dopamine-β-hydroxylase inhibitors, critical for the observed potentiation of behavior, might be related, not to compensatory changes in DA activity, but rather to possible direct effects on amphetamine metabolism (*24*). In any case, our hypothesis does not rest solely on data derived from the use of dopamine-β-hydroxylase inhibitors.

For example, it has recently been shown that amphetamine-induced stereotypy was completely eliminated following a 6-hydroxydopamine (6-OHDA, a catecholamine neurotoxin) regimen that preferentially depleted brain DA (by 88 percent) and largely protected NE (depleted by 20 percent). By contrast, stereotypy was only insignificantly affected by a regimen that produced an identical depletion of DA (that is, by 89 percent), and which also depleted NE by 80 percent (*25*). Treatment with 6-OHDA

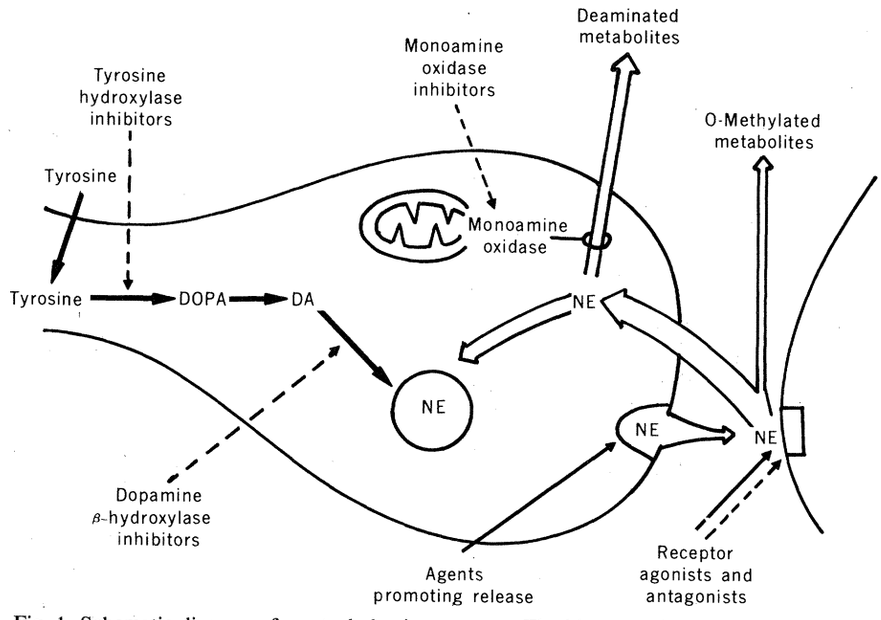

Fig. 1. Schematic diagram of a catecholamine synapse. The biosynthetic pathway for NE and the probable sites of action of the various types of drugs mentioned in the text are shown. The same relationships apply for DA-containing neurons, except that DA is not β-hydroxylated.

which selectively depressed NE (by 50 percent) while protecting DA (depleted by 12 percent) had no effect whatever on stereotyped behavior.

The data in this experiment may be important. They suggest that relatively selective damage to and, by implication, pharmacological interference with, brain DA systems may be more deleterious to the functioning of the organism than similar damage which is also accompanied by a substantial interference with brain NE. Stated another way, depression of NE activity may either prevent or counteract the effects of damage to, or pharmacological intervention in, DA-containing neurons. The exact outcome may depend on the time course of changes in NE relative to changes in DA and possibly on the extent of the damage to the two systems. Fortunately, the experiment described is not an isolated example of the therapeutic significance of our NE-DA interaction hypothesis. Additional examples and their relevance to practical, clinical treatments of certain disorders will be discussed below.

Motor Activity and Avoidance Behavior

In animals enhancement of both motor activity and the ability to avoid an electric shock by moving to the other side of a shuttle box (two-way active avoidance) has also been reported following treatments designed to interfere with brain NE. The dopamine-β-hydroxylase inhibitor U-14,624 has been reported to enhance the effectiveness of the stimulant methylphenidate (an NE- and DA-releasing agent) in inducing motor activity in rats (*26*). In contrast to U-14,624, when the synthesis of both NE and DA is inhibited by α-methyl-*p*-tyrosine, methylphenidate-induced activity is antagonized. These results suggest that methylphenidate-induced activity is dependent on the release of DA, and is enhanced by the inhibition of NE synthesis. In addition to inhibiting the synthesis of NE, U-14,624 and other dopamine-β-hydroxylase inhibitors such as FLA-63, disulfiram, and fusaric acid, increase the synthesis of serotonin (*27, 28*). However, increased serotonin activity is unlikely to be the basis of the effect obtained, since inhibition of serotonin synthesis actually potentiates methylphenidate-induced motor activity (*26*).

