Review

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Review

Dopamine Signaling in Substantia Nigra and Its Impact on Locomotor Function; not A NEW Concept, but Neglected Reality Simmering in Striatal Stew

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Abstract: The mechanistic influences of dopamine (DA) signaling and impact on motor function is nearly always interpreted from changes in nigrostriatal neuron terminals in striatum. This is a standard practice in studies of human Parkinson's disease (PD) and aging, and related animal models of PD and aging-related parkinsonism. However, despite dozens of studies indicating an ambiguous relationship between changes in striatal DA signaling and motor phenotype, this perseverating focus on striatum continues. Although DA release in substantia nigra (SN) was first reported almost 50 years ago. assessment of nigral DA signaling changes in relation to motor function is rarely considered. Whereas DA signaling has been well-characterized in striatum at all 5 steps of neurotransmission (biosynthesis and turnover, storage, release, reuptake, and post-synaptic binding) in the nigrostriatal pathway, the depth of such interrogations in the SN, outside of cell counts, is sparse. However, there is sufficient evidence that these steps in DA neurotransmission in the SN are operational and regulated autonomously from striatum, and are present in human PD and aging, and related animal models. To complete our understanding of how nigrostriatal DA signaling affects motor function, it is past time to include interrogation of nigral DA signaling. This brief review highlights evidence that changes in nigral DA signaling at each step in DA neurotransmission are autonomous from those in striatum and changes in the SN alone can influence locomotor function. Accordingly, for full characterization of how nigrostriatal DA signaling affects locomotor activity, interrogation of DA signaling in SN is essential.

Keywords: substantia nigra; dopamine; tyrosine hydroxylase; dopamine receptor; striatum; reuptake; phosphorylation; nigrostriatal; Parkinson's disease; aging

Introduction:

Ever since dopamine (DA) and norepinephrine (NE) neuronal pathways were identified and functionally characterized in vivo [1–7], the depth and breadth of studies of how both neurotransmitters affect cognitive and motor behavior has been immense. The viability and function of the neuronal pathways that produce these neurotransmitters, nigrostriatal and ceruleo-cortical respectively, are significantly decreased in Parkinson's disease (PD). As such, the 5 components of neurotransmission (biosynthesis, storage, release, reuptake, and post-synaptic function) have been studied for respective contributions to deficits in DA or NE signaling in PD. The range of approaches used to interrogate these pathways include defining PD-related genes and physiological regulation of catecholamine genes [8–11], expression of catecholamine-regulating enzymes and transporters [12–20], post-translational modification of biosynthesis enzymes [21–28], neuron electrophysiological properties [29–34], release and uptake [14,35–40], pre- and post-synaptic receptor function [22,30,34,41–45], basal ganglia circuit function [46–52], and growth factor signaling [53–64]. Clearly the investment of resources in these multiple areas of research is for the ultimate goals of understanding PD etiology, the consequences of DA or NE loss that arise from PD on motor and cognitive skills, and to identify a sound mechanistic rationale for effective treatments to delay or arrest disease progression. Notably, the vast majority of studies that focus on the relationship between motor function and DA signaling have evaluated one or more of the 5 components of neurotransmission in the striatum, the terminal field region of the nigrostriatal pathway. It is

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important to keep in mind that at the time of PD diagnosis, the striatal regions already show ~70-80% loss of DA-regulating proteins or aspects of DA signaling (such as DA release). This non-linear relationship brings up 2 yet to be resolved questions; why is motor impairment not detected prior to 80% loss, and second, why does the severity of motor impairment continue to worsen when loss in striatum reaches near 100% 4-5 years after diagnosis [20].

Insights of how striatal DA signaling affects locomotor function have reached a plateau

In the context of PD, DA is, by far, the most studied of the catecholamines, with NE running a distant second. Since 1962, there have been ~29,000 publications associated with DA and PD vs. ~1700 associated with NE and PD. The evidence for deficient nigrostriatal DA signaling as the primary cause of motor symptoms of PD is strong. Yet there still remains a critical unresolved issue that hampers progress; a continuous perseverating focus to attribute deficient DA signaling in the striatum as the sole culprit for motor impairment. This focus is undoubtedly driven by the longstanding working model of basal ganglia circuit dysfunction that arises from the loss of striatal DA due to the progressive loss of nigrostriatal neurons. It is argued that this striato-centric focus has generated a plateau in our understanding of exactly how any of the 5 steps of neurotransmission with deficient DA-regulating function in striatum actually impair motor function. [For definition purposes, the relation of nigrostriatal DA signaling to motor impairment will focus upon bradykinesia/hypokinesia, which is among 4 cardinal signs of PD which also include rigidity and postural instability, and tremor at rest.] Indeed, there are clinically-based examples of where improvements in striatal DA signaling did not equate to alleviate motor impairment in PD patients [60,64,65]. More evidence of this lack of alignment between striatal DA levels and severity of motor impairment is seen at the later stages of PD. Although the severity of motor impairment continues to worsen 4 to 5- years after PD diagnosis, loss of striatal DA-regulating proteins or signaling has already reached near 100% [20,66–69]. There is a comparable amount of evidence for this misalignment between striatal DA levels and motor function status in preclinical studies of rat PD models [22,57–59,70–76]. Motor impairment may be also present with far less than 80%, if any, striatal DA loss [54,65,70,72], or to the converse, motor impairment may not be present even though striatal DA loss meets or exceeds 80% [22,73,74]. Motor impairment can also be alleviated without any increase or recovery of striatal DA or DA-regulating protein loss [57,59,73–76]

