Phasic Versus Tonic Dopamine Release and the Modulation of Dopamine System Responsivity: a Hypothesis for the Etiology of Schizophrenia

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COMMENTARY

PHASIC VERSUS TONIC DOPAMINE RELEASE AND THE MODULATION OF DOPAMINE SYSTEM RESPONSIVITY: A HYPOTHESIS FOR THE ETIOLOGY OF SCHIZOPHRENIA

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Abstract—A novel mechanism for regulating dopamine activity in subcortical sites and its possible relevance to schizophrenia is proposed. This hypothesis is based on the regulation of dopamine release into subcortical regions occurring via two independent mechanisms: (1) transient or phasic dopamine release caused by dopamine neuron firing, and (2) sustained, "background" tonic dopamine release regulated by prefrontal cortical afferents. Behaviorally relevant stimuli are proposed to cause short-term activation of dopamine cell firing to trigger the phasic component of dopamine release. In contrast, tonic dopamine release is proposed to regulate the intensity of the phasic dopamine response through its effect on extracellular dopamine levels. In this way, tonic dopamine release would set the background level of dopamine receptor stimulation (both autoreceptor and postsynaptic) and, through homeostatic mechanisms, the responsivity of the system to dopamine in these sites.

In schizophrenics, a prolonged decrease in prefrontal cortical activity is proposed to reduce tonic dopamine release. Over time, this would elicit homeostatic compensations that would increase overall dopamine responsivity and thereby cause subsequent phasic dopamine release to elicit abnormally large responses.

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Abbreviations: DA, dopamine; HVA, homovanillic acid; NMDA, *N*-methyl-D-aspartate; 6-OHDA, 6-hydroxydopamine; PCP, phencyclidine; PET, positron emission tomography.

1. INTRODUCTION

Schizophrenia is known to affect approximately 1% of the world population, with its incidence apparently uncorrelated with socioeconomic status or cultural background.[262,303] This disease is particularly devastating in that its onset usually occurs in individuals in their 20s and 30s,[295] interfering with their function in society that, at least in Western cultures, occurs at a stage when they typically would be launching their careers and achieving financial independence. This disorder places a particularly heavy burden on the family, with parents often forced to arrange for chronic support and treatment of afflicted offspring. Unfortunately, very few health insurance or public welfare organizations provide for long-term clinical care of individuals with schizophrenia.[176] Because of this loss of productivity and the need for long-term institutional care, it has been estimated that schizophrenia places an economic burden on the U.S. of more than $20 billion annually. Although a combination of basic and clinical research has provided insights into the brain systems that may contribute to some of the symptoms of this disorder, an inadequate understanding of its etiology and the absence of an accurate neurobiological model have hampered progress toward more effective treatments of schizophrenia.

1.1. *The dopamine hypothesis of schizophrenia*

In studies of the neurobiological basis of schizophrenia, most investigations have been directed at elucidating the role of the neurotransmitter dopamine (DA) in this disorder. This interest is based primarily on two pieces of pharmacological evidence. The first indication that DA may have a causative role in schizophrenia can be traced to the pioneering experiments of Carlsson and Lindqvist,[47] who noted that administration of antipsychotic drugs to animals causes a specific increase in the metabolism of DA. These investigators proposed that neuroleptics exerted this effect as a consequence of their ability to block DA at its receptor site. This hypothesis was later substantiated by studies using receptor binding techniques, which further demonstrated that the clinical potency of antipsychotic drugs was highly correlated with their affinity for D_2 DA receptors.[71,272] The significance of DA in the etiology of schizophrenia gained further support from studies showing that administration of amphetamine to humans induces a psychological state that are clinically indistinguishable from paranoid-type schizophrenia.[26,66,131] Although amphetamine is known to affect both DA and noradrenergic systems, reports that this psychosis is more readily elicited by D-amphetamine,[11,12] which has comparatively stronger actions in the DA system than has L-amphetamine,[67,68] provided further support for the DA hypothesis of schizophrenia.

In its original and simplest form, the DA hypothesis of schizophrenia posits that this disorder arises from an excess of DA in the brains of schizophrenics.[279a,307] However, investigators have repeatedly failed to find evidence of increased brain levels of DA or DA metabolites in schizophrenics.[27,32,240,306] Indeed, recent data showing increases in the number of D_2 DA receptors in subcortical regions of schizophrenics that are independent of prior medication[74,164,197,217,244,270,323] and evidence suggesting that DA turnover may actually be depressed in schizophrenics[167,209] has led some investigators to the opposite conclusion: i.e. that schizophrenia may be a DA deficiency disorder.[106,167,209,326,329] The observation that neuroleptics block DA receptors soon after they are administered,[106,259,269] whereas weeks of neuroleptic treatment typically are required before therapeutic effects are obtained,[25,69,70,78,162,286] adds further doubt to the view that schizophrenia is caused by a simple hyper-dopaminergic state. Furthermore, and possibly more significantly, studies in animals and humans have revealed that the DA system is controlled by powerful homeostatic influences that are capable of compensating for rather large imbalances in DA levels.[294,335] Thus, a simple excess of DA should have little effect on brain function due to the tight homeostatic regulation of this system, wherein excess DA would be expected to cause a compensatory decrease in DA synthesis and release, feedback inhibition of DA cell firing, and desensitization of DA receptors, all of which would cause the system to return to a normal level of functioning.[105,215,263,265]

1.2. *Emerging role of the prefrontal cortext in schizophrenia*

The significance of the prefrontal cortex in schizophrenia has recently become the focus of numerous research efforts into the etiology of this disorder. Early evidence implicating frontal lobe dysfunction in schizophrenics led to the use of prefrontal leukotomy to control the more florid schizophrenic symptoms,[102,129,130,213,219] although in some cases prefrontal injury has been reported to induce a psychosis-like state in humans.[85,140,192,225,276] Moreover, despite initial evidence to the contrary, recent investigations using positron emission tomography (PET) scans and regional cerebral blood flow measures have provided evidence for decreased activity levels within the frontal lobes of schizophrenics.[51,94,152,314] In addition, data obtained from studies of phosphocreatine utilization using NMR spectroscopy support the presence of a prolonged hypo-frontal condition in schizophrenic patients.[235] The prefrontal cortex receives a distinct DA projection with unique physiological and pharmacological properties.[23,301] These DA afferents exhibit the largest degree of activation in response to stress among the DA projection systems studied,[93,140,301,302] and stress is known to play a role in the onset or exacerbation of schizophrenia.[40,208,315] Nonetheless, the majority of evidence supports an involvement of the subcortical DA projection sites in the schizophrenic psychosis: (1) therapeutically

effective antipsychotic drug treatments do not reverse the deficits in prefrontal cortical activity found in schizophrenics;[42,235] (2) neuroleptics must be administered repeatedly over weeks before alterations leading to a therapeutic response can be induced,[25,69,70,78,162,286] whereas the prefrontal cortical DA system is unique in not exhibiting time-dependent changes in DA turnover during the course of neuroleptic treatment;[23,184,264] (3) the therapeutic efficacy of neuroleptics is correlated with their ability to induce depolarization block in mesolimbic DA neurons;[57,319] and (4) an increase in the number of D_2 DA receptors has been observed in the striatum but not in the cortex in schizophrenics.[164,217,323]