As with stereotypy, support for our NE-DA interaction hypothesis, when applied to motor activity and active avoidance, is not restricted to the results of manipulations in which dopamine-β-hydroxylase inhibitors are used. For example, doses of 6-OHDA which deplete whole brain NE more than DA (by 61.5 percent compared to 35 percent) have been reported (*29*) to enhance significantly stimulant-induced hyperactivity, which in this case was produced by treatment with amphetamine. In contrast, selective DA depletion (88 percent for DA compared to only 12 percent for NE) markedly depressed amphetamine-stimulated activity (*25*). Only slightly less DA depletion, that is, 73.5 percent, however, when accompanied by considerable NE depletion (79 percent), fails to produce a significant decrement in the response to amphetamine (*29*). Thus again, it appears that NE depletion can normalize or counteract the effects of DA depletion under appropriate circumstances.

Preferential depletion of brain DA by intraventricular administration of 6-OHDA significantly reduced active avoidance responding (a stress-related behavior which does not require the use of a pharmacological stimulant) (*30*). By contrast, enhancement of active avoidance responding has been observed following treatments designed to interfere with NE. For instance, 6-OHDA–treated rats permanently depleted of whole brain NE (by 54 percent) and showing no significant change in DA displayed facilitated acquisition of a shuttle-box avoidance response (*30*). However, significant serotonin depletion was also obtained in this study, and since such depletion is known to facilitate avoidance responding (*31*), interpretation of these data is difficult. Nevertheless, in another study (*32*), neonatal rats selectively depleted of NE by 6-OHDA also displayed enhanced avoidance responding as adults, in the absence of serotonin depletion, suggesting strongly that NE depletion plays a major role in this effect. This interpretation is supported by the finding that treatment with the presumed NE receptor blocking agents dichloroisoproterenol or pronethanol also facilitates active avoidance responding in rats (*33*).

Aggression

Several different types of aggressive behavior have been described which may be dissociable pharmacologically. A number of recent studies has demonstrated that an enhancement of one form of aggression, that is, "irritable" or shock-induced fighting in rats can be produced by intraventricular administration of 6-OHDA or peripheral injection of 6-hydroxydopa, in doses which preferentially reduce the concentration of brain NE (*11, 34*). These findings have usually been ascribed to the action on supersensitive receptors of those NE-containing neurons remaining in the brain after treatment with these neurotoxins (*11, 34*). That is, although NE levels are decreased, the facilitation of behavior is, according to this view, due to an increase in the effectiveness of the remaining neurons.

However, recent evidence (*12*) suggests that the increase in shock-induced fighting observed following NE depletion may be subject to an alternative interpretation. For example, infusion of NE, but not DA, into the brains of 6-OHDA–treated rats significantly reduced shock-induced fighting (*12*). It is certainly possible to make this outcome compatible with the supersensitivity hypothesis by postulating that NE, by interacting with supersensitive receptors, over-stimulated and thus disrupted the animal's behavior. However, the additional finding that "low" doses of NE (0.5 or 2.0 μg) also suppressed shock-induced fighting in rats without 6-OHDA–induced lesions (that is, nonsupersensitive) makes this interpretation less compelling. In contrast to these effects of NE, infusion of 1.0 or 3.0 μg of DA significantly augmented this behavior. These data are consistent with the suggestion that augmentation of shock-induced fighting may be due to increased DA activation.

Depression of NE activity or administration of DA agonists have also been reported to enhance aggressive behavior in other situations. Thus, treatment with either FLA-63 or L-dopa (the amino acid precursor of DA) markedly increased success in a runway competition in which one rat is forced to compete with another in a narrow alley through which only one can pass (*35*). Diethyldithiocarbonate, a dopamine-β-hydroxylase inhibitor, has also been shown to facilitate the aggressive behavior of rats injected with monoamine oxidase inhibitor, pargyline (*36*). Finally, apomorphine and amphetamine, both of which are DA agonists, are also known to induce fighting in male rats (*37*). The apomorphine-induced fighting can be enhanced by the addition of tail-pinch (a manipulation which, as will be seen later, activates the nigrostriatal DA pathway), while the amphetamine-stimulated aggression is strongly and specifically reduced by DA antagonists (*37*).