It is not the position of this review to assert that striatal DA signaling does not influence on motor function. The weight of evidence showing the influence of striatal DA signaling on basal ganglia circuits is too great to list here. However, the incongruities between the level of locomotor function and DA signaling in striatum can no longer be ignored if we are to solve which critical dopaminergic element(s) are to be targeted to maximize effective therapeutic strategies. This brief review will present evidence that challenges the central dogma that compromised DA signaling in striatum is the sole deficiency of DA that impairs locomotor function. The overwhelming evidence that nigrostriatal DA signaling does affect locomotor function has been obtained from our knowledge of PD and from studies that experimentally modulate components of DA neurotransmission (biosynthesis, DA receptor function, etc.). The key question is where in the nigrostriatal pathway does DA have the greatest influence on locomotor function; particularly regarding the mechanisms that drive the initiation of self-generated movement. Although the evidence that nigral DA signaling can influence motor function is sparse, it has nonetheless been in existence since the 1980s [77–81]. The paucity of studies evaluating the SN is likely due to a prevailing presumption that neurotransmitter functions at the axon terminal are the sole influence of behavioral outcomes. Thus, interrogation of nigral DA signaling has not been considered in experimental designs to define how components of nigrostriatal DA signaling affect locomotor activity. In this light, it is reasonable to presume that the numerous ambiguities between striatal DA regulation and motor function that have accumulated in the literature over the past several decades could have been resolved if assessment of nigral DA signaling was included in the study design.

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Dissecting the impact of the 5 components of DA neurotransmission on locomotor function

As goes with the loss of nigrostriatal neurons in PD, the loss of DA-regulating proteins and processes involved in neurotransmission follows. Interference with the functions of any of these proteins or processes can also affect locomotor function in naïve (non-PD) animal models. Tyrosine hydroxylase (TH) is the rate-limiting step of DA biosynthesis, converting tyrosine to L-dihydroxyphenylalanine (L-DOPA). Inhibition of TH with alpha-methyl-p-tyrosine (AMPT) decreases DA inhibits locomotor activity [7,82–86]. In humans, inhibition of hyperkinetic movements, such as chorea, dystonia, or dyskinesia, can also be produced by AMPT [87,88]. At the DA storage step, a process controlled by vesicular monoamine transporter 2 (VMAT2) imports monoamines like DA into synaptic vesicles. This function is inhibited by reserpine, which also inhibits locomotor activity [89–91], as first identified by a parkinsonian symptom side effect produced in hypertension treatment [92]. VMAT2 is expressed in both striatum and SN [93,94], which confers the capacity for storing DA for eventual release in the entire nigrostriatal pathway.

Once DA is packaged in synaptic vesicles, it can be released by neuronal activity or by modulation of transporter function through stimulant action. At the extracellular level, DA release from the nigrostriatal pathway is the step that delivers tissue content, via vesicular delivery, to the synapse [95–98], wherein DA has 4 fates, binding to the pre- or post-synaptic DA receptors, reuptake into the neuron, or diffusion away from the release site [99]. Drugs that target DA receptors, the post-synaptic DA D_1 receptor or pre- and post-synaptic DA D_2 receptor, also influence locomotor activity, and are targets for pharmacotherapy in PD treatment [100]. An acute regimen of antipsychotics such as haloperidol or either DA D_1 or D_2 receptor antagonists reduce locomotor activity [101–105]. Conversely, DA D_1 or D_2 agonists increase locomotor activity in rodents and primates [106–108] and improve motor functions in late-stage human PD [109–111]. The release of DA can also be modulated by DA D_2 autoreceptor function [112] in both striatum and SN [31,113]. Functionally, the regulation of DA release by neuronal activity is critical for initiation of locomotor activity [114–118]. Deficits in DA release, as shown in aging studies or over-expression of alpha-synuclein, are associated with decreased locomotor activity [119–121], whereas increased DA release, as induced by amphetamine or methamphetamine [122–124], increases locomotor activity [125–127].

The termination of DA signaling occurs by reduction of extracellular DA levels in the synapse, largely (though not exclusively [99) through reuptake by the dopamine transporter (DAT) [128–130], a process that occurs in SN as well as striatum [131–133]. DAT protein expression is considerably greater in the striatum [94], and this difference may explain why DA release and uptake dynamics differ between these two regions [131–133]. Through constant trafficking between cytosol and plasma membrane, DAT function is dynamically regulated, including aging and in PD [134–136]. The DAT, like the DA D_2 receptor, also has considerable interaction with other components of DA neurotransmission, including DA D_2 receptors [34,113] and has considerable influence on maintaining DA tissue levels, TH expression and phosphorylation selectively in the striatum, but not in SN [137,138]. There is also evidence of plasticity in DA uptake under conditions where DA and DAT levels are particularly low. In such cases, the NE transporter may also transport DA, with inherently low DA innervation or from severe loss of nigrostriatal neuron terminals [139–141].

Given the considerable influence of DAT on DA homeostasis, locomotor activity is strongly affected by DAT expression levels. DAT knockout mice show a hyperkinetic phenotype [142,143]. This hyperkinetic phenotype is not likely explained by the low DA uptake capacity in the striatum due to DAT knockout, as DA tissue content levels are severely reduced to a level that is comparable to nigrostriatal lesion (>90% loss) [137,138]. Systemic delivery of nomifensine, a DAT inhibitor, increases locomotor activity [144], consistent with the hyperkinetic phenotype of the knockout [142,143]. While presumably this effect would be considered to be due to elevated extracellular DA levels in striatum from interference with DA uptake, we recently reported infusion of nomifensine in striatum did not increase locomotor activity in aged rats, despite a striatum-specific increase in extracellular DA levels produced by nomifensine infusion therein [145].

