Central Dopamine Hypoactivity and the Pathogenesis of Neuroleptic Malignant Syndrome

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There is compelling clinical evidence implicating disruption of dopaminergic neurotransmission by antipsychotic drug-induced dopamine (DA) receptor blockade in the pathogenesis of neuroleptic malignant syndrome (NMS).\(^1\)\(^2\) The cornerstone of this evidence is that all antipsychotics, including the newer atypical agents, have been reported to cause NMS and, despite diverse pharmacologic activities, all share the property of D\(_2\) receptor blockade.\(^1\) Furthermore, antipsychotics with greater potency as D\(_2\) receptor blockers are more frequently implicated in causing NMS. Moreover, NMS has been successfully treated with a variety of DA agonists. Other pharmacologic manipulations that reduce dopaminergic neurotransmission have also been linked to NMS-like conditions.\(^1\) These include depletion of DA storage pools with alpha-methyl-p-tyrosine, tetrabenazine, and reserpine; withdrawal of DA agonists or episodes of “freezing” during administration of levodopa in patients with Parkinson’s disease; and treatment with non-neuroleptic DA-blocking drugs such as metoclopramide and amoxapine. Finally, the disruption of dopaminergic neurotransmission in nigrostriatal, mesolimbic, mesocortical, and diencephalospinal DA pathways, hypothalamic DA neurons, and peripheral DA receptors could account for nearly all clinical manifestations of NMS.\(^1\)

However, the view that NMS results from DA receptor blockade may be simplistic, in that it fails to account for the rare occurrence of the syndrome and its unpredictable onset, even in patients with previous episodes.\(^3\) Obviously, other facilitating cofactors are necessary to trigger an episode. Previously, we had postulated that such cofactors might include interactions or relative imbalances between DA and other neurotransmitters, including serotonin, norepinephrine, GABA, and acetylcholine; postsynaptic second messenger system abnormalities; physiological state; underlying psychiatric illness; genetic factors; or peripheral cofactors, including dehydration, exhaustion, medical illness, or hot weather.\(^1\)\(^3\) In this article, we propose that in addition to D\(_2\) receptor blockade, NMS is the product of preexisting central dopaminergic hypoactivity that represents a trait vulnerability marker for this disorder, coupled with state-related adjustments in the DA system occurring in response to acute and repeated exposure to stress. First, however, we review, in some detail, an important new model of brain commu-
nizations circuitry that provides a unifying conceptual framework within which individual NMS symptoms may be localized to perturbations in specific DA pathways.

**INDIVIDUAL NMS SYMPTOMS AND DOPAMINE SYSTEMS**

**Anatomical Considerations**

A schema described by Alexander et al. identifies the frontal–subcortical circuits as one of the brain’s principal organizational networks underlying brain–behavior relationships. As indicated in Figure 1, the basal ganglia, along with their connected cortical and thalamic areas, are viewed as components of a family of “basal ganglia–thalamocortical circuits” that are organized in a parallel fashion yet remain largely segregated both anatomically and functionally. Each circuit involves the same member structures, including an origin in a specific area of the frontal cortex; projections to the striatum (putamen, caudate, and ventral striatum); connections to globus pallidus interna (GPI) and substantia nigra pars reticulata (SNr), which, in turn, project to specific thalamic nuclei; and a final link back to the frontal area from which they originated, thus completing the feedback loop.

Five circuits have been identified and are named according to their function or cortical site of origin (Fig. 1). They include the “motor circuit,” the “oculomotor circuit,” the “dorsolateral prefrontal circuit,” the “lateral orbitofrontal circuit,” and the “anterior cingulate–medial orbitofrontal circuit.” Additionally, within each circuit are dual opposing pathways linking the striatum with the GPI and SNr that represent the major outflow nuclei of the basal ganglia circuitry (Fig. 2): a direct monosynaptic pathway from the striatum to the GPI and SNr and an indirect pathway from the striatum first to the globus pallidus externa (GPe) and then to the subthalamic nucleus (STN) before connecting with the GPI and SNr. Each of the five circuits uses the same neurotransmitters in relaying information between analogous anatomic sites.