Electrical Self-Stimulation of the Brain

Since the initial discovery by Olds and Milner (*38*) that rats would electrically stimulate certain areas of their own brains, with the attendant implication that these areas may participate in basic reward processes, a considerable litera-

ture has accrued which suggests a critical role for both NE and DA in the mediation of this behavior. For example, self-stimulation has been obtained from the locus coeruleus (*39, 40*), which is an area rich in cells whose axons form the major ascending NE-containing pathways (*6*), and from one of the pathways of the locus coeruleus, the dorsal NE bundle (*6, 39–41*). The importance of DA in self-stimulation is suggested by the finding that apomorphine, a DA receptor stimulating agent, facilitates self-stimulation in a situation where response rate is not a factor (*42*). Furthermore, rats will self-administer intravenous injections of apomorphine (*43*), which suggests that DA receptor stimulation may be an important step in the reward process.

A critical role for DA in self-stimulation of the brain has received strong support from the finding that rats will also self-administer amphetamine and that the rewarding value of this drug is reduced by administration of the presumed DA receptor antagonist pimozide (*14*). Generally, a wide variety of DA receptor antagonists have been shown to greatly reduce electrical self-stimulation of the brain (*44*). It seems unlikely that these effects are an indirect consequence of an impairment in operant responding or of reduced arousal because: (i) animals treated with such drugs start to respond at near normal levels before showing a precipitous drop in response rates, a pattern strongly reminiscent of the extinction which normally results from terminating the electrical current (that is, withdrawing the reward); and (ii) the effects on arousal of drugs which are believed to block DA receptors when given in low doses, such as spiroperidol and pimozide, have been clearly dissociated from their effect on self-stimulation (*45*).

Although earlier hypotheses regarding the role of catecholamines in self-stimulation focused on NE or DA as exclusive substrates, recognition of the apparent involvement of both catecholamines in this behavior has led to the more recent proposal that two separate reward systems exist, one mediated by NE and the other by DA (*46*). Our own belief is that the neuropharmacology of self-stimulation is best understood in terms of still another alternative, that is, an interaction between NE and DA systems. This view is suggested by the discovery that inhibition of dopamine-β-hydroxylase by FLA-63 produces a marked facilitation of self-stimulation from electrodes placed in the nigrostriatal DA pathway as it projects through the far lateral hypothalamus (*47*). Since, as noted earlier, FLA-63 increases both the synthesis (*20*) and release of DA from striatal dopaminergic neurons (*23*) in addition to (and perhaps as a consequence of) inhibiting NE synthesis, these data point to an interaction between NE and DA at both neural and behavioral levels.

Consistent with these findings is the recent report of Koob *et al.* (*48*) that large, significant increases occur in lateral hypothalamic self-stimulation after unilateral lesions have been made in the locus coeruleus on the side ipsilateral to the stimulating electrode. The percentage increase in self-stimulation in this study correlated with the degree of NE depletion in the cortex ipsilateral to the lesion. When these data are considered in conjunction with the evidence reviewed previously which implicated DA directly in self-stimulation, it is easier to understand why several laboratories have recently reported that very low doses of DA receptor antagonists diminish self-stimulation obtained not only from such DA-containing sites as the substantia nigra but also from sites which are generally believed to be noradrenergic, such as the locus coeruleus and the dorsal bundle (*49*). That is to say, if the effects of NE-containing neurons on behavior are, at least in part, a consequence of their influence on DA function as we have suggested and as the data presented would appear to indicate, then it is perfectly consistent to expect DA antagonists to suppress self-stimulation obtained from electrodes located in NE-containing sites as well as in DA-containing sites.

