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Rationality in discovery

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Part III Neuropharmacology

What is the rational use of theory and experiment in the process of scientific discovery, in practice? In this part I discuss a case study and model of the rational use of theory and experiment in the practice of drug research for Parkinson's disease, as introduced in Chapter 3, in more detail. First I survey how the effects of drugs for Parkinson's disease are explained by the dopamine **theory** (Chapter 7). Then I report on the use of theory and experiment in **practice** (Chapter 8). I finish this thesis by discussing a model of both the dopamine theory and the studied practice of **discovery** (Chapter 9).

Chapter 7

Theory

7.1 Introduction

A short description of a theory and a practice in neuropharmacology, was introduced in Chapter 3 of this thesis. This third part provides a more detailed description and analysis of that same theory and practice of discovery.

The specific question for this part is: How are theory and experiments used in the practice of drug research for Parkinson's disease? To answer this question I will first survey the literature on the dopamine theory of Parkinson's disease in more detail. The particular question of this chapter is: how are Parkinson's disease and the effect of known drugs explained by theory?

Parkinson's disease is believed to be mainly caused by a deficiency of dopamine. Dopamine is a neurotransmitter, a chemical messenger between nerve cells in the mammalian brain. In this chapter I explore how dopamine is exactly related to Parkinson's disease, and how theory about that relation is used to understand the function of drug interventions for Parkinson's disease. Before discussing pharmaceutical interventions I will first discuss the dopaminergic cell and the basal ganglia in some detail to understand the rationale of these treatments.

In section 7.2 I start with a general introduction to Parkinson's disease. I go into the basics of the dopaminergic nerve cell in section 7.3. Then, in section 7.4, I go into the basal ganglia, the neural circuitry that partly controls voluntary movement, and how a defect in it causes parkinsonian symptoms. I end this survey of Parkinson's disease literature with a short overview of a selection of therapeutic drug interventions in section 7.5.

7.2 Parkinson's disease

People with Parkinson's Disease suffer from a motor behavior impairment, usually at an older age. The primary symptoms include: muscular rigidity, resting tremor, difficulty with movement initiation (bradykinesia), slowness of voluntary movement, difficulty with balance, and difficulty with walking. This disease was named after the English MD. James Parkinson, who in 1817 was the first person to describe these symptoms as 'the shaking palsy'. (Bernstein, 1995; Wichmann & DeLong, 1993)

Dopamine deficiency

More than a century later, one believes that the cause of the disease is a dopamine deficiency in the basal ganglia of the brain. Dopamine (DA) is a neurotransmitter, a chemical messenger in the nervous system, see Figure 7.1. In Parkinson's disease the neural cells which produce dopamine, the dopaminergic cells, deteriorate. When these neurons start to disappear, the normal rate of dopamine production decreases. It was discovered that when the degeneration of dopaminergic cells is more than 70-80%, Parkinson's symptoms start to appear. Next to Parkinson's disease's primary symptoms mentioned above, a patient may also start to suffer from secondary symptoms which include: depression, senility, postural deformity, and difficulty in speaking.

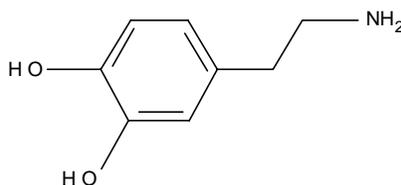


Figure 7.1: Structure diagram of dopamine

Diagnosis with L-dopa

It is difficult to diagnose Parkinson's disease in an early stage. The earliest symptoms may be non-specific, such as weakness, tiredness, and fatigue. So the disease may be unrecognized for some time. Today there are no conclusive tests for Parkinson's disease, yet there are several methods for evaluating its possible presence.

A first diagnosis is based on an evaluation of the presence and severity of the primary symptoms. If this test is significant, a trial test of anti parkinsonian drugs may be used to further diagnose the presence of Parkinson's disease. This test is usually performed with L-dopa. L-dopa is a precursor in the biosynthesis of dopamine in nerve cells, and causes the remaining dopaminergic cells to increase the production of dopamine. If the patient fails to benefit from L-dopa, the diagnosis of Parkinson's disease is questionable.

Parkinsonism

Computed tomography (CT) or magnetic resonance imaging (MRI) scans of the brain may be helpful in ruling out other diseases whose symptoms resemble Parkinson's disease. These diseases may include other neurological disorders leading to parkinsonian symptoms. Such symptoms can be caused by a brain tumor, repeated head trauma, or prolonged use of certain drugs. Such a condition is referred to as Parkinson's syndrome, or atypical Parkinson's. These kinds of parkinsonisms should not be confused with Parkinson's disease proper.