DA is in a key position to influence activity in each of the circuits. Mesocortical DA pathways originate from DA neurons located in the ventral mesencephalon. Although the cortical dopaminergic innervations in rodents are derived primarily from the ventral tegmental area (A10 cell group), in primate species they arise predominantly from DA neurons in the substantia nigra pars compacta (SNc; A9 cell group) and the retrorubral field (A8 cell group) with a smaller contribution from the ventral tegmental area than would be anticipated on the basis of rodent data. Mesocortical DA pathways project directly to circuit origin sites in the supplementary motor area, frontal eye fields, and the three prefrontal cortical areas. Additionally, DA modulates each circuit through its projections to the striatum. Although significant overlap exists, most dopaminergic input to the dorsal striatum (caudate and putamen) comes from the SNc (nigrostriatal pathway), whereas the ventral tegmental area provides the bulk of dopaminergic innervation to the ventral striatum (mesolimbic pathway). Furthermore, within the circuits, DA has differential effects on the direct and indirect pathways. The motor, the anterior cingulate–medial orbitofrontal, and the lateral orbitofrontal circuits represent major candidates for involvement in the pathogenesis of NMS.

**Muscular Rigidity**

Muscular rigidity in NMS may relate to dysfunction in the motor circuit (Fig. 2). The motor circuit originates from neurons in the supplementary motor area and parts of the motor, premotor, and somatosensory areas that project topographically to the putamen (Fig. 1). This projection, like all circuit pathways between the cortex and the striatum, is glutamatergic, and hence excitatory. The putamen then projects both a direct and an indirect pathway to the GPI and SNr. The direct monosynaptic pathway to the GPI and SNr uses GABA as its transmitter and is inhibitory. Cortical activation of the direct pathway thus produces a suppression of GPI and SNr output, which is itself GABA-ergic and inhibitory, thereby disinhibiting the GPI and SNr thalamic projection neurons. The thalamus then sends excitatory glutamatergic projections to the circuit’s cortical areas of origin. The net effect is that the direct pathway provides positive feedback for cortically initiated movements and has a princi-
Figure 2. The basal ganglia–thalamocortical "motor" circuit. SNC = substantia nigra pars compacta; GPe = globus pallidus externa; STN = subthalamic nucleus; GPI = globus pallidus interna; SNr = substantia nigra reticulata; VA/VL = ventral anterior/ventral lateral nuclei of the thalamus; + = excitatory; - = inhibitory. (From Lou J-S. Pathophysiology of basal ganglia disorders. CNS Spectrums. 1998;3:36-40. Reprinted by permission of CNS Spectrums. Copyright 1998. All rights reserved.)
pal role in sustaining ongoing patterns of motor behavior. In contrast, cortical activation of the GABA-ergic putaminal neurons of the indirect pathway inhibits the GPe, which, in turn, uses GABA to inhibit the STN. The excitatory STN sends a glutamatergic projection that drives the Gpi and SNr to inhibit the thalamus. This then suppresses excitatory thalamic feedback to the cortex. The net effect is that the indirect pathway provides negative feedback for cortically initiated movement and is used to suppress ongoing patterns of motor behavior.

Consistent with basal ganglia–thalamocortical circuit organization, DA exerts differential effects on the direct and indirect pathways. Nigrostriatal dopaminergic input excites GABA-ergic putaminal neurons projecting to the Gpi and SNr via the direct pathway, but inhibits those projecting to the GPe via the indirect pathway. Accordingly, by modulating the amount of DA released in the putamen, the SNCs can favor either the direct pathway (or the sustaining of ongoing patterns of motor behavior) or the indirect pathway (or the suppression of motor activity). In Parkinson's disease, loss of dopaminergic input to the putamen would suppress activity in the direct pathway, where DA facilitates transmission, but enhance activity in the indirect pathway, where DA is inhibitory. The overall outcome would be increased output from the Gpi and SNr yielding excessive inhibition of thalamocortical neurons, accounting for the cardinal features of Parkinson’s disease. In particular, increased activity in the indirect pathway, which is used to suppress motor activity, could cause tonic suppression of movement and resultant rigidity.