Eating

Consonant with the behaviors discussed above, eating which occurs in response to activation or stress appears dependent on the integrity of DA systems and is potentiated by interference with NE activity. Thus, eating induced in sated rats by a mild, nonpainful tail-pinch is selectively attenuated by those neuroleptics which antagonize striatal DA receptors or by lesions of the nigrostriatal DA pathway (*7, 50*). The involvement of the nigrostriatal DA system in this phenomenon is further suggested by the finding that mild tail-pinch produces increased unit firing in the pars compacta of the substantia nigra (the origin of the nigrostriatal DA pathway), but no changes in the electrical activity of the neighboring pars reticulata (*50*).

Evidence for an NE-DA interaction in the mediation of this behavior comes from the finding that tail-pinch–induced eating is prolonged by FLA-63 (*7*). Furthermore, the attenuating effects of the DA receptor antagonists spiroperidol and haloperidol on tail-pinch–induced eating were completely reversed by FLA-63 and methimazole (*51*), another dopamine-β-hydroxylase inhibitor (*52*).

The results obtained when these dopamine-β-hydroxylase inhibitors and DA receptor antagonists were combined are reminiscent of the similar palliative effects obtained by Hollister *et al.* (*25*) and Evetts *et al.* (*29*) when 6-OHDA depleted both NE and DA as opposed to preferentially affecting DA (*25*).

Pharmacological manipulation of deprivation-induced eating indicates that this type of feeding can also be potentiated by interference with NE activity as well as by DA agonists. Using direct, intrahypothalamic administration of catecholamine agonists and antagonists, Friedman *et al.* (*53*) reported that the feeding of rats deprived of food for 22 hours was enhanced by inhibition of NE synthesis by FLA-63 or diethyldithiocarbamate. Feeding was also increased by the administration of L-dopa, and this response was augmented by FLA-63. Similar effects have been reported by Starr and Coons (*54*), who also found an enhanced feeding response to the presumed NE receptor antagonist, phentolamine. Phentolamine is also known to induce increased consumption of milk, a highly palatable food (*55*).

We have now considered a variety of behaviors within the framework of our NE-DA interaction hypothesis. Certain clear trends emerge across a number of these behaviors:

1) All of the behaviors considered seem to depend in large part, for their normal expression, on the functional integrity of DA-containing systems in the brain. Thus, lesions of or pharmacological interference with DA-containing pathways have been reported to disrupt stimulant-induced stereotypy or motor activity, shuttle-box avoidance, several forms of aggressive behavior, electrical self-stimulation of the brain, and stress-related feeding.

2) On the other hand, manipulations designed to reduce NE activity produce just the opposite effects. That is, administration of dopamine-β-hydroxylase inhibitors or NE receptor blocking agents, or lesions of central NE-containing pathways, have been reported to potentiate all of the same behaviors.

3) Finally, when NE and DA are depressed simultaneously, the behavioral deficits normally seen after more selective DA depletion are either reversed or significantly lessened. This was evident in the studies on stimulant-induced stereotypy and motor activity in which 6-OHDA was used, and in the reversal of

neuroleptic depression of stress-induced feeding by dopamine-β-hydroxylase inhibitors.

The Role of Activation

We have continuously alluded to the importance of stress or activation as a determinant of the behavioral augmentation which can occur following interference with NE function. We will now consider this hypothesis more deliberately. First of all, in virtually every instance discussed, behavioral potentiation occurred under activating circumstances. For example, depression of NE activity enhanced stimulant-induced motor activity, shuttle-box avoidance behavior, shock-induced aggression, electrical self-stimulation of the brain, and tail-pinch– and deprivation-induced feeding.

We should now consider the question of what happens when decreased NE function occurs in the absence of activating conditions. The answer, we think, is that either no change or, perhaps more likely, a depression of behavior occurs under such circumstances. For example, in a study considered earlier (*29*), equal depletion of NE and DA (75 to 80 percent, whole brain) produced no decrement in amphetamine-induced hyperactivity, while preferential depletion of NE (61 percent compared to 35 percent for DA) significantly enhanced this activity. By contrast, these same treatments produced, respectively, a depression and no change in spontaneous (that is, unactivated) motor activity. The same trend is evident when the influence of the presumed NE receptor blocking agent phentolamine and FLA-63 on feeding is considered. Phentolamine (applied intrahypothalamically) has been reported to enhance the intake of a highly palatable liquid food in undeprived animals (*55*) and of a regular laboratory diet in animals deprived of food for more than 20 hours (*52*). Both the palatability of the milk in the one experiment and the length of deprivation in the other can be thought of as activating stimuli. Conversely, when phentolamine is administered to animals maintained on a regular diet but deprived of food for only 12 hours (which is certainly a less activating condition than more than 20 hours of deprivation), a considerable decrease of food intake is observed (*56*). Similar results have been obtained with FLA-63. Whereas we have reported that this drug will significantly prolong stress-related eating in sated animals (induced by tail-pinch) (*7*), we have also found that precisely the same dose administered by the same route has no effect on intake in undeprived, unstressed animals (*51*).

