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Mathematical Models: Interactions Between Serotonin and Dopamine in Parkinson's Disease

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1. Introduction

Parkinson's disease (PD) has traditionally been thought of as a dysfunction in the dopamine (DA) signaling system caused primarily by cell death in the substantia nigra pars compacta (SNc). However, strong evidence has been accumulating that the serotonin (5-HT) signaling system is also involved. First, 5-HT influences normal motor function through a dense innervation of the striatum. Second, substantial cell death of serotonergic neurons occurs in PD and in some cases may occur earlier than DA cell death. And, finally, there are indications that interactions between the 5-HT system and the DA system may be responsible for some of the symptoms of PD and some of the side effects of treatment by levodopa. Some of the evidence for these assertions is reviewed below.

The 5-HT system is itself very complex. The serotonergic neurons in the raphe nuclei (RN) send ascending projections to a large number of different brain regions including medial prefrontal cortex (mPFC), motor cortex, hypothalamus, hippocampus, amygdala, and the basal ganglia. And, some of these brain regions, substantia nigra, amygdala, mPFC, and hypothalamus send projections back to the RN (Monti, 2010). Thus it is not surprising that 5-HT is linked to so many behaviors including feeding and body-weight regulation, social hierarchies, aggression and suicidality, obsessive compulsive disorder, alcoholism, anxiety, and affective disorders (Feldman et al., 1997). Since the pharmacology and the electrophysiology of both the serotonergic and the dopaminergic systems are only partially understood, it is a daunting task to understand how these two systems affect one another. This is particularly true in the presence of a degenerative disease that involves massive cell death in both systems.

In this complicated situation, mathematical models can potentially provide insight into mechanisms and interactions. The purpose of the models is not to summarize what is already known. The purpose is to provide a platform for *in silico* biological experimentation. Using models one can try out ideas, validate or refute hypotheses, settle disputes in the literature, and sometimes discover new phenomena. Of course, to be useful the models have to be well-grounded in real physiology and the creation of such models is not easy. However, if one

has a model that represents (part of) the underlying physiology well, then *in silico* experiments are quick and inexpensive. The model provides a quantitative way of thinking about the phenomena being investigated and may suggest new hypotheses that can be checked by animal experiments. Thus, modeling, when combined with animal experiments and clinical trials, can shed some light on the complicated pharmacological, electrophysiological, and behavioral issues in PD.

In Section 2, we discuss the evidence for the role of 5-HT in PD and the side effects of levodopa therapy and in Section 3 we discuss possible mechanisms. In Section 4, we describe a mathematical model that we recently created to study homeostatic mechanisms in serotonergic signaling. In Section 5 we use the model, and a previous model of a DA terminal, to discuss the effects of gene polymorphisms, the stability of extracellular DA in the striatum in the face of cell death in the substantia nigra, and the mechanism of action of selective serotonin reuptake inhibitors. Finally, in Section 6 we outline how we plan to use existing models and new models to investigate the interactions between the 5-HT system and the DA system in PD.

2. PD and the serotonergic system

Tremor, rigidity, and bradykinesia, the classical motor symptoms of ideopathic PD, primarily result from loss of dopaminergic neurons in the SNc. However, neural degeneration also occurs in other sites of the brain, ranging from the brain stem to cortex, as the synaptic protein α-synuclein accumulates pathologically to form Lewy bodies (LB) or Lewy neurites. The clinical diagnosis of PD is based upon presence of the motor symptoms indicating dopamine deficiency (Chaudhuri et al., 2006; Jankovic, 2008). Postmortem analysis finds LB not only in remaining substantia nigra cells but in other specific brain regions where cells are lost (Gibb & Lees, 1988). Braak and colleagues (Braak et al., 2003) have proposed a scheme of six stages describing the development of ideopathic PD, characterized by the spatial extent of LB inclusions. Braak stage 1 involves LB inclusions in the region of the brain stem; neurodegeneration of the substantia nigra does not begin until stage 3. Braak's hypothesis concerning the progression of PD predicts that symptoms such as diminished olfactory sensitivity (Lim et al., 2009) or REM behavior disorder (Ahlskog, 2004) should precede the cardinal motor symptoms of the disease, a pattern observed in some but not all cases of PD (Linazasoro, 2007). Indeed, the retrospective nature of Braak's study obscures the actual course of progression (Halliday & McCann, 2010). In a longitudinal study, Halliday & McCann (2010) found that approximately half of ideopathic PD cases follow Braak's scheme. In all cases studied by Halliday and McCann, LB occurred not only in the substantia nigra but also in other brain areas including brain stem. Thus, extra-nigral aspects are always present in PD, and their significance can rival that of the cardinal motor symptoms (Chaudhuri et al., 2006).