MPTP model

The cause of Parkinson's disease is still unknown. There is one known viral infection that damages the extra pyramidal nervous system and causes Parkinson's disease indirectly. However, the majority of sufferers were young people with different symp-

toms than we usually see in Parkinson's disease. Most of these cases resulted from an epidemic in the 1920's. More recently it was discovered that several young people who developed parkinsonian symptoms had used an illegal synthetic drug that was contaminated with the compound MPTP. It was found out that this compound is metabolized in the brain to a toxin that damages the extra pyramidal nervous system, causing a rapid decay of dopaminergic cells. Consequently it was hypothesized that Parkinson's disease is caused by an environmental toxic agent like MPTP. Yet, no toxin that has this effect other than MPTP is found in Parkinson patients. MPTP is now used in animal studies to understand how it causes these symptoms, which might lead to a better understanding of Parkinson's disease.

7.3 Dopaminergic cells

Research on Parkinson's disease focuses on the function of dopamine. This neurotransmitter is synthesized in the presynaptic terminal of a dopaminergic nerve cell by several metabolic pathways (see Figure 7.2 and Cooper, Bloom & Roth, 1996, pp. 293-351). First tyrosine in the cell is converted to L-dopa with the help of the enzyme tyrosine hydroxylase (TH). L-dopa in turn is converted into dopamine by the enzyme aromatic amino acid decarboxylase (AADC). The synthesized dopamine molecules in the presynaptic terminal are then taken up by synaptic vesicles. After the dopamine is released from the vesicles into the synaptic cleft, the remaining molecules are taken back into the synaptic terminal by transporters in the membrane. There they are transported back into vesicles or broken down to DOPAC by the enzyme monoamine amine oxidase type B (MAO-B) (Vermeulen, 1994).

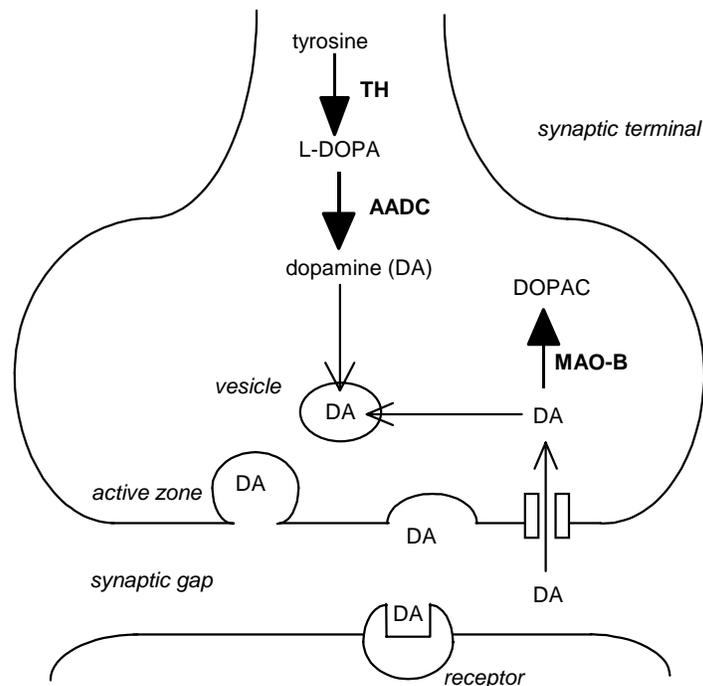


Figure 7.2: Prototypic dopaminergic terminal with cycle of synthesis, storage, release and removal of dopamine.

The signal to open or close ion-pumps is not determined by the chemical properties of a transmitter alone. The same transmitter chemical, *e.g.* dopamine, can both inhibit and excite other neurons, depending on the properties of the receptor it stimulates. Stimulated neurotransmitter receptors influence the membrane potential of a neuron directly or indirectly by various different mechanisms. There are ion channels with special receptor areas that directly bind with a transmitter. When bound to a transmitter these channels undergo a change that opens the channel immediately. The second type of receptors gate ion channels indirectly with a second messenger system. A transmitter bound to such a receptor causes in several steps the release of regulatory proteins within the cell membrane, that act on a family of ion channels.

7.4 Basal ganglia

Post mortem examinations of patients with Parkinson's disease revealed that parts of their brain were pathologically changed. This led to the believe that this part, called the basal ganglia, plays an important role in controlling voluntary movement. It was shown that signals from the cortex are led through the basal ganglia, to the thalamus, which influences motor control centers in the brain. (Côté & Crutcher, 1991)

Extrapyramidal system

The basal ganglia became known as a component of the so-called extrapyramidal motor system, which was first presumed to operate independently of the pyramidal or corticospinal system. However, today it is known that both systems are interconnected, and cooperate. Furthermore, other parts of the brain are shown to play a part in voluntary behavior as well, and the basal ganglia also have a role in cognitive functioning.