These data suggest that when NE functioning is decreased, the augmentation or depression of behavior (and, of course, the continuum in between) may be determined largely by the degree to which activation is part of the context in which a particular behavior is examined.

The neural processes which underlie this heavy dependence on activation are still obscure, although one possibility is suggested by a recent study. Animals with large, unilateral, electrolytic lesions of the locus coeruleus responded to amphetamine or apomorphine by showing strong (but transient) circling behavior in a direction away from the side of the lesion (*57*). The most effective lesions caused the largest NE reduction (55 percent). However, DA levels were actually elevated in the striatum on the side of the lesion. These data led the authors to suggest: (i) that unilateral lesions of the locus coeruleus produced a reduction in impulse traffic in the nigrostriatal DA pathway on the same side [hence the buildup of DA, an effect which is known to occur when impulse flow in DA-containing neurons is inhibited (*58*)]; (ii) the reduced stimulation resulting from the lowered impulse flow produced a compensatory increase in the sensitivity of the striatal DA receptors on the side of the lesion; and (iii) since it is well known that circling or rotation tends to occur in a direction away from the striatum in which DA receptors are most strongly stimulated, the turning away from the side of the locus coeruleus lesion may have been due to stimulation of supersensitive DA receptors either directly by apomorphine, or indirectly by amphetamine-induced release of accumulated DA. In more recent replications of this finding (*57*), these authors have presented an impressive array of additional evidence to support the contention that ". . . the circling caused by unilateral locus coeruleus lesions results from an asymmetry in dopaminergic rather than noradrenergic receptor stimulation." They also suggest that damage to the ventral NE projections of the locus coeruleus may be the critical feature in the development of circling behavior.

Although there are alternative explanations for these data, the hypothesis is, nevertheless, intriguing. It suggests, first of all, that NE-containing pathways originating in the region of the locus coeruleus, may facilitate (and, at the same time, regulate) the functioning of the nigrostriatal DA pathway. Moreover, it could also provide a possible explanation of why stressful or activating circumstances appear to be necessary to induce the wealth of behavior-potentiating effects observed following interference with NE function. In other words, if lesions of the locus coeruleus do, in fact, cause cessation or reduction of impulse flow in nigrostriatal DA neurons and a consequent increase in receptor sensitivity and buildup of DA, then potent (that is, activating or stressful) stimuli may be required to release the accumulated DA. Conversely, in the absence of activating circumstances, there would be no impetus for the mobilization of accumulated DA stores; therefore, behavioral depression might occur.

It should be emphasized that the behavioral depression seen under nonactivated circumstances and the exaggerated behavior obtained during stress are both reflections of the same underlying pathology resulting from removal of the regulatory influence of NE on DA. We believe that this concept of "deregulation" is of considerable theoretical and clinical value, and we will discuss the broader implications of our hypothesis in the last section of this article.

Recent evidence has pointed to the critical importance of potent environmental stimuli in activating behaviors in DA-depleted animals (*59*). We are suggesting that this factor becomes even more decisive when NE systems are also damaged. This point, which we think has considerable and widespread relevance across a number of behavioral situations, may be particularly applicable to a recent study in which we explicitly investigated the interactions between catecholamine depletion and variations in arousal on male sexual behavior in rats (*10*). In the initial experiment of this study, we found only a slight, very transient depression of male copulatory behavior following an intraventricular 6-OHDA regimen that produced a 74 percent depletion of striatal DA, and 81 and 56 percent depletions of cortical and hypothalamic NE, respectively. Evidence reviewed here would suggest that the NE depletion may have counteracted the effects of the DA damage and, therefore, might at least partially explain the relative ineffectiveness of our treatment. Furthermore, the display of "normal" copulatory behavior in males that had recovered from this treatment was heavily dependent on external activation which, in this case, was provided by the female partner. That is to say, as long as sexually receptive females continued to display hopping, darting, and ear wiggling (responses collectively termed soliciting behavior), 6-OHDA–treated males copulated and ejaculated at control levels. However, when soliciting, but not lordosis (the accepting position)

was prevented by treating the female with the DA receptor blocker haloperidol, 6-OHDA–treated males demonstrated severe deficits in their ability to initiate copulatory activity.