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Approaches and outcomes needed to discern role of striatal and nigral DA signaling

In summary, there is considerable evidence that the proteins and processes associated with the 5 steps of DA neurotransmission in the nigrostriatal pathway are operational in both striatum and SN. Modifications of these functions can alter DA signaling dynamics in either region, although there are notable differences in the functional dynamics between these regions at some of these steps, such as DAT expression and reuptake capacity [94,131,140]. The release of DA occurs in both striatum and SN with activation of nigrostriatal neurons [96,115,146–148], and is associated with self-directed movement in rodents [115,148]. Thus, with DA release occurring in striatum and SN, it would seem to be experimentally challenging to decipher the role of DA signaling in either region in locomotor function. However, with localized delivery of DA-modulating compounds into striatum or SN, it is plausible to target one or more of these steps in one region to modify and isolate DA signaling dynamics. Thus, interference with a step in neurotransmission in one region would influence extracellular DA levels (or interfere with receptor function) therein, which would address the fact that DA release occurs simultaneously in both regions from neuronal activity. The critical outcome needed from this approach would be whether this region-specific modulation affected DA signaling not only in the targeted region, but also did not affect DA signaling in the non-targeted region (ie. targeting SN would not influence DA dynamics in striatum). This approach is feasible, and therefore it is possible to parse out the relative contributions of DA signaling in striatum or SN and respective impact on locomotor function [44,54,84,118,145,149–151]. Most importantly, as the functional status of each step in DA neurotransmission is established in normal and disease states in either striatum or SN, it is possible to infer what the loss of such functions in disease states has on locomotor function, based upon the results obtained from region-specific modulation of DA signaling.

Autonomy of DA biosynthesis in SN and impact on motor function in aging and PD

An experimental approach that can modulate DA signaling by targeting one of the 5 steps of neurotransmission in a specific region of the nigrostriatal pathway represents a means to emulate specific mechanisms of DA signaling that exist in vivo in normal or disease (including aging) states. For example, if TH levels are reduced selectively in the SN in a disease or aging model, then targeting TH activity in that region in a naïve or control animal can be useful to determine if the loss of TH is contributing to deficient DA signaling and locomotor function [149]. The specific targeting of SN or striatum to modulate DA signaling by targeting one of the 5 steps of neurotransmission is a critical experimental approach because differences in DA regulation exist at multiple steps in normal (or naïve) rodents, PD models, and in models of aging-related parkinsonism. Moreover, because such differences have also been identified in human PD and aging, it is feasible to determine, by experimental modulation within the SN or striatum, if any specific change in DA signaling is driving locomotor impairment. Most of the evidence that has evaluated how DA signaling from SN or striatum affects locomotor function has been obtained at the DA biosynthesis step.

Differences in TH expression, TH phosphorylation, and DA tissue content exist between the SN and striatum under normal [84,138,153,154], PD- [18,20,22,57,58,66–69,72,156] or aging-related conditions [54,61,84,145,150,152,155–157], both in animal models and in human PD [20,66–69,156–158] and aging [156–162]. In naïve (young and without nigrostriatal lesion) rodents and across multiple rat strains, TH protein expression is 3- to 4-fold greater in the striatum [18,22,61,62,84,138,145,150,152]. This difference in TH expression between striatum and SN is matched by differences in DA tissue content, which is ~15- to 25-fold greater in striatum [18,22,84,138,145,152]. The greater disparity in DA tissue levels as compared to the differences in TH protein between these two regions is likely due to 3- to 10-fold greater ser31 TH phosphorylation in the striatum [22,84,138,145,152–154]. Increased ser31 TH phosphorylation can alone increase DA biosynthesis [163] and the level of ser31 phosphorylation is highly correlative to DA tissue levels when accounting for inherent TH protein levels across 4 DA regions in vivo [84,138,152–154]. These results collectively indicate that DA biosynthesis capacity differs between striatum and SN at the levels of TH protein, ser31 TH phosphorylation, and DA tissue.content. As such, the effect of

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nigrostriatal lesion (reflecting PD) and aging on these components of DA biosynthesis would presumably play a significant role on regulation of DA signaling and ultimately locomotor function.

Nigrostriatal DA signaling and aging-related parkinsonism: relevance to PD

Bradykinesia (or hypokinesia) is the most prevalent motor symptom of aging-related parkinsonism. As shown in rat models of aging-related parkinsonism and PD, 3 indices of DA biosynthesis in the SN, but not striatum, are associated with changes in locomotor function. From the standpoint of aging, studies from rodent [119,120,145,150,152], primate [164–166] and human [160–162] all indicate that loss of DA or TH in striatum varies considerably, from virtually no loss to 50% of young cohorts. Notably, no aging study has reported that striatal DA or TH loss reaches the accepted 80% loss threshold associated with PD motor symptom onset [19,20,73,167,168]. In an established rat model of aging, there was nigra-specific loss of TH protein and TH phosphorylation that was specific for ser31; other phosphorylation sites, ser19 and ser40 were unaffected by aging [152]. This loss was also associated with a 40% decrease in DA tissue levels, with no loss in striatum. To determine if this nigra-specific loss of DA was contributing to decreased locomotor activity (which would be bradykinesia/hypokinesia in humans), we infused the TH inhibitor AMPT into the SN of young rats to produce DA reduction comparable that in aged rats. This delivery in the SN did not affect DA levels in striatum. Locomotor activity was decreased during the time established for DA reduction in the SN [149]. In another study, we targeted the striatum with AMPT to decrease DA. Although DA reduction was specific for the striatum, there was no effect on locomotor activity [150].