Recently, several models of brain function have been advanced that focus on the interaction between the prefrontal cortex and subcortical DA systems, and its possible relevance to the etiology of schizophrenia. The interdependence of the prefrontal cortex and subcortical DA systems was first observed in studies of animal behavior. Thus, damage to the prefrontal cortex in rats was found to potentiate the effects of amphetamine on locomotor behavior[4,154,195] and the production of stereotypy by apomorphine.[265a] Furthermore, experiments by Pycock and coworkers suggested that this suppressant action of the prefrontal cortex on subcortical DA systems is dependent on the mesocortical DA afferents projecting to this site.[49,242,243] In their studies, 6-hydroxydopamine (6-OHDA) administered into the medial prefrontal cortex of rats was reported to cause a 40–50% increase in the number of high-affinity DA uptake sites, a 15–50% increase in DA turnover, and a 15–35% increase in DA binding sites in the striatum and nucleus accumbens. This resultant hyperdopaminergic state could be accounted for if one assumes that lesioning the DA input to the frontal cortex releases the corticostriatal neurons from dopaminergic inhibition, resulting in increased subcortical glutamate release.[23,314] The glutamate, in turn, would cause increased release of DA in these subcortical sites.[116]

Despite the attractive nature of this "supervisory" role of cortical DA afferents over subcortical DA systems, data gathered in recent studies have refuted several key components of Pycock's original observations.[63,137,186,187,255] Moreover, although this model suggests that schizophrenia is due to higher than normal levels of subcortical DA release, studies of schizophrenics have failed to find evidence for an increase in DA turnover.[27,32,240,306] An increase in subcortical DA release would also be inconsistent with the reported increased number of D_2 DA receptors in subcortical sites in schizophrenics.[74,164,197,217,244,270,323] Finally, although the subcortical hyper-dopaminergic condition is hypothesized to arise from abnormally increased levels of cortically induced DA release, one of the more consistent findings in schizophrenics is the presence of a hypometabolic state in the frontal cortex[41,94,235] and attenuated activation of the prefrontal cortex during specific tasks.[51,94,152,314] Thus, the hypofrontality observed in schizophrenics would be expected to decrease glutamate-mediated DA release in subcortical nuclei instead of producing the predicted abnormally high levels of DA activity in these sites.

In these and many other models of mental illness that are based on abnormal neurotransmitter levels, a fundamental characteristic of the nervous system (and of the DA system in particular) is often overlooked: i.e. the capacity of these systems to homeostatically compensate for long-term aberrations in neurotransmitter levels. Thus, alterations in the steady-state level of a neurotransmitter may induce compensatory changes in neurotransmitter synthesis, release, receptor sensitivity, and neuronal firing in order to restore the system to its original state. The subcortical DA system in particular is known to be governed by powerful homeostatic influences, as reflected in its ability to compensate for depletions of 90% or more of striatal tissue DA content.[169,294,335] Conversely, this system also can down-regulate its activity to counteract an overstimulation of DA receptors, as occurs in response to repeated administration of DA agonists.[105,215,263,265] Thus, models of mental disorders should be capable of accounting for both the initial neurotransmitter imbalance underlying the disorder and for maintenance of the imbalance in the presence of powerful counteracting homeostatic influences. This hypothesis has been presented previously in abstract form.[122]

2. HYPOTHESIS: TONIC MODULATION OF THE PHASIC DOPAMINE RESPONSE AND THEIR PROPOSED IMBALANCE IN SCHIZOPHRENIA

The hypothesis of schizophrenia presented here takes into account the pharmacological evidence of hyper-dopaminergic states of schizophrenia in the presence of hypo-frontality, and provides an explanation for how this imbalance is maintained despite the presence of homeostatic compensatory processes. This model is based on the interaction between two independently regulated DA releasing processes in the striatum. (1) Phasic DA release—a transient DA release produced by the activation of DA neuron firing in response to behaviorally relevant stimuli. This large amplitude but brief pulse of DA is proposed to activate postsynaptic DA receptors but is rapidly removed from the synaptic space by fast, low-affinity/high-capacity re-uptake systems[142a,155,298] before it can trigger homeostatic responses. (2) Tonic DA release—the release of DA from DA terminals activated presynaptically in a spike-independent manner by glutamate released from prefrontal cortical afferents. DA released in this manner is proposed to underlie the background, steady-state level of extracellular DA in subcortical structures. Since DA levels in the extracellular fluid would determine the baseline level of DA receptor stimulation, changes

in tonic DA release should elicit homeostatic compensations that act to restore background DA receptor stimulation to its original level. By modulating tonic levels of DA receptor stimulation to induce homeostatic changes in the responsivity of the DA system, corticostriatal afferents could dynamically modulate the amplitude of the phasic DA response within subcortical regions. In this manner, increases in tonic DA levels would trigger processes that functionally oppose the phasic DA response.

In the schizophrenic, a pathological decrease in prefrontal cortical activity is proposed to cause a prolonged decrease in tonic extracellular DA levels within the ventral regions of the striatum and nucleus accumbens (hereafter referred to as the ventral striatum). The resultant decrease in baseline DA receptor stimulation would then activate homeostatic processes to up-regulate DA system responsivity. The compensatory processes activated in response to decreased tonic DA levels should be analogous to those produced by lesion-induced decreases in DA levels (i.e. decreased autoreceptor-mediated inhibition of DA synthesis and release,[7,95,96,136,185,281,287,288] increased tyrosine hydroxylase activity,[334,335] increased numbers of postsynaptic DA receptors,[72,73,198–200] etc.). Thus, in the schizophrenic, behaviorally relevant stimuli that activate DA neuron firing would produce abnormally large phasic DA responses in the compensated ventral striatum. On this basis, the induction of DA system up-regulation leading to the increased phasic DA response in the schizophrenic could account for what would otherwise be a paradoxical finding: i.e. the increased levels of D_2 DA receptors in the ventral striatum of schizophrenics (which should occur with decreases in DA levels) despite pharmacological evidence for a hyper-dopaminergic state in this disorder. Another attractive feature of this model is that the proposed DA imbalance would not be counteracted by the powerful homeostatic mechanisms that restore function in severely altered DA systems; in fact, in this model the homeostatic processes as they relate to maintaining extracellular DA levels are responsible for the induction of this hyper-responsive state.

3. EVIDENCE FOR TWO FUNCTIONALLY RELATED BUT INDEPENDENT COMPONENTS OF DOPAMINE RELEASE

Although a number of studies have been conducted that supported the correspondence between DA cell activity and DA turnover,[9,227,257,312] several studies revealed discrepancies between changes in extracellular DA levels measured *in vivo* (e.g. using push–pull cannulae, *in vivo* dialysis, voltammetry) and DA cell firing.[2,53,56,183,252,253] Indeed, based on extensive studies of DA release using push–pull cannulae, it has been hypothesized that release of DA from terminals is determined primarily by local factors, with impulse flow relegated to a minor role.[52,115,253] These data could be brought into perspective, however, if one assumes that DA release is mediated by multiple processes. Indeed, studies of the modulation of DA release *in vitro* have provided evidence for two physiologically relevant modes of DA release: (1) DA release that is dependent on depolarization and spike activity, and (2) DA release that is dependent on *N*-methyl-D-aspartate (NMDA) receptor stimulation and does not require DA neuron spike activity.