Does NE Inhibit or Facilitate DA in the Intact Animal?

In all of the studies discussed, an interaction between NE and DA has been inferred from the behavior of animals deprived either pharmacologically or surgically of normal NE function and subjected to activating or stressful circumstances. The findings derived from these animals may provide some clues about the nature of NE-DA interactions in the intact (that is, nonmanipulated) animal.

The most obvious interpretation of the increase in DA-dependent behavior following interference with NE function is that NE-containing systems normally inhibit the activity in DA systems, a suggestion made previously by others (*12, 60*). While this possibility cannot be ruled out, it should be noted that these data can also be accommodated by the alternative hypothesis; that is, NE systems facilitate DA activity, and in this way regulate DA function.

Evidence presented in the preceding section suggested that unilateral damage to the locus coeruleus produced decreased striatal DA function on the side of the lesion (*57*). These data indicate, as the authors suggest, that NE systems originating in the locus coeruleus normally exert a facilitatory influence on the nigrostriatal DA system.

Additional support derives from the finding that clonidine, at doses thought to stimulate selectively postsynaptic NE receptors, potentiates the action of the DA-receptor agonist, apomorphine, in inducing locomotor activity (*61*). This effect cannot be explained by the direct action of clonidine on either DA systems themselves (*62*) or on the metabolism of apomorphine (*63*).

Most recently, in one of the few studies specifically directed at investigating the relationship between NE and DA, Anden and Grabowska (*64*) have demonstrated that an agent which promotes the release of NE resulted in enhancement of DA synthesis and utilization in the striatum and rest of the forebrain. Conversely, drugs which antagonized NE function inhibited the synthesis and utilization of DA in these structures. Additional data provided by this study indicated that the effects were not due to the direct action of these drugs on DA function (*64*).

The data cited in this section suggest that NE may actually exert a facilitatory influence on DA systems. However, since the number of studies which have actually investigated the possibility of an NE-DA interaction is extremely limited, any firm judgment regarding the inhibitory or facilitatory nature of such an interaction would be premature (*65*).

Is There a Known Neuroanatomical Basis for an NE-DA Interaction?

In the preceding sections, evidence has been presented which suggests an interaction between NE- and DA-containing systems in the brain. Biochemical support for such an interaction was also provided. We now consider evidence for the existence of neuroanatomical pathways through which this interaction might take place.

The possible existence of a direct pathway from NE-cell fields in the caudal brainstem to the origin of the nigrostriatal DA pathway in the substantia nigra has been inferred from behavioral and other types of evidence (*57, 66*). However, although NE-containing fibers are known to project through the substantia nigra (*67*), there is no evidence to indicate that these fibers actually synapse in this area.

There are a number of circuits through which NE can indirectly influence DA activity. Two such circuits, related specifically to the nigrostriatal DA system, are shown in Fig. 2 (*68*).

In one of these circuits, NE fibers projecting from the locus coeruleus to the neocortex (*6, 67*) may influence DA function indirectly by modulating a descending corticostriatal pathway. This pathway (*69*) may synapse on the same interneurons which receive input from the ascending nigrostriatal DA system (*70*), and in this way influence the consequences of DA activity. The nature of the transmitter utilized by this descending pathway has not been clearly identified, although recent evidence obtained by McGeer (*71*) suggests that it may be glutamate.

In the second circuit, NE fibers originating in the caudal brainstem may affect the activity of the nigrostriatal DA system by modulating the influence of a serotonin-containing system projecting from the dorsal raphé to the substantia nigra (*72*).

Although the neuroanatomical circuits just outlined relate only to the possible basis of an interaction between NE and the nigrostriatal DA pathway, other DA-containing systems may also be involved. Biochemical evidence suggests that NE may also interact with DA pathways innervating the neocortex (*73*) or with a short-axon DA system found in the hypothalamus and thought to influence anterior pituitary function (*74*).