Ahlskog (2004) reports that LB have been found in pontomedullary neurons of brains without substantia nigra pathology but that the reverse has not been observed. Among the nondopaminergic systems profoundly affected in PD is the serotonergic system. The extent of damage to the serotonergic system in PD is variable and is less severe than the loss of dopamine: Kish found that, while striatal dopamine concentrations decreased by more than 80%, serotonin markers decreased by less than 70% (Kish et al., 2008). It has not been clearly established to what extent this reduction in serotonin markers is due to raphe cell loss

(Jellinger, 1991), serotonergic terminal loss in the striatum, or molecular regulatory changes (Kish et al., 2008).

In post-mortem analyses of brains from PD patients, Kish et al. (2008) found that serotonin and dopamine have substantially different patterns of loss within the striatum. Serotonin markers show greater loss in the caudate than in putamen, while the dopamine loss is greater in the putamen. Thus the striatal subdivision with the more severe dopamine loss (putamen) was less affected by loss of serotonin markers, possibly reflecting compensatory sprouting of 5-HT terminals (Maeda et al., 2003). Serotonergic responses to dopamine depletion may also be evident in changes in the electrical activity of serotonergic neurons. Zhang et al. (2007) reports that, in an animal model of PD, raphe neurons have altered firing rates and fire bursts more frequently. Under levodopa administration, DA may also be released in bursts from these serotonergic neurons.

One of the clearest and best-studied involvements of 5-HT in PD symptoms is in the motor symptoms, including tremor and especially levodopa induced dyskinesias (LID). Experiments have found that the serotonergic system plays an essential role in both symptoms. Brooks (2007) reports that in order to generate tremors with the characteristic PD frequency of 3-5 Hz in animal models it is necessary to lesion not just nigro-striatal dopaminergic projections but also the midbrain tegmentum, which contains serotonergic cell bodies in the median raphe, rubrospinal, and dentatothalamic tracts. He also notes that loss of midbrain serotonin 5-HT_{1A} binding correlates with tremor severity in PD, unlike loss of striatal dopaminergic function. He speculates that this may explain why some parkinsonian tremors are relatively resistant to dopaminergic medications. 5-HT may not be equally involved in all motor symptoms of PD: it has been observed clinically that rigidity and bradykinesia are more responsive to dopaminergic drugs than is tremor (Fox et al., 2009).

Upon diagnosis of PD, patients can often use levodopa to effectively relieve symptoms for several years. However, more than 50% of patients develop motor complications in response to levodopa administration within 5 years (Olanow et al., 2000); after 10 years, the percentage is approximately 90% (Ahlskog & Muenter, 2001). These complications include a narrowing of the temporal window of efficacy (*i.e.*, the duration of benefit after a given dose of levodopa becomes progressively shorter until it approximates the plasma half-life of levodopa) (Olanow et al., 2006), sudden failures of efficacy known as "on-off fluctuations" (Nicholson & Brotchie, 2002) and, most troublesome, the appearance of involuntary movements (LID) (Carta et al., 2008; Nicholson & Brotchie, 2002).

3. Possible mechanisms of serotonergic involvement in PD motor symptoms

In order to understand the emergence of LID, it is useful to first review how levodopa may achieve therapeutic effect. The idea of administering levodopa is to provide dopamine replacement therapy. Dopamine itself is unable to pass the blood brain barrier, but its immediate precursor, levodopa, is able to reach the brain following peripheral administration when given in combination with a decarboxylase inhibitor to prevent metabolism while in the blood stream (Carta et al., 2008). The motor symptoms of PD typically emerge when a sufficient proportion of dopaminergic cells in SNc have been lost that dopaminergic terminals in the striatum are no longer able to maintain a high enough concentration of extracellular DA. Supplemental levodopa can be taken into the remaining dopaminergic terminals, converted to DA and stored in vesicles for synaptic release.