The basal ganglia themselves are a conglomeration of five distinguishable interconnected nuclei. They are called the:

- globus pallidus, internal (GPi) and external segment (GPe)
- subthalamic nucleus (STN)
- substantia nigra, pars compacta (SNc) and reticulata (SNr)
- striatum, consisting of caudate nucleus and putamen

From the cortex there is a direct and an indirect signal pathway through this conglomeration, maintained by circuits that use different neurotransmitters, such as GABA, glutamate, enkaphalin and substance P. There is a delicate balance between these two pathways that is partly maintained by dopamine release from the substantia nigra to the striatum. Dopamine release inhibits the indirect pathway by stimulating dopamine D2-receptors, and excites the direct pathway by stimulating the dopamine D1-receptor (see Figure 7.3A, Timmerman 1991, Vermeulen, 1994). The thickness of the arrows represents the strength of the signal. In the case of Parkinson's disease the indirect path is less inhibited, so becomes stronger. The direct path will lack amplification and will become weaker.

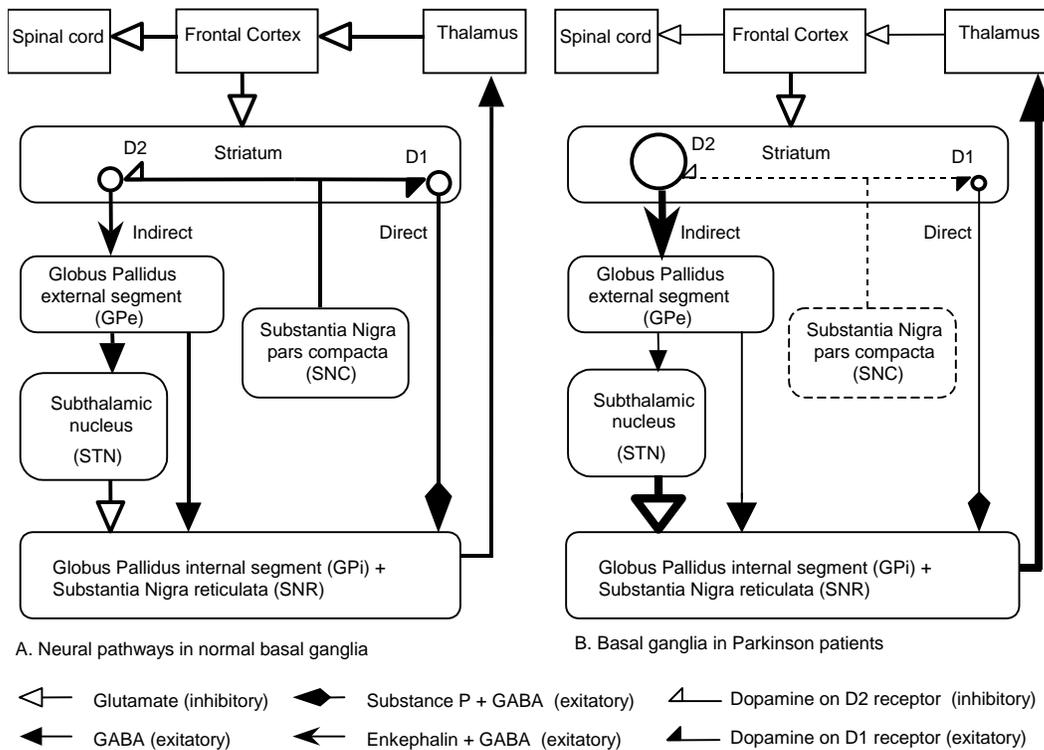


Figure 7.3: Major neural pathways in normal and Parkinsonian basal ganglia

Substantia nigra

In postmortem studies it was discovered that the substantia nigra (meaning "black substance"), had lost its pigment in Parkinson patients. Subsequent studies showed that dopamine levels in the striatum were drastically reduced. Because the basal ganglia contains most of the dopaminergic neurons of the brain, these observations suggested that the dopaminergic pathway between the striatum and substantia nigra is degenerated in Parkinson's disease patients. It was theorized that the depletion of dopamine disbalances the direct and indirect pathways from the striatum, which causes the thalamus to be overstimulated. As a result the frontal cortex is less activated, which would contribute to the Parkinsonian symptoms (see Figure 3B).