These circuits are presented only to exemplify possible neuroanatomical substrates for NE-DA interaction. Any attempt to match more precisely specific features of the behavioral findings previously reviewed with the dynamics of these and alternative networks requires a

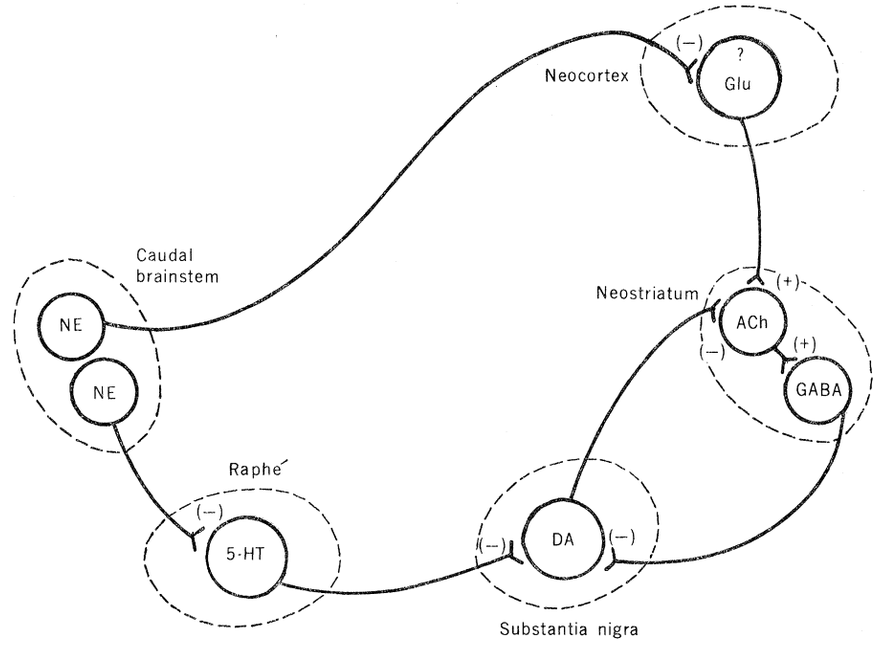

Fig. 2. Schematic diagram depicting two of the known pathways through which NE could influence the DA activity of the nigrostriatal system. Abbreviations: *Ach*, acetylcholine; *5-HT*, serotonin; *GABA*, γ-aminobutyric acid; *Glu*, glutamate [see (*68*) for elaboration].

more detailed knowledge of the interrelationships among these pathways than is now available. The task of precisely identifying parallel behavioral, neurochemical, and electrophysiological manifestations of the interaction between NE and DA remains a challenge for the future.

Clinical and Theoretical Implications

Finally, our hypothesis has some clinical and theoretical implications. Our suggestion that under appropriate circumstances interference with NE could counteract the effects of decreased DA function may be especially relevant to a further understanding of clinical disorders such as Parkinson's disease.

Parkinson's disease has been characterized as a "striatal dopamine deficiency syndrome" (*1*). This definition emphasizes the primary biochemical abnormality found in brains of patients with Parkinson's disease. However, as Hornykiewicz (*75*) points out, even the mildest clinically detectable symptoms of this disorder are associated with an inordinately high degree of striatal DA deficiency. This implies that much of the DA deficiency is somehow compensated for functionally. Evidence suggests that at least part of this compensation might be accounted for by an increased turnover in the remaining DA neurons (*75*). However, in addition to the degeneration of DA-containing neurons in the nigrostriatal bundle, Parkinson's disease also appears to involve prominent pathology of the locus coeruleus and consequent deficiency of NE (*75*). In view of our suggestion that NE deficiency can, under appropriate circumstances, counteract or mask the effects of DA deficiency, this finding may be important. If our hypothesis is correct, the NE depletion occurring in Parkinson's disease may be an important contributory factor in maintaining relatively normal function in the presence of substantial striatal DA deficiency.

Our hypothesis, as applied to the possible contribution of NE depletion to Parkinsonism, stands in stark contrast to what might be considered a more commonsense proposal; that is, that NE depletion combines with and exacerbates the debilitative effects of DA damage (*76*). This latter hypothesis suggests the possibility that an NE agonist, such as clonidine, might at least partially ameliorate the symptoms of this disease (*76*). It follows logically from this view that further disruption of NE would exaggerate the symptoms.