However, additional circuit features are relevant when considering the impact of antipsychotic drugs. It appears likely that the actions of nigrostriatal DA on GABA-ergic putaminal neurons of the direct pathway are mediated by D1 receptors, whereas those of the indirect pathway receive their dopaminergic influence via D2 receptors. Hence, consistent with the D2 receptor blockade hypothesis, the principal effects of antipsychotics could be to increase activity in the indirect pathway, which suppresses motor activity, leading to particularly prominent rigidity. This could begin to explain why rigidity during antipsychotic drug treatment might, under certain circumstances, be disproportionately profound in NMS compared with other parkinsonian manifestations. It remains to be clarified whether the newer atypical antipsychotic drugs, which appear to have reduced motor effects in the putamen, will have a decreased association with mechanisms involved in the rigidity of NMS.

**Diminished Arousal, Mutism, and Akinesia**

The anterior cingulate–medial orbitofrontal subcortical circuit may mediate diminished arousal, mutism, and akinesia in NMS and may also contribute to hyperthermia and autonomic dysfunction. This circuit engages a number of cortical and subcortical structures that are considered to be limbic in nature. It originates in the anterior cingulate area, the medial orbitofrontal area, and the association cortex of the temporal lobe (Fig. 1). These areas then project to the ventral striatum or limbic striatum, which is composed of the nucleus accumbens, the ventromedial part of the caudate–putamen, and the olfactory tubercle. The nucleus accumbens is further divided into core and shell subregions. The ventral striatum also receives extensive projections from limbic structures, including the hippocampus, the amygdala, and both entorhinal and perirhinal cortices. The ventral striatum provides input to the ventral pallidum, the rostromedial GPi, and the rostromedial SNr. In addition, the ventral striatum may involve an indirect pathway projecting first to the rostral pole of the GPe, and then to the medial STN before connecting with the ventral pallidum.

The ventral pallidum then provides input to the medial dorsal nucleus of the thalamus, which projects back to the anterior cingulate and medial orbitofrontal areas, completing the circuit. It also targets the entire mediolateral range of the SNc. Furthermore, it is of considerable interest that projections from the ventral pallidum to the medial STN extend to the medial aspect of the entopeduncular nucleus and adjacent parts of the lateral hypothalamus. This suggests that, in addition to direct effects on hypothalamic D2 receptors, antipsychotic drugs may cause hyperthermia and autonomic dysfunction in NMS through disruption of anterior cingulate–medial
orbitofrontal circuit pathways to the lateral hypothalamus.

Previously, we had proposed that the neurologic condition akinetic mutism could serve as a model for mutism, disturbances of consciousness, and akinesia in NMS. Akinetic mutism, which involves severe hypomotility, diminished arousal, and mutism, has been mistaken for psychogenic catatonia. Furthermore, certain cases of akinetic mutism have involved hyperthermia and autonomic dysfunction, making them difficult to distinguish from NMS. Akinetic mutism has resulted from various bilateral lesions of the centromedial brain, including brain stem areas, periventricular nuclei in the hypothalamus, the mamillary bodies, and the anterior cingulate area. This distribution of lesions is highly correlated with the anatomic location of the mesocortical DA pathway to the anterior cingulate area as it courses rostrally in the medial forebrain bundle. Accordingly, this appeared to support a pathogenic role for interruption of the mesocingulate DA pathway in causing mutism, decreased responsiveness, and akinesia in NMS.