7.5 Drug treatments

L-dopa

Given the observations in the basal ganglia in the early 1960's Birkmayer and Hornykiewicz reasoned that it would possibly help Parkinson patients if the level of dopamine was restored to normal levels. It is not possible to administer dopamine itself as a drug because it will not pass the blood-brain barrier between the blood vessels and neurons. However, L-dopa, the precursor in the synthesis of dopamine will. So they reasoned they could boost the dopamine production up to higher levels by providing the few remaining healthy dopaminergic neurons with large amounts of extra L-dopa. (Côté & Crutcher, 1991; Vermeulen, 1994)

The first tests led to a successful initial remission of the symptoms. Yet this positive effect was countered by serious side effects such as nausea, vomiting, blood pressure changes, and collapse. This could be explained by the fact that the enzyme AADC, which converts L-dopa to dopamine, is also present in the liver, kidney and many other places in the body. So while the dopamine levels in the striatum became more normal, the extra dopamine production disturbed chemical balances elsewhere in the body.

AADC inhibition

After further studies it was demonstrated that the effect of the L-dopa treatment was enhanced when the dose of L-dopa is increased more gradually. So the focus of research became the reduction of the side effects. In the early 1970's the first AADC inhibitors that could not pass the blood-brain barrier were introduced. This made it possible to increase dopamine levels in the brain only, because the conversion of the extra L-dopa in the peripheral organs could be inhibited selectively.

MAO-B inhibition

Another way to increase dopamine levels is to block the enzyme MAO-B that is converting dopamine to DOPAC. It is demonstrated by studies that the administration of MAO-B inhibitors slows down the progression of Parkinson's disease, and increases the life expectancy.

It is argued that this slow down can also be explained by the hypothesis that Parkinson's disease is caused by a toxin similar to MPTP. It was shown that MPTP needs to be converted to MPP⁺ by the enzyme MAO-B to have its destructive effect. So if some toxin like MPTP causes the cell death in the basal ganglia of Parkinson's disease patients, the inhibition of MAO-B would slow down this process.

Yet it is also argued that the positive effect of MAO-B inhibition can be (solely) attributed to the effect that it inhibits the break down of dopamine, and hence increases the dopamine level.

L-dopa treatment only symptomatic

While L-dopa is the best available remedy to ease the lives of Parkinson patients, it is not even near a cure. Treatment that aims to increase dopamine levels turns out not to stop the further deterioration of dopaminergic cells, and hence does not work well in the long term. Long-term use of L-dopa frequently results in fading of the therapeutic effect and the development of serious side-effects, such as further motor impairment and psychiatric complications. Furthermore, while the lack of dopamine causes most of the Parkinson symptoms, Parkinson's disease patients also suffer a loss of noradrenergic and serotonergic neurons, which contributes to the disease as well.

Dopamine receptor agonists

To bypass the problem of the side effects of L-dopa treatment, research was initiated to synthesize compounds that would directly act on the dopamine receptors. These compounds, called receptor agonists, would take over the role of dopamine, so no administration of L-dopa would be needed. And hence the side effects induced by large amounts of L-dopa would be countered.

To date this ideal has not yet been reached. While long-term treatment with the available dopamine receptor agonists results in less dyskinesias, the therapeutic effect is less than that of L-dopa. And increasing the dose only leads to other serious side effects such as psychotic reactions. Better effects result from a combination of a low doses of L-dopa with an agonist.

There are also others reason for research into dopamine receptor agonists. It has also been put forward that long term treatment with L-dopa accelerates the degeneration of dopaminergic cells. This could be caused by the enhanced generation of toxic free OH-radicals through dopamine auto-oxidation (Vermeulen, 1994). The higher the amount of dopamine in the cell through extra L-dopa, or MAO-B inhibition, the higher the risk of toxication. If this claim is true, it is preferable to use receptor agonists.

Furthermore, synthetic agonists have the advantage that they can be made highly selective for a particular receptor. There are now five known types of dopamine receptors, and further knowledge of how they are integrated in neural circuits that regulate motor behavior may result in an agonist with less (but also different) side effects.

7.6 Conclusion

In this chapter I asked: How are theory and experiments used in drug research for Parkinson's disease, according to the literature? Theories about the neurophysiology and biochemistry of the brain are used to explain the pathology of Parkinson's disease, and the function of known drug interventions. In neuropharmacology theory serves to guide the search for new and better drugs. In this chapter I surveyed the dopamine theory of Parkinson's disease, and how theories about dopamine's metabolism and function imply suggestions for treatment. In the next chapter I survey part of a practice of research on Parkinson's disease.

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