By contrast, our NE-DA interaction hypothesis predicts the opposite outcome. Recent evidence provides a direct test of these alternatives. For instance, administration of clonidine, rather than having a therapeutic effect, has actually been shown to exacerbate Parkinsonian symptoms (*77*). Conversely, when the effects of fusaric acid (a highly specific dopamine-β-hydroxylase inhibitor that has few of the untoward effects of similar compounds) were studied in patients with Parkinson's disease, either no change (*78*) or an actual alleviation of symptoms (*28, 79*) has been reported.

If, as our hypothesis suggests, degeneration of NE-containing neurons in the locus coeruleus masks the debilitative effects of progressive nigrostriatal DA degeneration and thus delays the onset of clinical signs until very considerable DA deficiency has occurred, then it may be possible to develop a method for early detection of Parkinsonian symptomatology (where the disease is suspected) by inducing a temporary reversal of NE depletion with an NE agonist.

There is one additional, and very critical, feature of the NE-DA interaction hypothesis, that is, activation, which should be considered within the context of Parkinson's disease. As the disease develops, with the accompanying progressive deterioration of both NE and DA, it may take nothing more than the activation provided by a fairly normal stimulating environment to mask early expression of symptoms. Suggestive evidence for this hypothesis is provided by our own previously discussed findings that, in rats, the stimulation normally obtained by interacting with a sexually receptive female is sufficient to completely mask the effects of substantial catecholamine depletion (*10*).

Once the disease has fully developed, as, for example, in nonambulatory patients, activation can still be effective in producing a temporary recovery of function. Numerous reports exist of "paradoxical kinesia," a condition in which sudden stress produces well-coordinated behavior in otherwise akinetic patients (*80*). This may not be unlike the finding that experimental stress can induce a variety of behaviors in animals that were akinetic and cataleptic as a consequence of extensive lesions of brain catecholamine systems (*10, 59*).

Just as the NE-DA interaction hypothesis predicts that reduced NE activity would at least partially ameliorate symptoms arising from decreased DA activity, it conversely suggests that lowered NE activity might actually aggravate those disorders such as schizophrenia where increased DA function appears to play a key role (*81*). Consistent with this prediction is the recent report (*82*) that fusaric acid aggravates psychotic symptoms in "stage 3" of the manic episode in patients with manic-depressive psychosis (this stage is thought to closely resemble acute schizophrenia). Our hypothesis predicts that neuroleptics which are relatively more selective in blocking DA receptors (for example, butyrophenones and diphenylbutylpiperidines), as opposed to those which block both NE and DA receptors (for example, phenothiazines), might also be more effective in treating schizophrenia, a difference which has been suggested (*83*), although no clear supportive evidence has been obtained.

An explanation for the apparent inverse relationship between NE activity and the severity of schizophrenic symptoms which is based on increased functional activity of DA neurons might also provide a rapprochement between two seemingly contradictory points of view. One view focuses on a chronic reduction in dopamine-β-hydroxylase and thus NE synthesis as a causative factor in schizophrenia, while the other emphasizes increased functional activity in DA-containing systems (*4*).

Finally, the NE-DA interaction hypothesis may be relevant in a more general sense to manic-depressive disorders. An admittedly speculative, but nevertheless intriguing, parallel might be drawn between the prediction of a swing from suppressed to potentiated behavior when NE-depleted animals are exposed to an activating environment, and the stress-induced "switch" from depression to mania which has been reported for manic-depressive patients (*84*). This hypothesis is made more tenable by the fact that DA has been strongly implicated in the development of manic symptoms (*85*), and is also consistent with current beliefs that the same underlying defect may be present in both mania and depression (*84*).

Summary

The proposed hypothesis is directed toward explaining a number of disparate findings in terms of a stress-related interaction between the NE- and DA-containing systems in the brain. The deleterious behavioral effects of decreased DA activity, for example, may be counterbalanced by a similar decrease occurring in NE activity, such compensation being most likely to occur under conditions of stress. This hypothesis may have application to the understanding of neurological and mental disorders such as Parkinson's disease and schizophrenia.

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