However, a new theory of antipsychotic drug mechanisms argues against the direct involvement of the mesocingulate DA pathway in the etiology of NMS. Furthermore, this work points to a key role for each of the basal ganglia–thalamocortical circuits in mediating the effects of antipsychotic drugs throughout disparate areas of the brain. Holcomb et al. studied the localization of haloperidol action in the schizophrenic brain using positron emission tomography with a [18F] fluorodeoxyglucose tracer. The analysis demonstrated that haloperidol enhances glucose metabolism in both the dorsal and the ventral striatum, areas rich in D2 receptors. Hypermetabolism is presumed to be due to antipsychotic drug-induced increases in turnover and uptake of striatal DA. However, haloperidol decreased glucose metabolism in the frontal and anterior cingulate cortices, which have low densities of D2 receptors. In addition, glucose metabolism was increased in the anterior thalamus.

Accordingly, these authors proposed that haloperidol exerts its primary DA-blocking action in the striatum with secondary and tertiary effects being propagated to other related brain areas through the basal ganglia–thalamocortical circuits. In this formulation, striatal D2 receptor blockade activates the indirect pathway providing excitatory input to the GPi and SNr, which, in turn, inhibits thalamic neurons. Augmented GABA-ergic signaling from the GPi and SNr to the thalamus could account for the increased glucose use observed in the anterior part of that structure. Overinhibition in the anterior thalamus would result in decreased glutamatergic excitatory transmission to the frontal and cingulate cortices as reflected by decreased glucose metabolism observed in these areas. As such, this work suggests that mutism, akinesia, and diminished arousal in NMS are not the product of direct effects of antipsychotics on the mesocingulate DA pathway. Rather, these symptoms appear to result from a primary action of antipsychotic drugs in the ventral striatum that is then propagated via the anterior cingulate–medial orbitofrontal circuit to the ventral pallidum and then the anterior thalamic nucleus, and ultimately to anterior cingulate and medial orbitofrontal cortices, resulting in decreased excitatory input to that area. The lack of direct involvement of the mesocingulate pathway or other mesocortical DA pathways in the pathogenesis of NMS is consistent with the predominance of D1 and D4 over D2 receptors in the cerebral cortex.

Catatonic Features

The lateral orbitofrontal–subcortical circuit may also be implicated in the pathogenesis of NMS. The lateral orbitofrontal circuit originates in the lateral orbitofrontal cortex and projects to a ventromedial sector of the caudate nucleus (Fig. 1). This part of the caudate projects to the rostromedial SNr and the mediiodorsal GPi. The ventromedial caudate also sends an indirect pathway first to the dorsal GPi and then to the lateral STN before connecting with the SNr and GPi. The rostromedial SNr and mediiodorsal GPi then project to the medial portions of the ventral anterior and medial dorsal thalamic nuclei that, in turn, project back to the lateral orbitofrontal cortex, closing the circuit. Imaging data reveal hyperactivity of the lateral orbitofrontal circuit in patients with obsessive–compulsive disorder. Bilateral lesions of the lateral orbitofrontal cortex...
or dysfunction in the orbitofrontal–subcortical circuit has been associated with use and imitation behaviors. These behaviors involve automatic imitation of the gestures and actions of others or automatic and inappropriate use of objects such as tools and utensils.

As Cummings points out, use and imitation reflect enslavement to environmental cues. These behaviors share striking similarities with catatonic features such as echopraxia, echolalia, stereotypy, mannerisms, and gegehalten, all of which have been viewed as stimulus bound or motor perseverative phenomena consistent with frontal lobe dysfunction. Catatonic signs have been frequently observed in NMS, and NMS has been conceptualized as a severe variant of the catatonic syndrome. We have posited that NMS represents a toxic or iatrogenic organic form of the lethal catatonia syndrome. Mutism, stupor, and rigidity are the most common catatonic features reported in cases of NMS and, as considered above, may better correlate with perturbations in the motor and anterior cingulate–medial orbitofrontal circuits. Still, it seems reasonable to propose that the lateral orbitofrontal circuit mediates use and imitation-like catatonic manifestations in psychogenic catatonia and in NMS.