Using the same approach in aging rats, we infused nomifensine into either region to determine if augmenting extracellular DA levels, by blocking DA reuptake, would increase locomotor activity [145]. Essentially this approach was to counteract aging-related diminished DA release that was previously established to occur in either region [119,120]. Again, the infusion approach was able to produce a region-specific increase in extracellular DA levels. We found that increasing DA in the SN was associated with increased locomotor activity, whereas increased DA in the striatum by nomifensine had no effect on locomotor activity. These results indicate that aging-related decreases in DA release in the nigrostriatal pathway that are responsible for decreased locomotor activity are due to decreased release in the SN. Thus, by experimentally modulating DA locally in SN or striatum to mimic or counteract aging effects at the biosynthesis or (indirectly) release steps, the results point to deficient DA signaling in the SN as a contributing mechanism to reduced locomotor activity in aging rats. It would be logical therefore to presume that the inhibition of motor activity following systemic AMPT [7], or the enhancement of motor activity following systemic nomifensine [119,144] or elimination of reuptake in the DAT knockout [142,143], is being driven, at least in part, by modulation of nigral DA signaling.

To summarize, aging-related parkinsonism cannot be explained by loss of TH protein or DA tissue levels in striatum. In either humans or animal models of aging, striatal TH or DA loss does not reach the consensus of 80% loss associated with the onset of motor symptoms in PD. Instead, the deficiencies in DA signaling of the nigrostriatal pathway that are affected by aging and drive aging-related parkinsonism occur in the SN (Figure 1). Our work, along with others, makes the case for multiple steps of DA neurotransmission in the SN being affected. The first likely event in the lifespan is an aging-related decrease in DA D_1 receptors (to be discussed further below) followed by decreased expression of TH protein and a phosphorylation site-specific decrease in ser31 (and not ser40). It is unknown if the decrease in TH protein is due only to neuronal loss that has been documented to also occur. As a result of these decreases, DA tissue content is reduced, which likely drives the decrease in DA release previously reported in the SN [164]. Importantly, the decreases in TH protein, neuron loss, and tissue DA in the SN in aging are comparable to those reported in the SN in human PD and PD models at the onset of bradykinesia [19,20,35,156,167,168]. This consistency with the changes in the SN that occur in PD makes it further plausible that deficient DA signaling in the SN is responsible for decreased locomotor activity or parkinsonism in aging.

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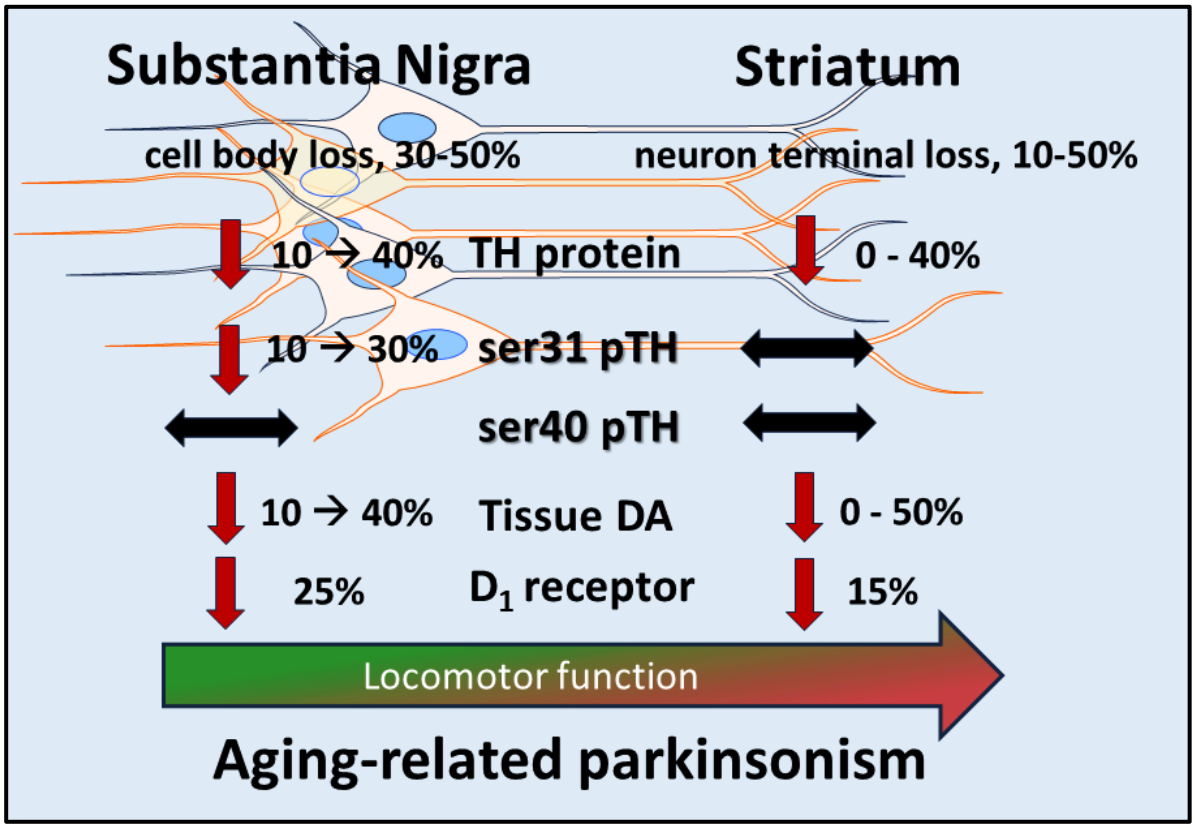