3.1. *Dopamine neuron discharge underlies the phasic dopamine response*

The classic model of neurotransmitter release centers around the invasion of terminals by action potentials, causing the opening of voltage-dependent calcium channels and the triggering of neurotransmitter efflux (cf. Ref. 168). The spike-dependent component of DA release occurs in response to DA cell discharge and is proposed to underlie phasic DA release. Electrically stimulating the DA axons within the medial forebrain bundle would be expected to release DA through the same process, since in both cases DA release is produced by spike invasion of the axon terminals. This impulse-dependent component has been defined in *in vitro* studies as being: (1) calcium-dependent, (2) depolarization-mediated, (3) sensitive to tetrodotoxin and procaine, which are blockers of sodium and calcium spikes, respectively, and (4) insensitive to antagonists of glutamate or NMDA receptors.[55,221,317]

3.1.1. *Amplitude and duration of dopamine released by dopamine cell firing.* The phasic DA response is proposed to consist of a large amplitude, transient increase in DA release that stimulates postsynaptic DA receptors (Fig. 1). However, because of its rapid removal from the synaptic cleft by re-uptake, phasic DA release should not contribute to extracellular DA levels, and thus would not be expected to elicit homeostatic changes in the responsivity of this system. Anatomical and physiological studies of DA neurons provide supporting evidence that DA cell firing can elicit massive DA release over a brief time period, as a consequence of: (1) the high degree of axon collateralization of single DA neurons, (2) the ability of DA neurons projecting to topographically overlapping sites to fire synchronously, (3) the recruitment of nonfiring DA neurons during activation, (4) the potentiation of DA release by the induction of DA cell burst firing, and (5) the increase in DA cell firing rate produced by external stimuli. Thus, DA neuron axons are known to be highly collateralized, with single DA neurons estimated to produce 500,000–1,000,000 synaptic contacts in the striatum.[8,84] These synapses probably occur within spatially restricted target sites, due to the topographic organization of these projections.[45,133] Recordings have shown that neighboring DA neurons, which would be expected to innervate overlapping regions within the striatum as a consequence of their topography, are capable of exhibiting simultaneous spike discharge.[101,123,321] This synchronization of activity

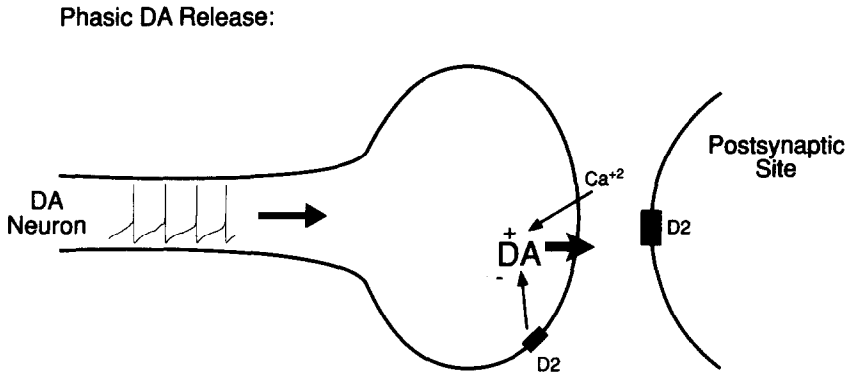

Fig. 1. In this model, DA is proposed to be released in two components: a phasic component and a tonic component. The phasic or transient component is the DA release produced by spike activity in DA neurons and occurs in response to behaviorally relevant stimuli, and is rapidly terminated by re-uptake into the DA terminals. This release is illustrated here as a spike-dependent depolarization, which releases DA by opening voltage-dependent calcium channels in a manner analogous to that underlying classical neurotransmitter release mechanisms.

between adjacent DA neurons is consistent with reports of gap junctions between cells in this brain region.[24,123,222,246] Finally, despite the low maximal firing frequency of DA neurons, the DA release occurring during their activation can be amplified by: (1) eliciting activity from the pool of normally inactive, "reserve" DA neurons,[43,126] and (2) switching to a burst firing pattern,[44,124,125] which itself is reported to enhance spike-dependent DA release by two- to three-fold.[120,121] Thus, short-term activation of DA neurons should be capable of producing substantial responses by inducing a brief burst of spikes in a group of electrically coupled DA neurons, leading to a massive DA release from highly collateralized axon terminals synapsing within circumscribed regions of the striatum.[127] Indeed, recordings of DA cells in freely moving rats have shown that DA cells exhibiting slow, irregular patterns of spike discharge can switch rapidly into a vigorous burst firing mode.[101] The massive but localized release of DA thus produced would also be brief in duration, due to: (1) the long inhibition of DA cell firing that occurs following a burst of spikes,[125] and (2) the rapid re-uptake of DA.[39,90,142a,320] Thus, a fast transition of a DA neuron into a high-release state also activates processes that should in turn rapidly terminate the phasic release of DA.

3.1.2. *Correlation between dopamine cell firing-induced dopamine release and extracellular dopamine levels.* The effects of impulse flow on DA release has been examined in experiments where the DA cell axons are activated directly. This has been done experimentally by stimulating the DA-rich mesencephalic regions or the mesostriatal axon bundle, and has been shown to cause release of DA in the striatum in a frequency-dependent manner.[90,151,183,311] However, in order to produce measureable changes in extracellular DA levels, the DA axons must be stimulated at frequencies of 10–20 Hz or greater.[120,128,182,183,186,205] In contrast, electrophysiological recordings from identified DA neurons show that these cells typically fire at frequencies averaging 3–4 Hz,[124] and can rarely be driven to frequencies above 8–10 Hz.[126] Nonetheless, stimulation of this pathway at frequencies consistent with those observed in spontaneously firing DA neurons (i.e. 4–5 Hz) can support self-stimulation behavior (which evidence suggests is a DA-dependent process[66a,89,99,220,322] without producing measurable changes in DA overflow.[98,128,223,224] Investigators have accounted for this finding by hypothesizing that behaviorally active levels of DA are released at the slower, physiologically relevant stimulation frequencies; however, this DA is taken up by DA terminals so rapidly that it does not escape the synaptic cleft[91,205] and therefore cannot be detected by sampling the extracellular fluid using dialysis, voltammetry, or push–pull cannulae. In fact, the kinetics of this low-affinity, high-capacity uptake system[142a] should cause it to be maximally activated by such rapid, high-amplitude increases in synaptic DA concentration. In contrast, very fast, non-physiological stimulation rates will induce DA overflow from the synaptic cleft, but probably does so by overwhelming the DA uptake process.[91,183,205] Even so, the increase in extracellular DA levels produced by these non-physiological rates of stimulation is very brief, reverting to baseline levels or below within seconds after terminating the stimulation.[91,128,164a,170,297] Thus, impulse-dependent DA release appears to produce functionally significant levels of DA release at frequencies of stimulation that do not elicit measurable changes in extracellular DA levels in the striatum. It is important to note that this component of DA release is not sampled by dialysis or push–pull perfusion methods, but nonetheless may be of primary importance for the postsynaptic effects of DA.

3.1.3. *Behavioral relevance of dopamine cell firing.* It is proposed that this phasic DA release may be triggered in response to behaviorally relevant stimuli. Several attempts to correlate DA neuronal firing with behavior have been made by performing extracellular

recordings from identified neurons in freely moving animals under various behavioral paradigms. With the exception of a few reports showing increased DA cell activity when the animals orient to a stimulus, many investigators have been unable to find changes in DA neuron activity that correlate with behavior.[80,156,289] However, almost all of these negative findings involved recordings from DA neurons located in the substantia nigra.[156] In contrast, recordings from the limbic-related DA neurons in the ventral tegmental area have consistently shown that this group of DA neurons exhibits activation of firing in response to stimuli that have behavioral relevance, or that had been conditioned to elicit a response.[92,172,214,266a,268] It should be noted that recording the responses of single DA neurons may significantly underestimate the magnitude of the overall response, given that recruitment of previously inactive DA neurons into synchronous firing would not be observed. Thus, both self-stimulation studies and recordings from DA neurons in freely moving animals support the hypothesized activation of DA cell firing by behaviorally relevant stimuli.