As the number of remaining dopaminergic cells continues to decrease, the levodopa may increasingly be taken up by other cell types including serotonergic neurons and glial cells. Serotonergic cells may play a special role here, as they also express the enzymes used in dopaminergic cells to convert levodopa to DA (amino acid aromatic decarboxylase, AADC) and to package DA into vesicles (vesicular monoamine transporter 2, MAT). Indeed, experiments have verified that serotonergic cells can store and release DA in vivo and in vitro (Nicholson & Brotchie, 2002). Evidence that serotonergic cells may be playing a role in LID comes from animal models of PD. (Tanaka et al., 1999) showed that, in levodopa treatment of a hemiparkinsonian rat, extracellular DA (eDA) decreased substantially when the serotonergic system was lesioned. Glial cells also contain AADC and so could contribute to the conversion of levodopa to DA; however, experiments by Kannari et al. (2000) in which he used reserpine to block vesicular packaging showed a great reduction of eDA, suggesting that most of the levodopa-derived DA is released by exocytosis of vesicles rather than by glia, at least at physiological levels of levodopa administration. Carta et al. (2007) have provided further evidence implicating serotonergic cells in LID in a rat model by showing that either toxic lesion of the serotonergic system or pharmacological impairment of the system with selective serotonin autoreceptor (5-HT_{1A} and 5-HT_{1B}) agonists resulted in a nearly complete elimination of LID.

The observation that LID becomes increasingly problematic as the disease progresses suggests that LID may result from the fact that DA released from serotonergic cells is not subject to the DA homeostatic mechanisms present in dopaminergic cells. Many approaches to eliminating LID therefore tend to focus instead on manipulating factors that regulate serotonergic cell activity, such as serotonergic autoreceptors that participate in serotonergic homeostatic mechanisms. Simply decreasing serotonergic cell activity by administering serotonin autoreceptor agonists has the drawback of also reducing the amount of dopamine released into the extracellular space, tending to worsen PD symptoms (Iravani et al., 2006). Carta et al. (2008) argue that it is reasonable to use 5-HT autoreceptor agonists especially because the DA intermixed with the 5-HT released by the serotonergic cell effectively lowers the binding of 5-HT to 5-HT autoreceptors and induces the cells to be over-active. A more detailed look at the serotonergic system, using mathematical models, may help suggest more nuanced approaches.

There are many types of serotonin receptors. 5-HT_{1A} receptors are present on the cell body and dendrites of serotonergic neurons in the dorsal and median raphe; they function as autoreceptors and they decrease firing as extracellular 5-HT (e5-HT) goes up. 5-HT_{1B} receptors are present on axon terminals in serotonin projection regions where they function as autoreceptors and decrease the release of serotonin as e5-HT goes up in the terminal region. Applying agonists only to 5-HT_{1A} or only to 5-HT_{1B} autoreceptors in a rat model of PD treated with levodopa can partially reduce LID (Bibbiani et al., 2001; Jackson et al., 2004). Carta et al. (2007) found that providing subthreshold doses of both 5-HT_{1A} and 5-HT_{1B} agonists (that is, doses that would have little or no effect alone) could completely eliminate LID. This is very strong evidence that the absence of the normal control mechanisms by the DA autoreceptors is connected to LID.

Post-synaptic mechanisms may play a role in LID. Given that serotonergic cells may be responsible for releasing much of the levodopa-derived DA in advanced PD and that these cells lack DA homeostatic mechanisms, the intermittent administration of levodopa may

result in large swings in the extracellular concentration of DA. The resulting pulsatile stimulation of striatal DA receptors may be the proximate cause of abnormal movements (de la Fuente-Fernandez et al., 2001) and may induce post-synaptic changes. In animal models of PD, alterations have been identified in the D_1 signaling pathway as well as in NMDA and AMPA receptor function and distribution (Bibbiani et al., 2005; Hallett et al., 2005; Robelet et al., 2004), and these changes have been linked to the induction and maintenance of abnormal movements (Gardoni et al., 2006; Hallett et al., 2005; Picconi et al., 2008; Santini et al., 2007). In fact, studies utilizing pumps to provide a fairly continuous dosing with levodopa or DA agonists have found fewer side effects (Nutt et al., 2000).
Changes in gene expression also have been found following treatment with levodopa (Santini et al., 2007), and these may relate to the phenomenon of priming. Some PD patients can be treated with DA receptor agonists without developing dyskinesias. But eventually, as the disease progresses, they generally need to add levodopa in order to achieve relief from symptoms. The phenomenon of priming is that patients started on levodopa and then moved to DA agonists will exhibit dyskinesias even if placed on DA agonists without levodopa (Nicholson & Brotchie, 2002).