Figure 1. Molecular changes in components of DA signaling in SN are autonomous from those in striatum during aging. Unlike PD, loss of TH protein and tissue DA in striatum is substantially less in aging, with maximum loss ~50% being the most ever reported. Conversely in the SN, there are several aging-related changes occurring at the biosynthesis and receptor levels. Loss of the DA D_1 receptor occurs in the middle to middle-late stages of the lifespan and is associated with the onset of locomotor decline [150]. Loss of TH protein occurs in the SN toward the latter (aged) part of the lifespan, with a decrease in DA tissue content [152]. Notably, there is also a decrease in site-specific TH phosphorylation at ser31 that occurs only in the SN. The magnitude of nigral TH protein and tissue DA loss in aging [152] is comparable to TH and DA loss at the onset of locomotor impairment in PD [19], suggesting that DA tissue loss arising from decreased ser31 TH phosphorylation and TH protein are mechanisms of hypokinesia seen in aging and in early PD.

Nigrostriatal DA signaling and PD-related motor impairment

From the perspective of deficient DA signaling impact on motor impairment in PD, a long-standing unresolved issue is why motor impairment does not occur until there is 70-80% TH or DA loss in striatum. It was long thought that increased DA turnover reflected increased DA signaling during progressive loss of the nigrostriatal neuron terminals [19,73,169–171], thus compensating for TH protein loss to enable normal locomotor activity. L-DOPA, the product of TH, remains the gold-standard for treating motor symptoms. Thus, it stands to reason that compensating for TH loss through engagement of innate compensatory mechanisms would promote maintaining locomotor function until striatal TH loss was too severe.

Increased DA turnover was proposed to be an indicator of enhanced DA signaling to compensate for TH protein loss during nigrostriatal neuron loss [19,52,73,169–172]. However, Bezard and colleagues definitively showed in an elegant timeline study using MPTP-lesioned primates that increased DA turnover occurred only after bradykinesia manifest; there was no evidence of increased DA turnover during the asymptomatic period [19]. There was also 80% TH and DA loss in striatum at the onset of bradykinesia. Notably even 60% TH loss in striatum was observed during the asymptomatic period. Fortunately, this study also assessed TH loss in the SN, and found at the onset of motor impairment, there was ~40% loss in the SN; far less than 80% loss seen at the axon terminals.

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This disparity in TH loss between SN and striatum has strong translational relevance because this disparity consistently manifests in human PD [20,66–68]. Nonetheless, the lack of evidence to support a role for increased DA turnover in striatum to offset onset of locomotor impairment gave rise to consider non-DA related mechanisms to be responsible for delaying the onset of motor impairment [52].

Recent work from our group indicates that the compensatory mechanism to mitigate the severity of hypokinesia and delay its onset is related to increased DA signaling in the SN, and not striatum [22]. This mechanism involves an increase in ser31 TH phosphorylation, specifically in the SN, that begins early after nigrostriatal loss induction by 6-hydroxydopamine (6-OHDA) and is maintained at least until neuronal loss reaches 80% in the SN. As a result of this increase in ser31 TH phosphorylation, there is less loss of DA as compared to TH throughout neuronal loss [22]. This differential in DA and TH loss also manifests in the SN, contralateral to the lesioned side, as TH loss begins there at a later time. When correlating the loss of DA in SN and striatum against the severity of motor decline, only DA loss in the SN has significant correlation [22]. In striatum, we found no difference in TH and DA loss, as both exceeded 90% early after lesion induction, commensurate with decreased ser31 TH phosphorylation, but increased DA turnover throughout neuron loss. However, in the SN, DA turnover decreased as neuron loss increased. Our findings of diminished lesion impact on DA tissue content in the SN are also reflected in the extracellular realm, wherein baseline DA levels are unaffected by 6-OHDA lesion despite severe neuronal loss [173]. Together, these results frame a new perspective on the mechanism by which motor impairment is delayed by increased DA biosynthesis in the SN, despite progressive nigrostriatal neuron loss that occurs in PD (Figure 2). Moreover, these results are disease-relevant, and further support a role for nigral DA signaling in locomotor function.