3.2. *Prefrontal glutamatergic projections to striatum and accumbens regulate the tonic dopamine response*

The second component of DA release is not dependent on impulse flow in DA neurons, but instead is mediated by a presynaptic action of glutamate on DA terminals. Experiments have shown that administration of glutamate agonists into the striatum or nucleus accumbens elicits DA release.[49,64,113,114,163,203,248,249] Unlike spike-mediated DA release, glutamate-induced DA efflux occurs in the absence of additional depolarization and is not affected by the blockade of sodium or calcium spikes by tetrodotoxin and procaine, respectively.[50,54,65,113,159,203,221,249,279] Thus, glutamate is capable of eliciting DA release in subcortical structures through a mechanism that is not dependent on DA neuron firing.

3.2.1. *Prefrontal cortical modulation of subcortical dopamine release—anatomy and pharmacology.* Tonic DA release (Fig. 2) is proposed to be mediated by the corticostriatal glutamate-containing projection from the prefrontal cortex[81,118,173,206,207,245,267,285] and possibly other cortical afferent sites (e.g. hippocampus, amygdala[207,304]) that project to the ventral striatum. Thus, stimulation of frontal cortex can increase DA release *in vivo* in the striatum,[226] possibly via an NMDA-mediated increase in membrane calcium conductance,[196] although other glutamate receptor subtypes also may play a role.[23a,221a] Corticostriatal afferents have been shown to synapse primarily on dendritic spines of the medium spiny class of striatal neurons,[31,135,171,283] often in close apposition to the DA terminals.[31,104,238,275,304] Indeed, each medium spiny neuron has been calculated to receive 4500–8000 DA terminals, with half of these DA terminals located in close register with corticostriatal afferents onto the same dendritic spine.[84]

Although the mechanism for the interaction between glutamate and DA afferents in the absence of identified axo-axonic synapses[31,104,238] is not clear, the close apposition of these synapses suggests that the cortex may still be capable of influencing DA release by modulating the extracellular concentration of glutamate in the vicinity of the DA terminals. In fact, evidence indicates that basal extracellular glutamate concentrations in vertebrate brain regions are likely to range between 2 and 8 μM.[1,37,38,157,160,177,190] This level of glutamate is already within the range

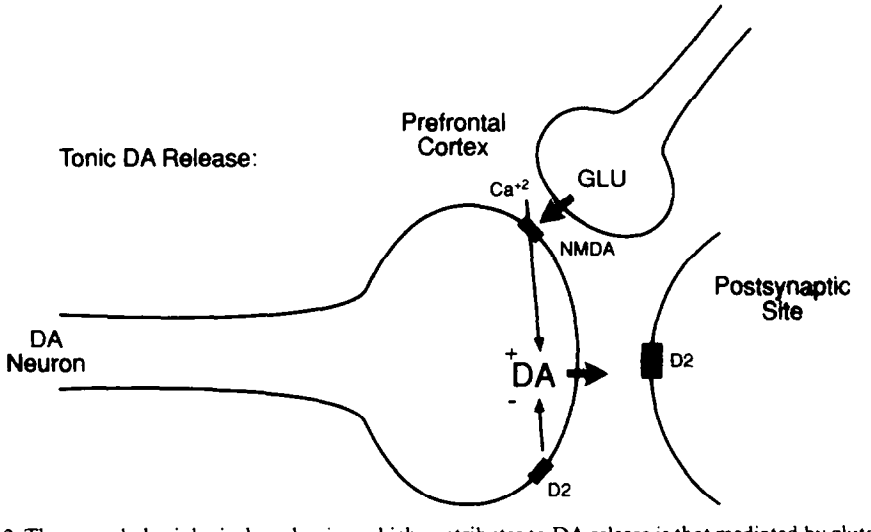

Fig. 2. The second physiological mechanism which contributes to DA release is that mediated by glutamate stimulation of NMDA receptors located on DA neuron terminals, causing an influx of calcium and DA release. This tonic component of DA release is proposed to exhibit a prolonged time-course and thus underlies the "background" steady-state level of DA in the extracellular fluid of postsynaptic sites. In this manner, the tonic component of DA release would serve to regulate the intensity of the response to phasic DA release by setting the background level of DA receptor stimulation.

required for NMDA receptor activation (i.e. ED_{50} of approximately 5 μM[260,261] and threshold of approximately 2 μM[161]). Tonic levels of extracellular glutamate may therefore be releasing DA presynaptically by stimulating the NMDA receptors located on DA terminals. Furthermore, the pulsatile glutamate release occurring at the glutamatergic synapse would be expected to cause lower amplitude but longer duration changes in extracellular glutamate concentration at extrasynaptic sites as the distance from the glutamate terminal increases. Thus, synaptic glutamate release would cause fast, transient activation of the less sensitive (i.e. $ED_{50} = 28\ \mu$M[261]) kainate and/or quisqualate receptors in the synaptic cleft, whereas at the more remote DA terminal the glutamate release would appear as a much slower change in background glutamate concentration, and thus increase the tonic level of stimulation of the more sensitive NMDA receptors[260,261] that regulate DA release.

3.2.2. *Time-course of tonic dopamine release.* As reviewed above, stimulation of the prefrontal cortex or administration of glutamate to striatal slices induces an NMDA-dependent release of DA. Furthermore, this DA release occurs slowly, with a prolonged onset, delayed peak, and extended duration; the entire process occurring over periods of tens of minutes to hours, depending on the procedure used (e.g. Refs 3, 226, 274). Unlike the phasic component of DA release, this glutamate-induced DA release can be measured as an increase in extracellular DA levels. Although it is unclear why tonic DA release is not rapidly eliminated by re-uptake, as occurs with impulse-dependent DA release, it is possible that this is a consequence of presynaptic DA release occurring at extrasynaptic sites and/or the low amplitude, slow time-course of change in tonic DA levels produced, since the extracellular concentration of DA (approximately 10^{-8} M) is lower than the K_m of the uptake system (10^{-7} M[142a]). An example of a behavioral state that preferentially alters tonic DA release may be that produced by stress, which is reported to cause a slow, long-term increase in extracellular DA and DA turnover in the striatum[3,169,274] without affecting DA neuron firing.[202,293] Furthermore, this stress-induced increase in DA turnover can be blocked by administering NMDA antagonists.[274] Thus, the characteristics of stress-induced increases in extracellular DA levels are consistent with an activation of tonic DA release via corticostriatal afferents.

3.3. *Changes in tonic dopamine levels and the modulation of the phasic dopamine response*

In this model, the stimulus-dependent, fast phasic DA release is proposed to elicit responses in the postsynaptic dopaminoceptive neurons, but is taken up so rapidly that it does not escape the synaptic cleft. Thus, this rapid time-course would prevent phasically released DA from activating homeostatic compensatory mechanisms. On the other hand, the evidence reviewed above suggests that extracellular DA is derived exclusively from the slower tonic DA component. By nature of its extended time-course, this tonic extracellular DA would be expected to elicit homeostatic responses and thereby set the level of responsivity of the DA system. Indeed, evidence indicates that extracellular DA levels in the striatum recover to baseline levels within weeks after depletions of up to 80% of tissue DA.[30,251,305,332] With larger lesions, additional homeostatic changes, such as an increase in the number of D_2 DA receptors[72,73,198–200,216] or DA axon sprouting,[229] are induced to restore baseline levels of DA receptor stimulation. This supports the proposition that homeostasis serves to primarily regulate the tonic DA response. Thus, the amplitude of the phasic response would depend on the level of responsivity set by tonic DA release. Consequently, in this model, the responsivity of the DA system to stimuli would be dynamically regulated by the influence of corticostriatal activity through the modulation of tonic DA levels.