4. Mathematical modeling of dopaminergic and serotonergic systems

As a first step in using mathematics to help understand the serotonergic and dopaminergic systems, we have created mathematical models of a serotonin terminal (Best et al., 2010b) and a dopamine terminal (Best et al., 2009). Here we briefly describe the model for a serotonin terminal and in the next section give applications. The substrates in the model are indicated in Figure 1 by the pink boxes and the blue ellipses contain the acronyms of enzymes or transporters. Blood tryptophan is considered a (possibly time-varying) input to the model and there are differential equations for the other nine substrates. Each differential equation is just a quantitative expression of mass balance; i.e. the rate of change of the concentration of a substrate is simply the sum of the rates of the reactions by which it is made minus the sum of the rates of the reactions in which it is used. For example, the concentration of 5-hydroxytryptophan, [5htp], satisfies:

$$\frac{d[5htp]}{dt} = V_{\mathrm{TPH}}(trp, bh4, e5ht) - V_{\mathrm{AADC}}(5htp) \tag{1}$$

where V_{TPH} is the velocity of the TPH reaction and V_{AADC} is the velocity of the AADC reaction. One must specify exactly how these velocities depend on the current values of various substrates. V_{TPH} is given by:

$$V_{\mathrm{TPH}} = \frac{V_{max}(trp)(bh4)}{(K_{trp} + (trp) + \frac{(trp)^2}{K_i})(K_{bh4} + (bh4))} \cdot \left(1.5 - \frac{(e5ht)^2}{((.000768)^2 + (e5ht)^2)}\right). \tag{2}$$

The first term on the right is of Michaelis-Menten form and gives the dependence of the velocity on the concentrations of trp and $bh4$. The enzyme TPH shows substrate inhibition (Best et al., 2010a; Friedman et al., 1974; McKinney et al., 2005), which is the reason for the $(trp)^2$ term in the denominator. The second term on the right expresses how the concentration of extracellular 5-HT influences the rate of synthesis via the autoreceptors. At normal e5-HT concentration (.768 nM) this factor equals one. As e5-HT goes up the factor can go as low as 0.5

and as e5-HT goes down, the factor can go as high as 1.5. We chose K_m and K_i values from the literature and chose the V_{max} so that the normal velocity of the the TPH reaction is in the range given by experiments. The form of the second factor is more speculative. Though it is certain that increasing extracellular concentrations of 5-HT inhibit synthesis via the autoreceptors (Adell et al., 2002), there is relatively little information in the literature about the range of e5-HT concentrations over which the effect takes place and about the strength of the effect in the low nanomolar range. Here, as in other choices of parameters and functional forms, we base our choices as much as possible on the experimental literature. Full details of the model can be found in Best et al. (2010b).

The model can be used to show how the steady state values of concentrations and rates change if parameters, like serotonin transporter (SERT) density, or inputs, like serum tryptophan, change. One can also compute the time courses of the concentrations and rates on long time scales (hours) or very short time scales (msec) as the system responds to the release of 5-HT due to individual action potentials. However, the model has limitations. Various physiological processes known to be important are not included, for example the movement of vesicles or SERTs from the interior of the terminal to and from the synaptic membrane. The detailed biophysics of the autoreceptors is not included; instead the model has terms that represent the effect of e5-HT on TPH and on release from the vesicles. And finally, this is a model for a terminal and thus has limited value in studying network questions about the full serotonergic system.

It is important to keep in mind that there is no such thing as *the* serotonergic terminal. Important parameters vary considerably from one projection region to another. For example, SERT density (which corresponds roughly to the V_{max} of V_{SERT}) varies by about a factor of 5 (Bunin et al., 1998; Daws et al., 2005; Lin et al., 2004). And, functional polymorphisms for the TPH, SERT, and MAO genes are known to exist. Indeed, one of the strengths of the model is that it can be used to study the likely effects of such variations on the functional behavior of serotonergic terminals.

5. Applying the models

In this section we describe several applications of our 5-HT and DA terminal models to show how they can be used. The DA terminal model is similar in structure to the 5-HT model, though the details of the kinetics are different (Best et al., 2009).