Hyperthermia and Autonomic Dysfunction
Our review of the anterior cingulate–medial orbitofrontal circuit indicated that disruption of its corticolateral hypothalamic circuitry might contribute to hyperthermia and autonomic dysfunction in NMS. Furthermore, mesodiencephalic DA pathways to the hypothalamus have also been identified, although their physiological role remains unclear. However, DA receptor blockade of intrinsic hypothalamic DA neurons may be paramount in causing hyperthermia and dysautonomia in NMS. Hypothalamic DA neurons have been identified in four regions of the hypothalamus (A11–A14). Substantial evidence suggests a prominent role for DA in hypothalamic thermoregulation. Studies indicate the presence of a DA-mediated heat-loss pathway involving hypothalamic DA neurons of the A14 group that project to the medial preoptic anterior hypothalamus, the key hypothalamic thermoregulatory site. Thus, antipsychotic drug–induced D2 receptor blockade within this dopaminergic heat-loss pathway could result in hyperthermia in response to a heat load.

In NMS, excess heat appears to derive primarily from hypermetabolism of skeletal muscle due to antipsychotic drug–induced extrapyramidal rigidity and, possibly, from direct effects of antipsychotics on skeletal muscle. DA neurons of the A11 group located periventricularly in the dorsal hypothalamus, posterior hypothalamus, and caudal thalamus give rise to a diencephalospinal DA pathway. This pathway provides dopaminergic innervation to the intermediolateral spinal column mediating inhibition of preganglionic sympathetic neurons. Its blockade could contribute to increased sympathetic nervous system outflow consistent with the “hyperadrenergic” manifestations of NMS.

Peripheral DA receptors may also mediate dopaminergic influences on autonomic function. Peripheral D2 receptors are located on postganglionic sympathetic neurons that inhibit norepinephrine release from sympathetic nerve terminals, leading to peripheral vasodilatation and decreased heart rate. Similar to the diencephalospinal pathway, blockade of peripheral D2 receptors by antipsychotic drugs could cause dysautonomia with increased excretion of epinephrine and norepinephrine manifesting in a “hyperadrenergic crisis.”

EVIDENCE FOR BASELINE CENTRAL HYPODOPAMINERGIA AS A TRAJECT VULNERABILITY MARKER FOR NMS
Several investigators assessed dopaminergic functioning in NMS by measuring cerebrospinal fluid levels of DA and its major metabolite, homovanillic acid (HVA). The results have been inconsistent, with different authors finding increased, decreased, or normal HVA levels. However, these studies were limited primarily to single cases and were without adequate control subjects on which to base conclusions.

More recently, Nisijima and Ishiguro measured cerebrospinal fluid levels of HVA in a series of 8 patients with NMS and 10 normal control subjects. The patients’ HVA levels were significantly lower during the acute phase of NMS compared with the HVA levels of the control.
subjects. Three patients with NMS had just started antipsychotic drug treatment and should have manifested enhanced DA turnover and associated elevation of HVA. These findings pointed to a reduced state of functioning in the DA system during the acute phase of NMS, supporting the DA receptor blockade hypothesis. Furthermore, cerebrospinal fluid levels of HVA were also significantly reduced after recovery from NMS (14 to 129 days from the last exposure to antipsychotic drugs). This led to the proposal that the decreased HVA levels after recovery from NMS represent baseline levels for patients susceptible to NMS, indicating a preexisting reduction in DA metabolism. Such individuals would be prone to a marked suppression of dopaminergic activity on exposure to antipsychotic drug–induced DA receptor blockade. Thus, in an extension of the concept of decreased dopaminergic activity in the etiology of an acute NMS episode, preexisting hypodopaminergia was postulated to be critical in determining risk for NMS. These same investigators later studied cerebrospinal fluid levels of HVA in a new series of 11 patients with NMS, this time comparing them with age-matched normal control subjects. They replicated their findings of lower cerebrospinal fluid levels of HVA in patients with NMS both during acute NMS and after recovery. Seven patients had a diagnosis of schizophrenia, but the subtypes were different among the cases. The additional 4 had diagnoses that included mania, depression, Parkinson’s disease, and mental retardation. Thus, the findings remained consistent across a variety of underlying disorders.