The homeostatic processes involved in the regulation of DA system responsivity have been investigated in normal, DA agonist-treated, haloperidol-treated, and DA-depleted rats, and appear to consist of several components with different time-courses of activation. These results are incorporated into the following model describing the up-regulation of the phasic DA response produced after decreases in tonic DA levels: in response to the decrease in tonic DA levels, the resultant decreased activation of DA release-modulating autoreceptors would potentiate impulse-dependent phasic DA release.[138,189,291] This is consistent with data suggesting that in many cases autoreceptor stimulation is produced by extracellular neurotransmitter levels in the vicinity of the terminal (i.e. the biophase), rather than depending on neurotransmitter released by a prior action potential from a given terminal.[165,292] When the decrease in tonic DA is maintained for an extended period of time, further compensatory processes are activated, including increased DA synthesis (from decreased activation of synthesis-modulating autoreceptors,[7,95,96,136,185,281,287,288]) increased numbers of DA receptors,[72,73,198–200,216] sprouting of DA axons,[229] as well as changes in receptor sensitivity "downstream" from the DA synapse: i.e. at synapses on neurons located postsynaptically to the DA target cells.[107,147,230,231,313] These homeostatic changes in the DA system thus maintain stable levels of tonic DA stimulation, with the amplitude of the phasic DA response subject to passive up- or down-regulation in a parallel manner.

One may question whether changes in the already very low concentrations of DA in the extracellular space are sufficient to trigger these homeostatic processes. This can be addressed by comparing the concentration of DA measured in the extracellular space to the affinity of the DA receptors thought to be involved in homeostatic responses. The receptor most

likely involved in homeostasis is the D_2 receptor, since this receptor mediates autoreceptor processes on DA terminals (cf. Ref. 62), is located on glutamate[218,250,258] and acetylcholine terminals,[188] and exhibits a greater sensitivity to DA than the D_1 receptors.[48,88,270,292] The dissociation constant (K_D) of DA for the high-affinity state of the D_2 receptor is reported to be 5 nM.[271,273] In comparison, recent estimates of the extracellular concentration of DA in the striatum and accumbens *in vivo* are in the range of 4–20 nM, although concentrations of up to 50 nM have been reported.[3,60,277,330,331] Thus, extracellular DA concentrations at basal, non-stimulated levels are within the range of the K_D of the D_2 receptor: i.e. the concentration at which receptors exhibit their maximum sensitivity to changes in neurotransmitter levels.[119] This comparison implies that D_2 receptors need not be located within the synaptic cleft to respond to DA release, but are sufficiently sensitive to be activated by tonic extracellular DA concentrations even at extrasynaptic sites. Indeed, effects of neurotransmitters at extrasynaptic sites have been proposed to account for a number of phenomena within the vertebrate CNS.[139,261,292,310]

3.4. *Role of the prefrontal cortex in the modulation of tonic and phasic dopamine release in schizophrenia*

With reference to this model, the tonic component of DA release sets the background level of DA receptor stimulation in postsynaptic target regions, which in turn modulates the amplitude of the phasic DA response. Since tonic DA release is proposed to be controlled by prefrontal cortical glutamatergic afferents, the cortex would be capable of dynamically modulating the amplitude of dopaminergic responses within subcortical sites. However, in the schizophrenic, a prolonged pathological decrease in prefrontal cortical activity is proposed to result in large, long-term decreases in background tonic DA levels, leading to abnormal potentiation of the effects of DA released phasically via DA neuron activity (Fig. 3). This model is consistent with the reported decrease in glutamate levels in the cerebrospinal fluid of schizophrenics[174] (but see Refs 179, 109, 233) and with the reported increased binding of glutamate agonists in the striatum of schizophrenics.[178]

4. THE PHARMACOLOGY OF SCHIZOPHRENIA: EFFECTS OF PSYCHOTOMIMETICS AND NEUROLEPTICS

A model of schizophrenia should be capable of accounting for the known pharmacology of this disease. This includes the mode of action of drugs known to mimic or exacerbate this disorder in humans, as well as the mechanism of action of therapeutically effective drugs. A proposed role for tonic and phasic DA release in drug action is advanced in this section.

4.1. *Mechanism of action of psychotomimetic drugs*

The term "psychotomimetic" refers to substances that produce a psychosis-like state in humans. This word generally has been associated with hallucinogenic drugs, such as lysergic acid diethylamide (LSD); however, investigators have challenged the assertion that the hallucinatory state produced resembles the schizophrenic condition.[142] In contrast, two other drugs, amphetamine and phencyclidine (PCP), produce behavioral states in humans that are clinically indistinguishable from some subtypes of schizophrenia.

4.2. *Amphetamine*

Repeated treatment with high doses of amphetamine or related stimulants has been shown to induce a paranoid psychosis in humans.[26,66,131] It is generally assumed that this results from an increase in DA activity because D-amphetamine, which is more potent than L-amphetamine in increasing DA release,[67,68] is also more potent in inducing this psychosis.[11,12] Amphetamine has been shown to potentiate DA release and block its re-uptake.[97,117,134,299,300,312] Since the primary mode of inactivation for DA released into the synaptic cleft is by uptake, one would predict that uptake blockers would selectively potentiate the phasic DA response. The observation that the behavioral effects of amphetamine require impulse activity in DA neurons,[58,284,294a,312] and the finding that amphetamine will potentiate impulse-dependent DA release,[312] are consistent with a preferential action of amphetamine on phasic DA release. Indeed, recent studies suggest that many of the behavioral effects of amphetamine are not correlated with changes in tonic extracellular DA levels.[46a] Based on this model, amphetamine would be expected to mimic schizophrenia because, in each case, there is an abnormal potentiation of the phasic DA response (Fig. 4).

4.3. *Phencyclidine*

Administration of PCP has been reported to induce a behavioral state that most closely mimics schizophrenia.[5,82,83,282] This is based on evidence showing that: (1) PCP induces psychosis-like states in control subjects,[5] (2) PCP exacerbates psychosis in schizophrenics,[153,194] and (3) unlike amphetamine, PCP is reported to produce negative schizophrenic symptoms.[158,234] However, the biological actions of PCP are less well characterized than those of amphetamine. PCP binds to DA terminals in the accumbens[103] and, like amphetamine, increases the release of DA and inhibits its re-uptake,[16,20,108,309] although its potency in releasing DA is only one-tenth that of amphetamine.[17,36,308] Furthermore, PCP is more potent in decreasing DA uptake in limbic regions of the striatum[80a] and will potentiate the actions of DA release on postsynaptic neurons.[160a] Thus, like amphetamine, these presynaptic actions of PCP

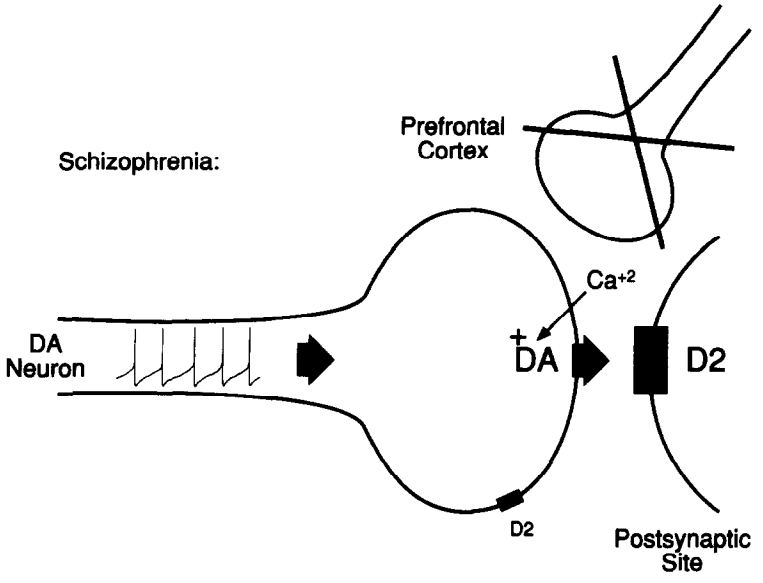

Fig. 3. Schizophrenia is proposed to result from an imbalance between the phasic and tonic components of DA release. Thus, inactivation of the prefrontal cortex, which has been reported to occur in schizophrenics, would cause a profound decrease in the tonic component of DA release. Over time, this would result in homeostatic compensations (e.g. D_2 DA receptor up-regulation, decreased feedback inhibition of DA synthesis and release) that would cause subsequent phasic DA release to elicit abnormally large responses. In this figure and in Fig. 5, the differences in the relative size of the symbols represents the proposed changes in the relative amplitude of the response.