5.1 Homeostatic effects of the autoreceptors

It is clear that the 5-HT autoreceptors create homeostasis by providing a kind of end-product inhibition. If firing rate goes up, then e5-HT will go up, which reduces synthesis and release via the autoreceptors. If firing rate goes down, then e5-HT will go down, which increases synthesis and release via the autoreceptors. Thus, the autoreceptors ensure that the average extracellular 5-HT in projections regions due to tonic firing of dorsal raphe neurons does not change very much.

It has been much less remarked in the literature that the autoreceptors provide another kind of homeostasis. The genes for many of the key proteins in the 5-HT system, for example TPH2, SERT, and MAO, have common functional polymorphisms. However, because of the autoreceptors, the polymorphisms have a much smaller effect on e5-HT than one might think. For, example the P449R polymorphism and the R441H polymorphism of TPH2 reduce its

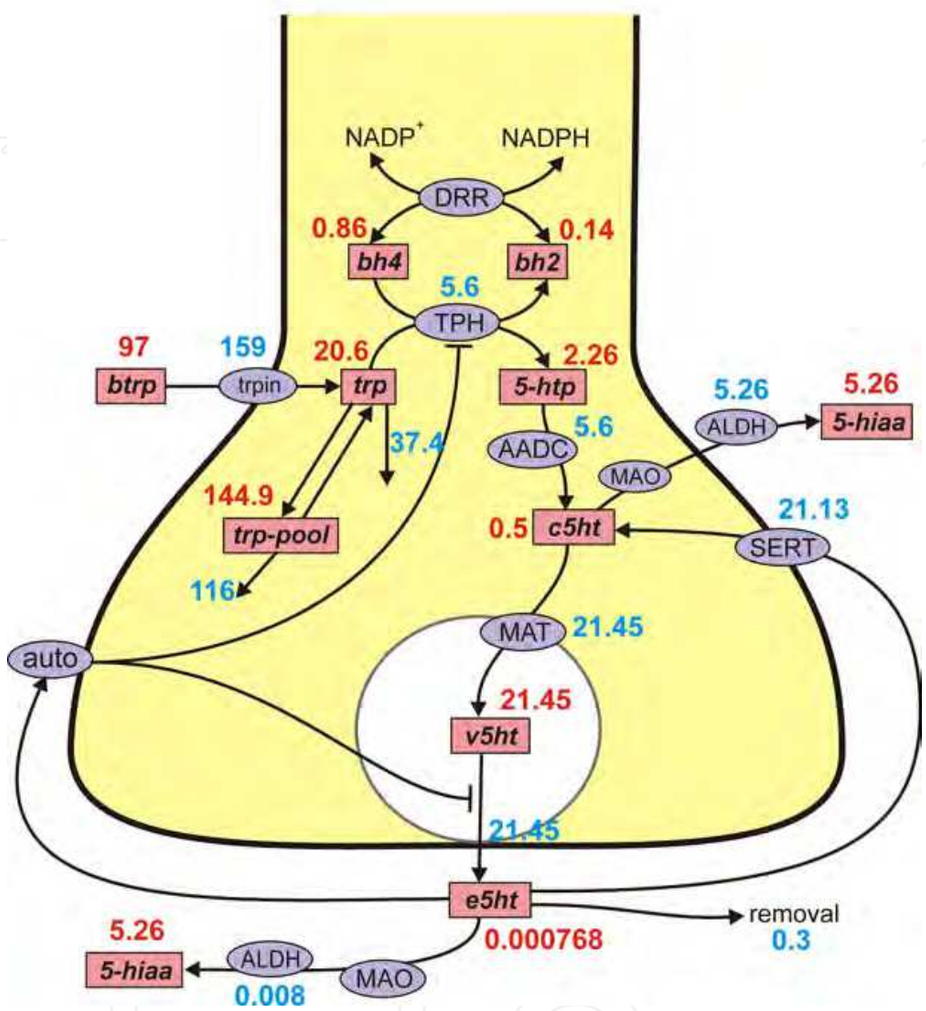

Fig. 1. Steady state concentrations and fluxes in the 5-HT terminal model. The figure shows the reactions in the model. The pink rectangular boxes indicate substrates and blue ellipses contain the acronyms of enzymes or transporters; steady state values in the model are indicated. Concentrations (red) have units of μM and rates (blue) have units of μM/hr. Full names of the substrates are: bh2, dihydrobiopterin; bh4, tetrahydrobiopterin; trp, tryptophan; btrp, serum tryptophan; 5htp, 5-hydroxytryptophan; c5ht, cytosolic 5-HT; v5ht, vesicular 5-HT; e5ht; extracellular 5-HT; 5-hiaa, 5-hydroxyindoleacetic acid; *trp–pool*, the tryptophan pool. Names of enzymes and transporters are: Trpin, neutral amino acid transporter; DRR, dihydrobiopterin reductase; TPH, tryptophan hydroxylase; AADC, aromatic amino acid decarboxylase; MAT, vesicular monoamine transporter; SERT, 5-HT reuptake transporter; auto, 5-HT autoreceptors; MAO, monoamine oxidase; ALDH, aldehyde dehydrogenase. Removal means uptake by capillaries or glial cells or diffusion out of the system.

activity to 65% and 19% of wild type, respectively. But the model predicts that e5-HT will decrease to 90% and 45% of wild type in these two cases; see Figure 4 of (Best et al., 2010b). Similarly, we show in (Best et al., 2009) that the D2 autoreceptors make extracellular DA much less sensitive to the expression level or activity of tyrosine hydroxylase (TH).

5.2 Passive stabilization of DA in the striatum

An interesting and important feature of PD is that symptoms do not appear until a very large percentage (typically 60-90%) of the cells in the SNc have died (Agid, 1991; Zygmond et al., 1990). Animal models have shown that tissue levels of DA in the striatum decline proportionally to cell loss, but eDA remains essentially normal until 85% of the SNc cells have died (Bergstrom & Garris, 2003; Bezard et al., 2001; Dentresangle et al., 2001), and this is widely believed to be the reason that symptoms do not appear until very late in the degeneration of the SNc.