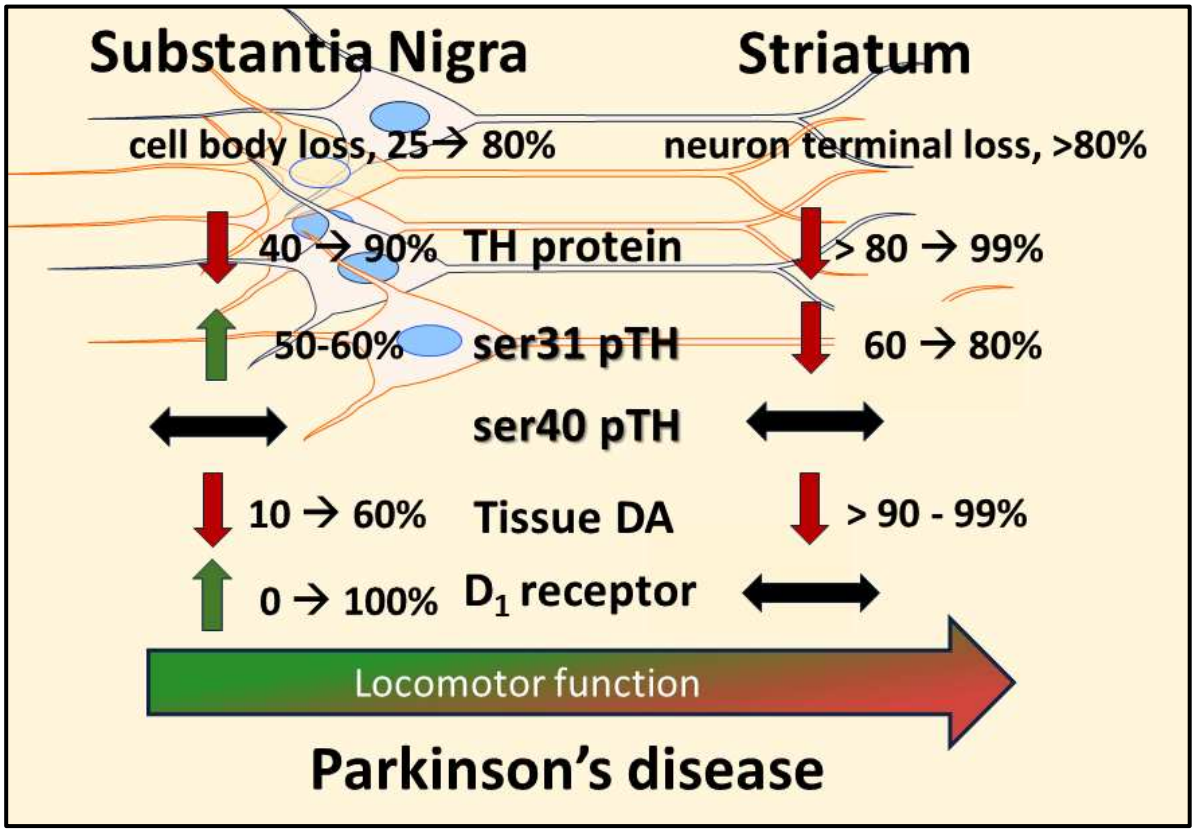

Figure 2. Dichotomous molecular changes in DA signaling components in SN and striatum in response to neuronal loss. Induction of nigrostriatal neuron loss by 6-OHDA produces a progressive loss of neurons over 4 weeks. Loss of TH protein in SN is less than the magnitude of loss in the striatum at the earlier time points post-lesion, and tissue DA loss is substantially and consistently less in the SN than in striatum. In response to TH loss, there is a site-specific increase in TH phosphorylation at ser31 only in the SN; in striatum, there is a progressive decrease. This increase in

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ser31 in the SN offsets the progressive loss of TH therein to keep DA loss at a lesser level than TH. As DA tissue loss increases in the SN, the DA D_1 receptor increases expression at the latter stages of neuron loss. The increase in both ser31 TH phosphorylation and DA D_1 receptor in the SN are compensatory mechanisms to delay the onset of locomotor impairment and alleviate its severity.

Autonomy of post-synaptic DA signaling in SN and impact on motor function

The activation of the DA D_1 receptor, expressed on striatonigral neurons, in the SN mediates GABA release [30,42,47]. This release of GABA decreases the inhibitory output of the basal ganglia; a process that facilitates the generation of movement. Both aging and PD can affect D_1 receptor expression. In the middle to late-middle stage of the lifespan, there is a 30% decrease in expression of this receptor in the rat SN, and smaller decrease in striatum [150] (Figure 1). This decrease is associated with an aging-related decrease in locomotor activity. In human aging, DA D_1 receptor expression also decreases proportionally with age [174]. This decrease may be associated with the onset of mild bradykinesia beginning in late-middle age in humans. Previous work by Trevitt and colleagues modulated D_1 receptor function in SN and striatum to evaluate relative impact on locomotor function in rats. They showed nigral infusion of a DA D_1 receptor antagonist was highly potent in reducing operant behavior and open-field activity [44]. Decreased locomotor activity is also produced by DA D_1 receptor antagonists following systemic delivery [105]. Thus, it is plausible that the locomotor-modulating action of DA D_1 receptor drugs, in animal models and humans alike, is driven by modulation of its post-synaptic functions in the SN [103,105–110]. Thus, applied to physiologically-based DA-meditated changes in locomotor activity, it is plausible that through local release of GABA in the SN, driven by activation of DA D_1 receptors following local DA release in the SN [30,42,47], the disinhibition of basal ganglia output from the SN *pars reticulata* neurons occurs. It is feasible that this sequence of events, initiated by DA release in the SN, provides the signal to increase locomotor activity (Figure 3). This work also suggests that the first onset of aging-related decreases in locomotor activity in the lifespan may be driven by decreased DA D_1 receptor expression in the SN. Prevention of aging-related deficits in motor function is associated with increased DA D_1 receptor expression, exclusively in the SN [145].