Further support for hypodopaminergia as a trait vulnerability marker in patients at risk for NMS comes from neuropathophysiological findings of Kish et al. in 3 patients with fatal hyperthermia syndromes. These authors reported normal levels of hypothalamic and striatal DA and D₂ receptor binding in all 3 patients, but noted evidence of reduced HVA in the striatum of 1 patient, lack of an elevated HVA:DA ratio in another, and reduced striatal HVA in the third, although this patient had been treated with a monoamine oxidase inhibitor that could have affected these results. They postulated that there had been a reduced capacity to compensate for stress or antipsychotic drug–induced receptor blockade due to a preexisting deficit in the DA system. Kish et al. reported a profound reduction in choline acetyltransferase in the cortex and limbic system, in addition to a marked reduction in hypothalamic noradrenaline. This prompted them to speculate that striatal dopaminergic dysfunction and cholinergic hypoactivity predispose to NMS, whereas noradrenaline depletion may result secondarily from stress and hyperthermia. In addition, Gertz and Schmidt posited dopaminergic hypoactivity in 1 case of NMS in which they noted a striking loss of melanin as a breakdown product in the substantia nigra.

A recent study of NMS susceptibility in patients with Parkinson’s disease supplies further clinical evidence for preexisting dopaminergic hypoactivity in NMS. Cerebrospinal fluid levels of monoamine metabolite, including HVA, 3-methoxy-4-hydroxyphenylglycol, and 5-hydroxyindolacetic acid, were assayed in 98 patients with Parkinson’s disease, including 11 who had experienced an NMS-like episode. The NMS group included 8 patients admitted because of an NMS-like episode and 3 patients with a history of a prior episode. In those with acute NMS, cerebrospinal fluid analyses were performed after recovery. Patients in the NMS group exhibited more severe parkinsonian symptoms and had lower cerebrospinal fluid levels of HVA. Results from logistic regression analysis indicated that only cerebrospinal fluid levels of HVA were significantly and independently related to NMS. Consistent with the thinking of Nisijima and Isiguro, reduced cerebrospinal fluid levels of HVA were ascribed to decreased dopaminergic function at baseline. The authors speculated that the NMS group might include a rapidly progressive variant of Parkinson’s disease (“malignant type”) resulting from accelerated neuronal loss in the substantia nigra or abnormalities in central DA turnover. In addition, a role for central noradrenergic hyperactivity in the development of NMS was deemed possible. This work suggests that measuring baseline cerebrospinal fluid levels of monoamine metabolites may provide a means of identifying NMS susceptibility in patients with Parkinson’s disease.

Animal models may provide support for base-
line hypodopaminergia in NMS. The porcine stress syndrome has served as a valuable animal model for malignant hyperthermia, a pharmacogenetic disorder of skeletal muscle that bears striking clinical similarity to NMS.\textsuperscript{2,25} Although the weight of evidence supports the principal involvement of central dopaminergic mechanisms in NMS and of peripheral skeletal muscle metabolism alterations in malignant hyperthermia and porcine stress syndrome, a role for pathogenetic overlap cannot be completely dismissed.\textsuperscript{2,25} Of note, correlations between central DA activity and malignant hyperthermia and porcine stress syndrome susceptibility have been proposed.\textsuperscript{2} Stress-susceptible pigs exhibit locomotor disturbances characteristic of basal ganglia disorders.\textsuperscript{2} Draper et al.\textsuperscript{26} demonstrated that stress-susceptible pigs had a 20\% to 40\% baseline reduction of DA in the caudate nucleus compared with stress-resistant animals, leading them to propose that porcine stress syndrome relates primarily to a disturbance of the basal ganglia DA system. This work is of additional interest in that it introduces the issue of stress and DA interactions in the pathogenesis of NMS-like conditions.