A number of researchers have proposed that this homeostasis of eDA results from active adaptive mechanisms such as increased DA synthesis and the formation of new terminals (Hornykiewicz, 1966; Stanic et al., 2003; Zygmond et al., 1990; 1984). However, Garris and co-workers proposed that the homeostasis is due to passive mechanisms such as release and reuptake and provided some experimental confirmation (Bergstrom & Garris, 2003; Garris et al., 1997; Garris & Wightman, 1994). Their idea is as follows. DA is released in the striatum and is then taken back up into the terminals by the DA transporters (DATs). As the cells in the SNc die the amount of DA released in the striatum decreases proportionally, but the number of DATs available for reuptake has also decreased proportionally. Thus a released DA molecule will spend about the same amount of time in the extracellular space no matter how many SNc cells have died. Garris and co-workers called this "passive stabilization." They did not explain why this homeostasis breaks down when the fraction, f, of SNc cells that are alive becomes small.

We investigated these proposals with our mathematical model of a DA terminal (Reed et al., 2009). We found that the passive stabilization mechanism proposed by Garris works as proposed and we determined why the mechanism breaks down when f is small. Not all released DA molecules are put back into DA terminals by the DATs. Some are taken up by glial cells or blood vessels and some diffuse out of the striatum. As SNc cells die and the DA terminals in the striatum become more sparse, a greater percentage of released DA is lost through these mechanisms. This is why the Garris passive stabilization mechanism breaks down when f is small. We provided quantitative calculations about these effects and showed that passive stabilization itself keeps eDA almost constant when f is between $\frac{1}{2}$ and 1. When more than half of the SNc cells have died, the terminal autoreceptors contribute substantially to the homeostasis of eDA. And, only when f is as low as .15 or .1 are the combined homeostatic effects of passive stabilization and the autoreceptors overwhelmed by the removal of DA from the striatum by the mechanisms discussed above. For details, see (Reed et al., 2009).

5.3 Burst firing in the raphe nuclei and SSRIs

The etiology of depressive illness remains unknown despite a large body of research. A hypothesis that has been central to much work in pharmacology and electrophysiology is that depression is caused by dysfunction in the serotonergic signaling system (Feldman et al.,

1997; Schildkraut, 1965). This hypothesis led to the development of monoamine oxidase inhibitors (MAOIs), tricyclic anti-depressants and the selective serotonin reuptake inhibitors (SSRIs). The idea of the MAOIs is that by preventing the degradation of 5-HT, more will be available for packaging into synaptic vesicles. The idea of the tri-cyclics and the SSRIs is that they block SERTs and inhibit reuptake of 5-HT from the extracellular space, therefore increasing "serotonergic signaling." These drugs have shown some efficacy in the treatment of depression, but the causal chain of events and the reasons why they benefit some patients and not others are unknown.