would be predicted to preferentially potentiate the phasic component of DA release. In addition, PCP is known to bind specifically to NMDA receptors, where it acts as a negative allosteric modulator.[325] Thus, the reported decrease in extracellular DA levels produced by PCP is thought to occur via its inhibition of NMDA-mediated DA release.[146,163,278,279] This action of PCP at the NMDA receptor would be expected to elicit effects that are functionally similar to those produced by lesions of the prefrontal cortex: i.e. both would decrease tonic DA levels in subcortical structures. Indeed, this PCP-induced decrease in tonic DA release may be related to the ability of this drug to induce the so-called "negative" symptoms of schizophrenia (see Section 5). Thus, reports that PCP produces behavioral states that most closely mimic schizophrenia are consistent with the model proposed here, since PCP decreases glutamate-stimulated tonic DA release and potentiates impulse-dependent phasic DA release (Fig. 4).

4.4. *Depolarization block and the mechanism of action of antipsychotic drugs*

One common feature of drugs used in the treatment of schizophrenic disorders is their ability to block DA receptors and produce an increase in DA turnover.[47] However, although DA receptor blockade is produced soon after administration of the neuroleptic, the therapeutic effects and many of the motor side-effects of these drugs typically require weeks of treatment to be expressed.[25,69,70,78,162,286] During this time, the gradually developing clinical response to neuroleptics appears to be correlated with a return of DA turnover toward pre-treatment levels.[33,77,236,237,240] Electrophysiological studies show that this decreased turnover occurs in parallel with inactivation of DA neuron firing.[43,57,318] This depolarization-induced inactivation of cell firing is similar in character to the "depolarization block" of spiking, first described in spinal motoneurons,[75,333] and appears to occur in DA neurons as a consequence of a long-term excitation of DA neuron firing.[126]

In addition to this correspondence between neuroleptic-induced depolarization block and the delayed onset of therapeutic actions in schizophrenics, the potential for neuroleptics to elicit extrapyramidal side-effects appears to depend on their effects on the nigrostriatal DA system. That system has been implicated in the control of motor behavior, since degeneration of DA neurons in the substantia nigra is the pathological factor underlying Parkinson's disease.[86,144,145] Although this system is not generally considered to have a direct involvement in schizophrenia, the administration of antipsychotic drugs (which block DA receptors) often precipitate motor imbalances and thus are thought to act on this nigrostriatal extrapyramidal DA system.[21,22,175] A distinct set of DA projections, the mesolimbic–mesocortical DA system originating in the ventral tegmental area, generally is associated with emotional or cognitive components of behavior, and dysfunctions in that system are proposed to play a role in schizophrenia.[204,280,290] Repeated administration of classical antipsychotic drugs, which are known to produce extrapyramidal side-effects, inactivate DA neurons in both the substantia nigra and ventral

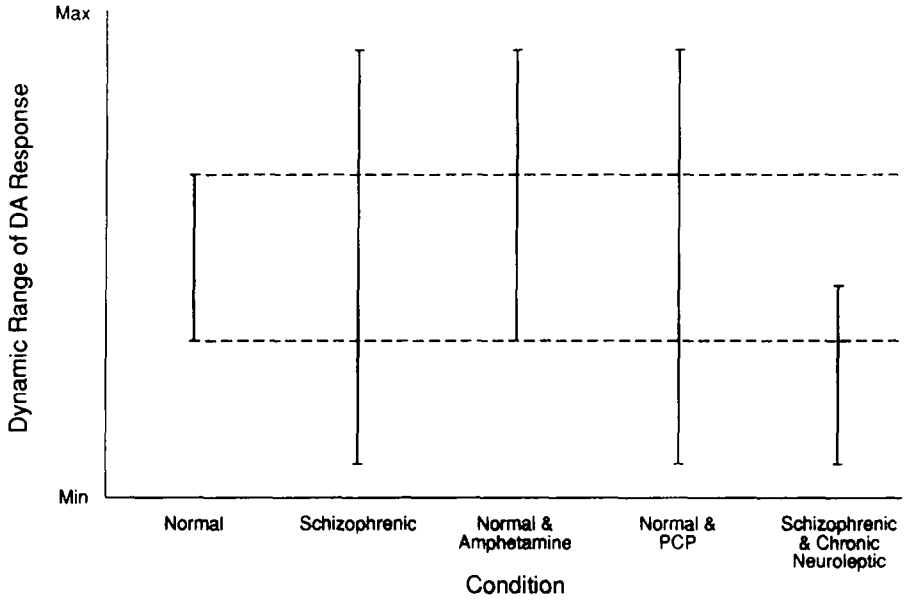

Fig. 4. Graph showing the proposed changes in the dynamic range of the DA response under the specified conditions. The vertical lines represent the dynamic range of the DA response under each condition, with the bar extending from the minimal DA stimulation to the maximal DA stimulation that can occur in each case. The horizontal dashed lines illustrate the range of responses observed in untreated, non-psychotic controls (first column). In schizophrenics, the DA system is proposed to exhibit the widest dynamic range, with the absence of tonic DA release associated with abnormally low baseline levels of DA stimulation and maximal phasic DA release causing abnormally high levels of DA stimulation (due to the hyper-responsivity of the system). The positive schizophrenic symptoms are proposed to be related to the amplitude of the maximal DA response, with the negative symptoms correlating with the level of the minimal DA response. Amphetamine, by preferentially enhancing the phasic DA response, is shown to elicit abnormally high maximal DA responses in normal subjects to cause the positive schizophrenic symptoms, with no change in the minimal DA stimulation and therefore no production of negative symptoms (at least with acute, high doses of the drug). In contrast, the actions of PCP are expected to more precisely mimic the schizophrenic state: the amphetamine-like properties of PCP should increase the maximal phasic response observed, whereas the NMDA antagonistic properties should lower tonic DA stimulation as well. This could account for the ability of PCP to mimic both positive and negative symptoms. Chronic treatment of schizophrenics with classical neuroleptic drugs is proposed to limit the maximal DA responsivity of the system to levels far below those of normals, due to the induction of the aberrant state of depolarization block in the DA neurons. DA receptor blockade by the neuroleptic should be offset by the receptor supersensitivity induced; thus, the minimal activation level may be unchanged with treatment. In this way, classical neuroleptics would have their primary therapeutic effect on the positive symptoms of schizophrenia.

tegmental area.[43,57,318] On the other hand, treatment with atypical antipsychotic drugs, which are associated with a much lower prevalence of extrapyramidal side-effects,[15,87,112,132,166,211] inactivate only ventral tegmental DA neurons.[57,319] Intracellular recordings from DA neurons in rats treated repeatedly with haloperidol have confirmed this excitation-induced depolarization blockade of spike generation.[126] Nonetheless, neuroleptics probably do not exert their therapeutic action by re-establishing the premorbid state of activity in DA neurons, because depolarization block presumably is not the "normal" state of activity of DA neurons in non-psychotic subjects. Furthermore, neuroleptics do not normalize the deficits in frontal cortical activation and metabolism found in schizophrenics.[42,235] Thus, the development of depolarization block in DA neurons, while probably not reversing the etiological defect in the schizophrenic brain, may alleviate schizophrenic symptomatology indirectly by inactivating DA neuron firing. Understanding what effects depolarization block produces on the DA system may shed light onto the defect this process is circumventing.