The recent finding of structural changes in the D\textsubscript{2} receptor gene in a patient with NMS furnishes additional evidence for a disturbance in baseline dopaminergic function.\textsuperscript{27} This mutation could alter the binding affinity, cellular membrane properties, or interactions with second messenger systems of the receptor.\textsuperscript{25} Familial findings include the occurrence of NMS in a mother and two daughters.\textsuperscript{28} Each had previously experienced either a febrile catatonic episode unassociated with antipsychotics or severe antipsychotic drug–induced extrapyramidal symptoms, leading to the speculation that they shared a genetic vulnerability in the central DA system predisposing them to NMS.\textsuperscript{28} Similarly, other authors have proposed that catatonia represents a state of deficient brain DA activity and thus should be viewed as a highly significant risk factor for NMS.\textsuperscript{29} Finally, in addition to Parkinson’s disease, reports of NMS-like conditions in association with other extrapyramidal disorders, including Wilson’s disease, striatonigral degeneration, Huntington’s disease, and tardive dystonia, suggest that patients with preexisting dysfunction of central DA systems as a trait marker may be more susceptible to NMS.

**STATE-RELATED EFFECTS OF STRESS ON DA FUNCTION AND THE PATHOGENESIS OF NMS**

Substantial evidence supports a role for psychological, physiological, and environmental stress in predisposing to NMS.\textsuperscript{1,3,30} A number of authors have reported that patients with NMS are significantly more likely to be agitated and psychotic prior to the onset of NMS.\textsuperscript{1,3,30} Furthermore, psychological stress may trigger hyperthermia and other features of NMS in humans\textsuperscript{31} and in animal models such as porcine stress syndrome.\textsuperscript{21} A large body of evidence supports the idea that the DA system is highly responsive to stress.\textsuperscript{32} Moreover, as first described more than 20 years ago,\textsuperscript{33} the dopaminergic innervation of the medial prefrontal cortex in the rat is unique in that it is activated by mild stressors such as limited footshock stress or conditioned fear paradigms. Activation of the mesocortical DA pathway may be associated with the animal attempting to cope with the stress.\textsuperscript{11} Extending the duration or increasing the intensity of acute environmental stress will result in increased DA use in the ventral striatum, and still greater stressors will enhance DA use in the dorsal striatum.\textsuperscript{34} Furthermore, there is evidence that the selective response of the medial prefrontal cortex to acute stress may play an important modulatory role in subcortical dopaminergic activity.\textsuperscript{35,36}

There are considerable data indicating a functional interdependence of DA systems innervating the medial prefrontal cortex and subcortical dopamine areas; in particular, changes in medial prefrontal cortex DA turnover seem to have an inverse relationship with dopamine turnover in the dorsal and ventral striatum.\textsuperscript{35,36} Mesencephalic DA neurons from the ventral tegmental area project to the medial prefrontal cortex, where they synapse on and inhibit corticostriatal neurons that are glutamatergic and augment subcortical DA release and metabolism.\textsuperscript{35,37} The removal of these corticostriatal neurons from mesocortical dopaminergic inhibition would be expected to increase dopaminergic activity in the dorsal and ventral striatum.\textsuperscript{37} Consistent with this, Pycock et al.\textsuperscript{38} demonstrated increased presynaptic and...
postsynaptic indices of subcortical DA function following 6-hydroxydopamine lesions of the medial prefrontal cortex. Many, but not all, investigators have been able to replicate these findings. Interestingly, it appears that this effect is most consistently produced in studies where animals are exposed to stressful conditions. In addition, the local injection of DA antagonists in the medial prefrontal cortex increases DA metabolism in subcortical areas, further supporting the negative correlation between cortical and subcortical DA. In view of the above considerations, Weinberger and others have proposed a model of schizophrenia in which presumed mesocortical dopaminergic underactivity (accounting for negative symptoms) could drive mesolimbic dopaminergic overactivity (accounting for positive symptoms).