The simple hypothesis that SSRIs would raise the level of 5-HT in serotonergic synapses by blocking reuptake was thrown into doubt by the discovery that the cell bodies of most 5-HT neurons also release 5-HT and have SERTs. Furthermore, increased e5-HT in the RN decreases the tonic firing rate of those cells via the 5-HT_{1A} autoreceptors (Adell et al., 2002; Gartside et al., 1995). Thus, there are two conflicting effects. Blocking the SERTs in the terminal region would tend to raise e5-HT there, and blocking the SERTs in the raphe nuclei (RN) would tend to decrease e5-HT in the terminal region. The balance between the two effects will depend on the densities of 5-HT_{1A} autoreceptors on different 5-HT populations in the RN and on the densities of SERTs in different projection regions, both quite variable. Thus one would expect that experimental results would depend on dose and on the projection regions being studied, and this was found to be true (Bel & Artigas, 1992; Hervas & Artigas, 1998; Malagie et al., 1995). In some cases, acute doses of SSRIs even decreased e5-HT in projection regions.

The next hypothesis focused on the 5-HT_{1A} autoreceptors on the RN cell bodies. It was shown that giving 5-HT_{1A} antagonists or knocking out the autoreceptors entirely potentiates the SSRI-induced increase of e5-HT in projection regions. Similarly, 5-HT_{1A} knockouts show increased release in projection regions (Chaput et al., 1986; Knobelman et al., 2001). Furthermore, a number of studies showed that chronic treatment with SSRIs desensitizes the 5-HT_{1A} autoreceptors in the RN (Blier et al., 1987; Chaput et al., 1986; Hervas et al., 2001; Invernizzi et al., 1992). And thus, one could explain the improvements of patients on the time scale of 3-6 weeks by the slow desensitization of autoreceptors. However, when e5-HT was measured in projection regions during the entire course of chronic SSRI treatment, it was found that e5-HT concentrations went up initially and then plateaued or declined somewhat over the course of treatment (Anderson et al., 2005; Smith et al., 2000). Thus the autoreceptor desensitization hypothesis seems unlikely to explain the delay of beneficial effects of SSRI treatments.

In (Best et al., 2011) we propose a new hypothesis for the efficacy of SSRIs and provide calculations with the 5-HT terminal model to support our ideas. The 5-HT cells in the RN fire tonically at about 1 Hz and occasionally individual spikes are replaced by short bursts (Feldman et al., 1997; Hajos et al., 1995; Heyn et al., 1982). Our physiological point of view is that tonic firing by the 5-HT neurons in the RN maintains 5-HT tone in target tissues by volume transmission and burst firing conveys specific information to one-on-one synapses that are known to exist (Maley et al., 1990; Parnavelas & Papadopoulos, 1989). Our hypothesis is that chronic treatment of depressed patients with SSRIs returns the response to bursts arriving in terminal regions to normal and we show that this is true in our model. The model behavior depends on the down regulation of SERTs on terminal membranes known to be caused by chronic exposure to SSRIs (Benmansour et al., 2002; Gould et al., 2003; Lau et al., 2008; Mizra et al., 2007). For details, see (Best et al., 2011).

6. Future work

We indicate briefly here some of the ideas that we plan to pursue. We plan to use our current model of a 5-HT terminal described above to investigate the consequences of levodopa uptake by 5-HT terminals. Both 5-HTP and levodopa will compete for AADC that will turn them into 5-HT and DA respectively, and the monoamine transporter will package them together into vesicles. Since there is leakage out of the vesicles driven by concentration gradients, the competition will limit the amounts of 5-HT and DA available for release. Our physiological point of view is that normal 5-HT or DA neurons maintain 5-HT or DA tone in target tissues by volume transmission and convey specific information via burst firing. The autoreceptors on DA neurons inhibit release when the extracellular concentration of DA goes up due to a burst, bringing the concentration back to the normal tonic level rapidly. However, levodopa therapy partially turns 5-HT neurons into DA neurons that do not have DA autoreceptors and one expects that stimulation of the 5-HT system will therefore cause larger than normal swings in extracellular DA in the striatum after levodopa therapy. This effect will be compounded by the fact that cell death in the SNc implies that there will be many fewer DATs in the striatum to take up the released DA. We plan to investigate this situation with our model. Finally, we are currently extending our models to include the competition between tyrosine, tryptophan, leucine, isoleucine, and valine at the blood-brain barrier. When this is completed we can study the tryptophan depletion and tryptophan loading experiments described in (Scholtissen et al., 2006).

