

An introduction to the substantia nigra in schizophrenia

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The substantia nigra (SN) is a paired midbrain structure that lies immediately ventral to the cerebral peduncles at the level of the superior colliculus and has a critical regulatory role in the CNS. The dysfunction of this structure is implicated in the pathology of several serious illnesses.

Substantia nigra translates from Latin as “black substance,” as it is recognized by its characteristic black-/brown-stained appearance, a result of the neuromelanin granules contained within the dopaminergic (DA) neurons as a by-product of DA metabolism. This is well known by the changes in Parkinson’s disease, where decreased DA metabolism causes a loss of neuromelanin in these neurons, and thus the loss of the dark coloration normal to the SN.

The SN forms an integral structure of the basal ganglia, a collection of subcortical nuclei with complex, reciprocal connections also comprising the striatum, globus pallidus, nucleus accumbens, and the subthalamic nucleus. The SN is the predominant DA-producing structure of the brain, along with smaller DA-producing cell populations in the ventral tegmentum area, hypothalamus, and zona incerta.

Structurally, the SN is often split into two distinct regions: the SN pars compacta (SNpc) and the SN pars reticulata (SNpr). The SNpc, the inner layer of the SN closest to the cerebral aqueduct, is a densely packed structure containing the large DA-producing neurons, modulated by accompanying interneurons, and is the source of the DA projections to the striatum, globus pallidus, and the SNpr. Input into the SNpc occurs via GABAergic and glutamatergic feedback mechanisms from striatal and globus pallidus centers [1,2], with the SNpc receiving almost all its regulatory input from the globus pallidus, but with a small input from the frontal lobe. By contrast, the SNpr is larger but far more diffuse and comprising much smaller, GABA-neurons than the SNpc, and occupies the outer layer of the SN. These neurons receive the SNpc DA projections and send GABAergic projections to the ventral anterior and ventrolateral thalamus, the superior colliculus, and the pedunculopontine complex, a brainstem nucleus caudal to the SN. These subdivisions have a reciprocal set of internal connections making a functional loop from the SNpc to the striatum, back to the SNpr to regulate the SNpc. The causes of excess SNpc DA in psychosis or decreased SNpc DA in Parkinson’s disease are not well understood, but a key focus of interest is the SN-striatal loop. Internal connectivity also occurs

via glutamatergic and GABA-modulated interneuron-dendritic interactions, modulating DA activity of the SN both within and between the SNpc and SNpr [2,3,4].

In schizophrenia the primary interest in the SN is due to it being the origin of the nigrostriatal pathway, the most prominent SN DA projection, with axons from the SNpc DA neurons ascending into the striatum in a topographic manner, although with a distinct cluster that terminates in the dorsal putamen, one of the sub-nuclei of the stratum. This pathway is part of the basal ganglia loop, a functional system thought to have an important regulatory role in cognition.

DA influence on striatal medium spiny neurons is receptor specific, with D_1 (excitatory) and D_2 (inhibitory) receptors leading to excitatory and inhibitory striatal responses, which permit discrimination of motor programs to suit the required task, the dominant function of the nigrostriatal pathway. Historically, psychosis has been treated using first-generation antipsychotics, which primarily bind to the D_2 receptors and have slow dissociation rates [5]. D_2 receptors are found in the striatum where they modulate SN DA signal from the nigrostriatal pathway into putamen. There is a strong correlation between therapeutic doses of antipsychotics and binding at the D_2 receptors [6], and D_2 antagonism can cause motor dysfunction such as pseudo-parkinsonism, which remained a problem with these early drug regimens. Second-generation antipsychotic drugs generally have lower rates of D_2 occupancy, decreasing the motor symptoms, but often have good therapeutic outcomes. This is thought to be due to their dual action on the serotonin system, primarily through 5-HT_{2A} antagonism in addition to multiple reported sites of action other than dopamine D_2 receptors, including dopamine (D_1 , D_3 , D_4), serotonin (5-HT_{1A}, 5-HT_{2C}, 5-HT₆, 5-HT₇), muscarinic cholinergic, and histamine receptors [7]. In direct comparisons there has been no difference in the efficacy of first-generation antipsychotics and second-generation antipsychotics in acute therapy in schizophrenia at similar doses [8]. However meta-analysis has shown some evidence that second-generation antipsychotics may be better tolerated over time [9], and have a greater effect on negative symptoms than first-generation antipsychotics [10], primarily modulated by the serotonergic effects of second-generation antipsychotics. Comparison of the effects of these drugs on cognition has not yielded clear findings, although some mild improvement in cognitive symptoms with second-generation antipsychotics has been reported [11,12]. As much of the basal ganglia DA

system is involved with the motor system the lack of effect of first-generation antipsychotics on cognition may, at first, not seem surprising. But the causative pathway from elevated nigrostriatal DA to the cortical disruption leading to psychosis is not known, and clearly there are downstream effects from striatal DA-modulated changes critical in regulating cortical function.

In recent years the SN has become more interesting to those who study schizophrenia and psychotic disorders with the increased importance of the DA hypothesis of schizophrenia, a key suggestion of which is that subcortical presynaptic DA dysfunction underlie many symptoms [13,14]. This model centers on DA dysfunction in the striatum [15], and schizophrenia is associated with elevated striatal DA level and synthesis [16,17]. One of the most interesting findings of recent years is that increased striatal dopamine synthesis capacity is evident in individuals with prodromal schizophrenia symptoms, suggesting that DA abnormalities predate the onset of first episode psychosis [18]. By contrast, there is no similar elevation in non-psychotic depression [19] or in patients with persistent subclinical psychotic symptoms who have not developed a psychotic disorder [20], suggesting specificity to psychotic illness [21]. While this focus has been on striatal DA, it should be reiterated that DA is synthesized in the SN and transported along the nigrostriatal pathway, meaning that the SN is the structure behind the extensive striatal DA changes. Direct examination of SN DA neurons suggests that excess DA synthesis is the cause of elevated DA, rather than insufficient DA breakdown. DA is synthesized from tyrosine via a two-step process: tyrosine hydroxylase (TH) converts tyrosine into dihydroxyphenyl-L-alanine, the rate-limiting step of DA synthesis, which is converted by aromatic acid decarboxylase into DA [22]. DA is broken down by two pathways: by dopamine- β -hydroxylase (DBH) to noradrenaline and by catechol O-methyltransferase (COMT) to 3-methoxytyramine. DBH is a vesicle-bound enzyme which has not been investigated well in mental illness, although it is known to have an important role in addiction. COMT exists in both intra- and extra-cellular forms, with the extracellular form often found in astrocytes, with astrocyte density being reported decreased in the SN in schizophrenia [23]. However no direct evidence has demonstrated that breakdown pathways have any role in SN DA function [24], in contrast to the prefrontal cortex where COMT activity has been reported to have a role in working memory [25].

Post-mortem studies have found altered tyrosine hydroxylase messenger RNA levels, increased TH levels, and increased variability in tyrosine hydroxylase levels in the SN of schizophrenia patients [20,26]. Indeed, detailed examination of the DA neurons suggests that their soma and nuclei are physically swollen in schizophrenia, which further suggests a very substantial increase in DA synthesis [23].

While we have much to learn about the regulation of the SN in schizophrenia and similar illness, the evidence so far suggests that excess SN/striatal DA may not be due to a fault within the SN itself, but rather a regulatory issue that most likely originates elsewhere within the basal ganglia.

As described above the SN is part of a complex network which we are only now beginning to functionally examine piece by piece, and we hope that in the near future the neurophysiology underlying these severe illnesses can be unraveled, and better therapies developed.

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