Conversely, increased mesocortical dopaminergic input to the medial prefrontal cortex has been associated with decreased subcortical DA release and metabolism. This may be of particular relevance for the pathogenesis of NMS. Stimulation of dopaminergic transmission by local microinjection of the DA agonist d-amphetamine in the medial prefrontal cortex of the rat has been shown to decrease DA levels in the ventral striatum. Similarly, injection of the DA agonist apomorphine in the medial prefrontal cortex reduces levels of DA metabolites in the dorsal striatum of the rat by approximately 20%. Further, application of apomorphine in the medial prefrontal cortex of the rat enhances the ability of haloperidol to produce catalepsy, again pointing to reduced dopaminergic functioning in the dorsal striatum. These findings suggest that if acute stress activates mesocortical dopaminergic transmission to the medial prefrontal cortex, it will have feedback effects in both the dorsal and the ventral striatum, rendering those areas hypodopaminergic and predisposing to NMS on exposure to antipsychotic drug–induced D2 receptor blockade.

The DA system appears to respond differently to stress that is chronic or repetitive. Previously, Frischione had invoked Friedhoff's restitutive hypothesis to explain how stress and the onset of psychosis could eventuate in state-specific subcortical hypodopaminergia and the promotion of NMS. The restitutive hypothesis posits that the DA system functions in a homeostatic fashion to protect against the emergence of psychotic symptoms through physiological downregulation of its own activity in the face of biological and psychological stressors that are chronic and inescapable. In this situation, the DA system appears to participate in a spontaneous response, which is similar to that produced by an antipsychotic drug.

To further pursue this hypothesis, Friedhoff et al. studied the ability of both acute and chronic stress to inhibit the conditioned avoidance response to aversive stimuli. It is well established that all antipsychotic drugs, including the atypical agents, inhibit the ability of rats to perform the conditioned avoidance response. Following acute tailshock stress, rats continued to perform the conditioned avoidance response at baseline levels. However, rats subjected to tailshock stress twice daily for 8 days showed marked inhibition of the conditioned avoidance response and reduction in DA use in the ventral striatum. Other data suggest that reduction in dopaminergic activity in the dorsal striatum is also required for inhibition of the conditioned avoidance response. Hence, these findings are compatible with the existence of an endogenous DA-dependent mechanism that mimics antipsychotic drug effects in response to repeated stress. Accordingly, it appears reasonable to propose that antipsychotic drug–like effects of chronic stress, coupled with antipsychotics themselves could contribute to the triggering of an NMS episode.

CONCLUSION

There is compelling evidence for the involvement of antipsychotic drug–induced D2 receptor blockade in the pathogenesis of NMS. An understanding of the basal ganglia–thalamocortical cortical circuits provides a unifying conceptual framework within which individual NMS symptoms may be localized to perturbations in specific dopaminergic pathways. Blockade of dopaminergic transmission in the motor circuit may mediate muscular rigidity and other extrapyramidal features of NMS, whereas decreased DA input to the anterior cingulate–medial orbito-
frontal circuit might represent the mechanism for diminished arousal, mutism, and akinesia. Furthermore, blockade of the lateral orbitofrontal circuit may underlie selected catatonic manifestations of NMS. DA antagonism in the anterior cingulate–medial orbitofrontal circuit may also contribute to hyperthermia and autonomic dysfunction in NMS in concert with D2 receptor blockade involving diencephalospinal DA pathways, hypothalamic DA neurons, and peripheral DA receptors.

What remains unclear is why NMS develops only rarely in certain individuals and on selected occasions. As such, postulation of facilitating trait- and state-related cofactors would seem essential in accounting for the idiosyncratic triggering of NMS episodes. In this article, we have pursued several lines of evidence indicating that preexisting central dopaminergic hypoactivity represents a trait vulnerability marker for NMS. Baseline hypodopaminergia would render individuals susceptible to a marked suppression of dopaminergic activity on exposure to antipsychotic drug–induced DA receptor blockade. Furthermore, we have reviewed findings implicating the enhanced responsiveness of the DA system to stress as a state-related cofactor in the pathogenesis of NMS. Data suggest that both acute and repeated exposure to stress may contribute to decreased DA metabolism in the dorsal and ventral striatum, thus predisposing to NMS during antipsychotic drug treatment. Finally, the comprehensive role for DA in the model outlined here provides strong support for the use of DA agonists in the treatment of NMS.47

REFERENCES