Surprisingly, although chronic neuroleptic treatment inactivates DA neuron firing, it does not abolish DA release in the striatum or accumbens. Instead, repeated neuroleptic treatment reduces DA turnover toward levels approaching those of control (untreated) animals.[18,19,59,191,256,259,266] Similar results have been observed in neuroleptic-treated schizophrenic patients.[33,77,236,237,240] This maintained release of DA in the presence of DA cell depolarization block appears to reflect a unique regulatory process occurring in these neurons, since in an acute model of this state[141] the onset of depolarization block in DA neurons is not associated with a change in extracellular DA levels in the striatum.[2] This outlines the potential problem associated with predicting DA cell electrophysiological activity from extracellular[148a] or tissue[9a] levels of neurotransmitter. If neuroleptic-induced

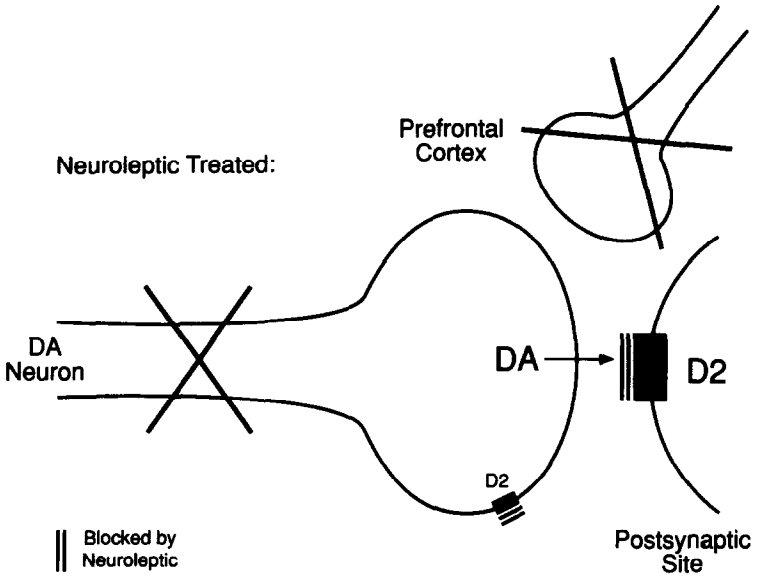

Fig. 5. As illustrated in Fig. 3, a decrease in the tonic, steady-state levels of DA in the schizophrenic would induce homeostatic compensations and thus exacerbate the response to DA release occurring via changes in DA neuron firing (i.e. the phasic component of DA release). Chronic administration of antipsychotic drugs is known to cause depolarization blockade of DA neuron firing with a time-course that parallels the therapeutic benefits of treatment. However, studies have shown that, under these conditions, extracellular DA levels or DA turnover are not dramatically decreased from control levels. The primary function of neuroleptic-induced depolarization block is proposed to be the prevention of the abnormally increased phasic DA response by blocking DA cell firing-mediated DA release. In this way, depolarization block would tend to restore the balance between phasic and tonic DA release processes at a new, lower level. However, since tonic DA release would still be attenuated with respect to controls, the neuroleptic treatment should be less effective at reducing the negative symptoms, and thus would fail to restore the system to normal states.

depolarization block does not alter DA levels in the extracellular fluid, then one may question what therapeutic value could be exerted by inducing depolarization block. In the context of the model reviewed above, depolarization block could nonetheless serve an important function: i.e. eliminating the ability of stimuli to increase DA cell firing rate.[122] In this manner, the antipsychotic medication would circumvent the abnormally large phasic DA response (Fig. 5). This ability of antipsychotic medication to inactivate phasic DA release is consistent with the findings reported by Rompré and Wise,[254] in which pharmacological treatment which induces what is proposed to be DA cell depolarization block prevents self-stimulation behavior; a behavioral task that is known to depend on intact dopaminergic transmission.[89,247,322]

5. A RECONSIDERATION OF SCHIZOPHRENIA IN THE CONTEXT OF PHASIC AND TONIC DOPAMINE RESPONSES

In the model presented here, the emergence of the schizophrenic psychosis is seen as a response to decreased activity in prefrontal cortical projections to the ventral striatum, leading to an enhanced responsivity to DA in these subcortical regions. A unique feature of this model is the concept that the time-course of neurotransmitter release and inactivation can determine its net effect on target neurons: neurotransmitter released in a pulsatile manner triggers the fast postsynaptic response to the stimulus, whereas the continuous presence of a neurotransmitter causes a down-regulation of the response to pulsatile transmitter release. This is functionally equivalent to changing the "signal-to-noise" ratio of the response, somewhat analogous to that proposed for the electrophysiological actions of norepinephrine on central neurons. Norepinephrine was reported to act on neurons to enhance the "signal-to-noise" ratio of information transfer: i.e. the norepinephrine "sharpened" the response of the neuronal population to a given stimulus by decreasing the background "noise" of neuronal firing while enhancing the response of cells to excitatory inputs (the "signal"[100,324]). In the phasic–tonic model of DA release an analogous set of conditions is proposed to lead to a functionally similar result, with the tonic DA release corresponding to the background level of DA receptor stimulation and the phasic DA release being the "signal" that is enhanced by suppressing the background tonic DA activity. Furthermore, this adjustment of subcortical dopaminergic responsiveness by the prefrontal cortex is not opposed by homeostatic processes, but instead utilizes homeostasis to redefine the responsiveness of neurons to phasic DA release.

This model can also account for a number of phenomena observed experimentally in this system.

For example, the potentiation of the behavioral effects of amphetamine administration by prefrontal cortical lesions[4,154,195] could occur via a decrease in tonic DA release and the resultant up-regulation of the amphetamine-sensitive phasic DA response. Furthermore, it provides an explanation for the increased number of D_2 DA receptors in the striatum of schizophrenics[164,217,270,323] while remaining consistent with the data regarding the exacerbation of schizophrenia by dopaminergic agonists and its alleviation by DA blockers. This model could also account for the general action of neuroleptics on psychoses of different origin. Thus, regardless of the pathological origin of the psychosis, neuroleptics are effective therapeutic agents in their treatment.[76,106,241,328,329] This supports the view that a diverse range of psychoses arising from multiple pathological origins involve the same final common mechanism: a decrease in tonic DA release within the limbic striatum. With respect to schizophrenia, the actual dysfunction in the psychotic state could arise either within the prefrontal cortex, in a system that controls prefrontal cortical activity, or in a system that also can produce glutamate-stimulated DA release within the ventral striatum. Thus, several limbic and temporal lobe structures that project to the prefrontal cortex and the ventral striatum[207] have been reported to exhibit structural abnormalities in schizophrenics.[247a] Indeed, one possibility is that the site of the lesion may relate to the subtype of schizophrenia produced.