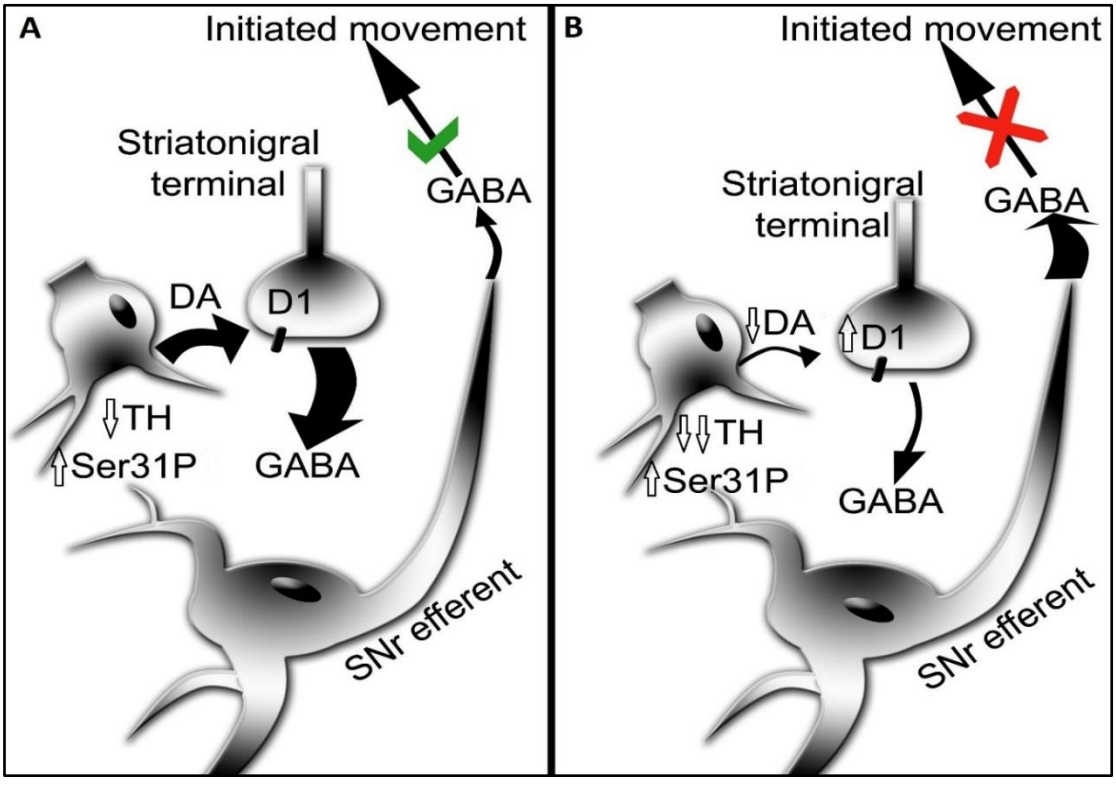

Figure 3. Compensatory response in substantia nigra to maintain DA signaling. A. Early stage of nigrostriatal neuron loss. During the loss of nigrostriatal neurons, TH protein loss in SN precedes

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neuron loss. To maintain DA tissue levels in response to TH protein loss, TH phosphorylation at ser31 increases, offsetting the loss of DA that would otherwise occur (as seen in striatum) [22]. The local release of DA in the SN is sufficient to maintain GABA release from striatonigral terminals which is needed to mitigate tonic GABA release from the SNr efferents to promote locomotor activity. **B. Late stage of nigrostriatal neuron loss.** Although ser31 TH phosphorylation is still increased, the progressive loss of TH protein is sufficient to diminish DA tissue levels, although DA loss is still less than TH protein loss [22]. The decrease in DA tissue content is expected to diminish release. In response, the post-synaptic DA D_1 receptor is upregulated on post-synaptic striatonigral terminals to increase responsivity against diminished synaptic DA levels. The overall plasticity of increased DA biosynthesis and DA D_1 receptor expression in the SN is hypothesized to mitigate the severity of bradykinesia/hypokinesia arising from TH and neuron loss.

In PD, the DA D_1 receptor has recently been identified as a novel target to treat motor impairment in the later stages of the disease [109–111]. The status of DA D_1 receptor expression or function is far less known than the DA D_2 receptor [175]. Our work in the 6-OHDA model indicates that the DA D_1 receptor is upregulated, specifically in the SN, as nigrostriatal neuron and DA loss increase therein [22]. We speculate this increase is a response by the striatonigral neurons to maintain DA signaling in the SN. Notably, D_1 receptor expression does not change in the early stages of neuronal loss, when DA tissue levels are unaffected. Thus, if the D_1 receptor is upregulated in the latter stages of PD, it stands to reason that a D_1 receptor agonist could substitute for DA, given the reduction in DA levels at the latter stage of neuron loss. In contrast to the changes in SN, D_1 receptor expression is unchanged in striatum, despite the severe loss of DA beginning early after nigrostriatal neuron lesion.

In summary, multiple lines of evidence from human PD and aging and related animal models indicate that DA signaling in the SN plays a significant role in locomotor activity levels. Changes at the biosynthesis, reuptake, and post-synaptic signaling steps in the SN occur autonomously from changes (if any) in the striatum, making a clear case that augmenting DA signaling in the SN alone could be achieved by several possible strategies to alleviate locomotor impairment. Moreover, targeting specific steps of DA neurotransmission that are affected in aging and PD can reveal which deficit (and where in the nigrostriatal pathway) is responsible for decreasing DA signaling to impair locomotor acitivity. As long as there is a means to modulate one or more steps in DA neurotransmission, such as inhibition of DA biosynthesis [84,149,150], or augmenting it by infusion of L-DOPA [39,176–178] it is possible to pinpoint the most critical losses responsible for locomotor impairment.