We are particularly interested in how levodopa therapy could produce dyskinesis and have some ideas that can be tried out through mathematical modeling. (Carta et al., 2007) provided strong evidence that release of DA from 5-HT neurons causes LID by showing that 5-HT_{1A} agonists that reduce RN firing and/or 5-HT_{1B} agonists that reduce release in the striatum both reduce the incidence of LID in an animal model. We plan to extend our 5-HT terminal model to include the cell body in the RN so that we can study release of DA in the striatum in the presence of either 5-HT_{1A} or 5-HT_{1B} agonists (or both) after cell death in the SNc reduces the number of DATs. This will provide a platform for trying out *in silico* the experiments in (Carta et al., 2007).

There is another intriguing possibility that we plan to investigate by modeling. Recall that the 5-HT neurons in the raphe nuclei release 5-HT from their cell bodies when they fire. The released 5-HT binds to the 5-HT_{1A} autoreceptors on the cell bodies and inhibits RN firing (Adell et al., 2002). This is a kind of lateral inhibition in the RN that limits total firing. However, in the presence of levodopa, the cell bodies will release a combination of 5-HT and DA, and the lower extracellular concentration of 5-HT will provide much less lateral inhibition. Thus is it likely that the 5-HT neurons in the RN fire more frequently after levodopa therapy and there is evidence for altered firing patterns (Zhang et al., 2007). This would have the effect of releasing more DA in the striatum. Notice, however, that raphe neurons project to many brain regions that send inhibitory projections back to the RN (for example the mPFC; see (Celada et al., 2001)). Such negative feedback systems often exhibit oscillations if they are forced hard enough, and such oscillations would mean periodic oscillations in the amount of firing of 5-HT neurons in the RN and thus periodic oscillations in the amount of DA released in the striatum. It is tempting to speculate that such oscillations may contribute to LID and that they could be initiated by intermittent levodopa therapy (Nutt et al., 2000; Olanow et al., 2006; 2000). We plan to investigate this hypothesis by developing mathematical models of the

lateral inhibition by diffusion of extracellular 5-HT in the RN and a model of the projections to the mPFC with negative feedback from the mPFC to the RN.

Finally, it is well-known that the brain is capable of rewiring itself after injury to use available neurons for new purposes. Note that, in a certain sense, that is what levodopa therapy is stimulating, the use of 5-HT neurons as DA neurons. And, it is known that lesioning the SNc causes hyperinnervation by 5-HT neurons in the striatum (Maeda et al., 2003). Such retraining and rewiring takes time, of course, and it is possible that it can't happen fast enough to compensate for the degeneration in PD, but the possibility is intriguing. Not enough is known presently for mathematical modeling to be helpful here. However, if and when anatomical and electrophysiological information becomes available about such compensatory processes, mathematical models, developed along the lines that we have indicated, could perhaps suggest treatment strategies that would facilitate the compensatory processes.

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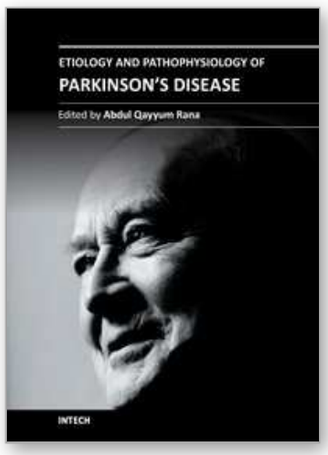

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This book about Parkinsonâ€™s disease provides a detailed account of etiology and pathophysiology of Parkinsonâ€™s disease, a complicated neurological condition. Environmental and genetic factors involved in the causation of Parkinsonâ€™s disease have been discussed in detail. This book can be used by basic scientists as well as researchers. Neuroscience fellows and life science readers can also obtain sufficient information. Beside genetic factors, other pathophysiological aspects of Parkinsonâ€™s disease have been discussed in detail. Up to date information about the changes in various neurotransmitters, inflammatory responses, oxidative pathways and biomarkers has been described at length. Each section has been written by one or more faculty members of well known academic institutions. Thus, this book brings forth both clinical and basic science aspects of Parkinsonâ€™s disease.

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