Either functional or anatomically based alterations that decrease prefrontal cortical activity would be expected to initiate a gradual enhancement of DA responsivity, eventually causing the emergence of the positive schizophrenic symptoms. Positive symptoms, consisting of hallucinations, delusions, and thought disorders, are most likely a result of a hyper-dopaminergic state: (1) only the positive symptoms are potentiated by amphetamine,[13,14,280] (2) they respond to neuroleptics,[236,237,240] (3) their alleviation during neuroleptic treatment is correlated with changes in levels of the DA metabolite homovanillic acid (HVA)[33,77,236,237,240,306] and (4) the severity of positive symptoms may be proportional to the magnitude of increase in the number of D_2 receptors in schizophrenics.[74] This model is consistent with the initial hypotheses of schizophrenia advanced by Hulings-Jackson:[148] that the primary defect in schizophrenia is cortically mediated and results in the negative signs, with the positive symptoms reflecting a "release" phenomenon in subcortical nuclei. This could also account for the observed high incidence of negative signs, characterized by a flattened affect, poverty of speech, loss of drive, and apathy, among schizophrenics exhibiting significant levels of cortical atrophy.[10,162,232,296]

Of course, not all schizophrenic patients exhibit prominent negative signs. In contrast to the positive signs, evidence suggests that the negative schizophrenic signs are derived from DA insufficiency: (1) they are correlated with low cerebrospinal fluid HVA in schizophrenics[193,329] or blunted HVA increases in response to acute neuroleptic administration,[33,34,35,76,306] (2) they are associated with structural damage, typically within the frontal cortex, hippocampus,[29] or amygdala,[28] each of which, if undamaged, could potentially contribute to glutamate-induced DA release in the ventral striatum,[207] (3) they are less responsive to treatment with classic neuroleptics,[14,162,180,212,316] (4) investigators have reported improvement in negative symptoms with the administration of DA agonists,[6,14,79,111,149,150,228] and (5) PCP differs from amphetamine by its ability to induce negative symptoms in control subjects, which may correspond to its unique ability to block NMDA-mediated DA release[278,279] and thereby decrease tonic extracellular DA levels.[146] When considered in the light of this model, it appears that the negative symptoms are best correlated with tonic DA levels, with severely depressed tonic DA leading to the emergence of the negative symptoms. Thus, the degree to which negative symptoms are expressed by schizophrenics may be dependent on the levels of tonic DA release, with prominent negative signs emerging as the tonic DA level decreases beyond a critical point (in a manner analogous to that suggested by Pogue-Geile and Harrow[239]) and thus could occur after the development of positive symptoms.

6. THERAPEUTIC IMPLICATIONS

The mode of action of antipsychotic drugs proposed above is based on their ability to decrease phasic DA release, thus re-establishing the balance, to some degree, between phasic and tonic DA responses. However, the use of DA blocking agents, while highly effective in treating at least a portion of the symptoms of schizophrenics, may not be the most effective therapeutic approach. DA blockers apparently exert their therapeutic effects by presenting an overwhelming "blunt force" to the system: i.e. shutting down phasic DA release by blocking DA receptors and inactivating DA cell firing. By forcing the DA system into such an extreme state of imbalance, neuroleptics would be expected to trigger a number of homeostatic responses to restore DA responsivity. This would serve to maintain or even potentiate the underlying DA imbalance caused by the decreased tonic DA release initially present in the schizophrenic. Such a condition would thus require continued DA antagonist treatment to maintain this delicate depolarization blocked state, resulting in the blunting of "normal" levels of DA responsiveness as may be required for normal behavioral functioning. This highly unbalanced state could also be responsible for the reported lesser efficacy of the classic neuroleptics in reducing negative symptoms,[212] or may contribute to the triggering of neuroleptic-induced side

effects[21,22] as the system attempts to homeostatically compensate for this extreme condition. Indeed, it is likely that current therapeutic drugs are not the most effective agents that can be developed to treat schizophrenia, since these drugs typically are screened according to their acute effects in animal behavioral models, whereas repeated treatment with neuroleptics is required to achieve therapeutic efficacy in humans.[106]

Perhaps a more effective therapeutic approach would be to increase tonic DA receptor stimulation, thus returning the system to conditions more closely approximating those present in non-afflicted individuals. However, administration of DA agonists to restore such a state would be expected initially to cause massive DA receptor stimulation, thus exacerbating the schizophrenic symptomatology. One possible way to circumvent this effect would be to somehow limit the maximal DA responsivity while at the same time providing basal levels of DA receptor stimulation. Partial DA agonists are one class of drugs that might produce these actions. Thus, instead of effecting changes in this system through extensive receptor blockade, partial DA agonists should instead constrain the abnormal DA response within normal ranges. This would be done by providing a basal level of D_2 DA receptor stimulation directly (thereby restoring the tonic DA response) while preventing the hyper-responsivity to phasic DA release by decreasing the maximum amplitude of DA receptor stimulation that can be produced. This pharmacological enhancement of basal DA stimulation combined with inhibition of maximal DA responsiveness could thus limit the dynamic range of the DA system to one that more closely approximates the normal condition. Indeed, evidence suggests that the highly effective[61,110,143,166,210] atypical neuroleptic clozapine may attenuate negative symptoms via a similar mechanism: i.e. decreasing the abnormal phasic DA release by causing depolarization block of mesolimbic DA neurons,[57,319] while producing an increase in tonic extracellular DA levels.[46,148b,201,210]

7. SUMMARY

Although research into the neurobiology of schizophrenia has provided evidence implicating a number of different brain regions or neurotransmitter systems in its etiology, two systems in particular have been linked consistently with this disorder: (1) the DA system and (2) the prefrontal cortex. Thus, pharmacological evidence gathered from studies of amphetamine psychosis and neuroleptic action supports the hypothesis that schizophrenia is due to an excessive activation of the DA system. More recently, metabolic mapping studies have uncovered evidence suggesting that the activity level of the prefrontal cortex, which participates in regulating subcortical DA systems, is abnormal in schizophrenics. Nonetheless, no evidence has been advanced that supports an increased turnover of DA in the brains of schizophrenics. Furthermore, since the DA system is known to have a high capacity for homeostasis at the synaptic level, it would appear that a simple hyper-functioning of the DA system could be effectively counteracted through a homeostatic down-regulation of DA synthesis, release, and receptor sensitivity.

The model of schizophrenia proposed here is derived from studies of homeostasis within the DA system and can provide a logical explanation for the apparent contradictory data reported to date. This model is based on evidence suggesting that DA release in the striatum and nucleus accumbens may occur via two independent processes: (1) a transient or phasic DA release that is dependent on the firing of DA neurons, and (2) a steady-state tonic release of DA that is induced presynaptically by glutamate released from prefrontal cortical afferents. The response of the DA system to external stimuli is proposed to occur via changes in DA cell firing (i.e. the phasic component of release) and would be sufficiently transient in nature to avoid activation of compensatory responses to the released DA. The tonic component of DA release, on the other hand, is proposed to underlie the steady-state background levels of extracellular DA in target structures. Changes in tonic baseline levels of DA, by nature of their long time-course, would be expected to activate compensatory processes within the DA system. Thus, increases in tonic DA release would cause an increase in the background level of DA receptor stimulation, thereby triggering a down-regulation of DA system responsivity. In this manner, the level of tonic DA would serve to modulate the responsivity of this system to stimuli that activate phasic DA release.

A number of studies have substantiated the reported decreased level of activity within the prefrontal cortex of schizophrenics. With respect to this model, decreases in the activity of corticostriatal afferents would cause an attenuation of tonic DA release. This decrease in DA levels would activate homeostatic responses to restore tonic DA receptor stimulation to baseline levels (e.g. decreased autoreceptor-mediated inhibition of DA synthesis and release, DA receptor up-regulation, etc.). However, restoring tonic DA receptor stimulation by increasing the responsiveness of the DA system also would cause this system to exhibit abnormally large phasic DA responses to stimuli. It is this abnormally intensified DA response that is proposed to underlie the positive symptoms of schizophrenia.

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