Upstream regulators of DA signaling: the role of GDNF signaling in SN

There has been a great need to find treatment for PD that is disease modifying, in addition to a therapeutic approach that can reduce the amount of L-DOPA needed to maintain mobility without debilitating side effects such as L-DOPA-induced dyskinesia. In the 1990s, glial cell line-derived neurotrophic factor (GDNF) emerged as a top candidate for treatment of motor impairment in PD based upon encouraging preclinical studies in rodent and non-human primates [56–59]. Notably, GDNF had the rather remarkable attribute of long-term impact on constituents of DA signaling (such as increased DA tissue content and ser31 TH phosphorylation), particularly in the SN, after a single delivery [56–58,61,62,179]. These long-term effects of GDNF were eventually revealed in clinical trials, wherein motor benefits to patients endured for up to a year following discontinuation [180,181], and motor benefits realized while receiving GDNF [55,182]. In preclinical rat PD models, this long-term effect of GDNF may be driven by increased expression of its receptor, GFR-α1, specifically in the SN [53,183]. Notably, GFR-α1 itself alleviates TH and DA loss after 6-OHDA lesion in the SN, but not striatum [183], and can increase TH and DA levels, again selectively in the SN, with increased locomotor activity, in aged rats [54].

More recent clinical trials with GDNF reported failure to reach primary end point for improvement in motor scores in GDNF recipients relative to placebo control groups [60,64], leading the field to reconsider its value for treating the motor impairments of PD [184]. It should be briefly

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noted that in the failed trials there was evidence of increased DA signaling in the putamen [60,64]; an outcome representing more evidence of the ambiguity between striatal DA signaling and locomotor function. Retrograde transport of GDNF from striatum to the SN has been a well-documented physiological event [62,185–188]. Given the impact of GDNF or GFR-α1 in the SN on DA signaling and strong association with improved locomotor activity, it is likely that the trophic action of GDNF depends upon there being sufficient GFR-α1 levels in both striatum (for retrograde transport), and in the SN wherein the stimulating effects on DA signaling can occur [53,54,58,61,189]. This has been recently identified as a potential major challenge, as GFR-α1 expression progressively decreases in DA neurons as neuronal loss proceeds [63]

Conclusions:

We have known for nearly 50 years that DA is released from the somatodendritic region of nigrostriatal neurons in the SN [189,190] and that the 5 steps of DA neurotransmission that comprise DA signaling in striatum are also present, functional, and targetable in the SN. Moreover, substantial evidence shows that DA signaling is autonomously regulated in SN from striatum. Thus, it cannot be assumed that changes in DA signaling in one compartment are also occurring in the other compartment. Therefore, under physiological conditions, despite that DA release occurs in both striatum and SN during neuron activation, modulation at specific steps of DA neurotransmission in one of these two regions can alter the magnitude of DA release capacity in only one region. Given the multiple examples of studies that have shown incongruity between components of striatal DA signaling and locomotor function, it stands to reason that changes in DA signaling in the SN in these studies could have been the culpable mechanism. Given the autonomy of DA regulation between striatum and SN, changes in nigral DA signaling alone theoretically could influence locomotor function, and the evidence for this continues to increase. Indeed, although there is a substantially lesser number of studies of interrogating nigral DA signaling, and an even fewer number of studies that also measure locomotor activity against it, there is congruity with the direction of change in nigral DA. modulation and locomotor activity in a number of studies [44,54,71,78–80,118,145,149,151]. These results are also consistent with studies reporting changes in basal ganglia output from the SN as a result of modulating DA signaling specifically in the SN [30,47,191–194]. These results are applicable in PD and aging, as, the autonomy of DA signaling and components of DA neurotransmission exist at multiple levels [19,20,35,36,66–69,152,155,156,164,165,178]. This has direct implications to identify whether the striatum or SN is the source of DA signaling deficits that drives locomotor impairment and its severity in both conditions [195].

Future Directions:

The loss of nigrostriatal neurons in PD has paved the way in our understanding how DA loss affects motor function, and in general, how changes in DA signaling components affect locomotor function. However, it is past time to consider that the continuing loss of DA signaling components remaining in the SN may well be driving the worsening locomotor impairment in the patient. However, a collective epiphany in recognizing the role of nigral DA signaling in locomotor function will expand our understanding of the mechanisms, including those upstream of DA (such as GDNF signaling) that contribute to locomotor impairment. For example, with evidence for DA compensation occurring in the SN to mitigate the severity of locomotor decline, the inherent mechanisms driving it may represent targets to maintain locomotor function when TH protein loss is too great. It will be also important to delve further into understanding what striatal DA signaling is doing for maintaining locomotor function. For example, tremor at rest is a cardinal sign in PD. However in aging-related parkinsonism the evidence for its presence is scarce; notably TH and DA loss are nowhere near the severity in PD. Therefore, DA deficits in striatum may reach a level of severity that promote this involuntary movement. Finally, it should be a priority to determine what compartment of the nigrostriatal pathway should be targeted to maximize the efficacy of potential treatments, such as GDNF, on locomotor recovery. The potential for increased nigral DA signaling

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as a mechanism for locomotor recovery should stand as priority comparable to the attention that the striatum has garnered.

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