

Is chronotherapy effective for Parkinson's Disease?

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Abstract

Increasing evidence indicates a relationship between impaired circadian processes and Parkinson's Disease (PD). Altering these impaired circadian processes could be beneficial in treating certain symptoms of PD. Typical parkinsonian symptoms are motor problems. Besides motor symptoms, also non-motor symptoms as depression and sleep problems may occur. Chronotherapy uses entraining agents to change the internal rhythms of the body. Sleep deprivation and bright light therapy are common chronotherapeutic interventions. The use of these interventions is common in treating affective disorders, however, not in the context of PD. In general the overall effect of chronotherapy on PD is not clear. Therefore, a literature study is performed to enlighten these effects. The main research question was: 'Is chronotherapy effective for Parkinson's Disease?'. A very conclusive answer to this question cannot be given, since published research on this topic is scarce. Studies about bright light therapy in PD strongly indicate the positive outcome for PD patients. Motor symptoms, depression, and sleep problems all seem to improve. The effect of sleep deprivation is more questionable, however, one could suggest that this therapy is useful for motor symptoms and depression. It was found that a chronopharmacological approach with Levodopa is not relevant in treating motor symptoms. Up to now few studies have been dedicated to this topic, and the current knowledge about drug metabolism in a circadian manner strongly suggests that this statement about Levodopa is incorrect. It is clear that many aspects in PD are related to our circadian clock. Altering the circadian clock in such a way that it is beneficial in PD is not a conventional therapy, however, it is a well-tolerated and safe procedure. The relationship between the altered biological rhythms and PD indicates that chronotherapy possibly could be beneficial for patients with PD.

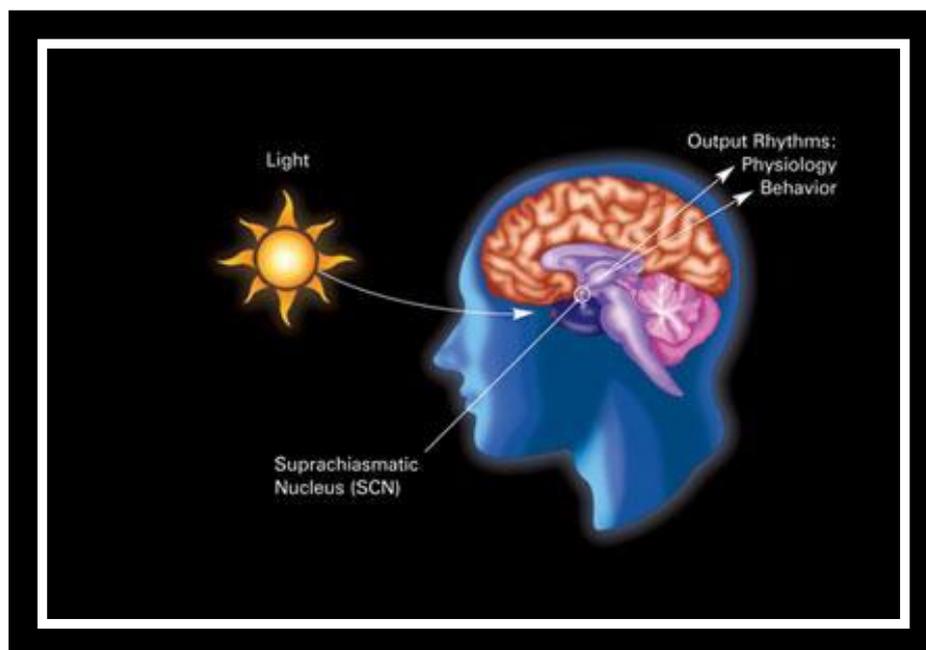


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Introduction

Each year, approximately 20 people per 100.000 are diagnosed with Parkinson's Disease (PD) (1). The main clinical feature of PD is parkinsonism (typical movement disorder), but patients with PD also experience non-motor symptoms. It is a progressive disease with neuronal dysfunction and cell death as the cause of all problems. A major consequence of the death of specific cells is dopamine depletion. The key in the current treatment for PD is dopamine replacement (2). Levodopa is the precursor for this neurotransmitter and is used for the treatment. In the beginning of the disease practically all patients benefit from this drug. However, after 5-10 years it generates problems. The majority of the patients develop adverse reactions to Levodopa. Furthermore, this therapy does not slow the natural progression of PD.

Increasing evidence indicates the involvement of impaired circadian processes in PD (3). Willis et al. state that for over 191 years the involvement of the circadian system of the body in various aspects of PD is recognized, however, never really charted (4). Certainly non-motor symptoms as depression and insomnia are related to our internal clock, though it is not clear to what extent altering the circadian rhythms of relevant substances is helpful for PD, nor is it clear if this is helpful for motor symptoms as well. Therefore, I would like to enlighten the effects of chronotherapy in Parkinson's Disease, with as main question: 'Is chronotherapy effective for Parkinson's Disease?'. In order to answer this question it is necessary to explain more about the circadian system and chronotherapy and about Parkinson's Disease. Therefore, the first two chapters will be dedicated to these subjects.

Circadian system

The internal clock

While most people are not aware of it, human behaviour is rhythmic, for example feeding, activity and body temperature all have rhythms. These rhythms are coordinated by an internal clock. In the absence of time cues, this clock free runs with a rhythm period which on average is slightly longer than 24 hours. To keep synchronized with the world (day/night) entrainment occurs. This entrainment of our circadian clock is accomplished by 'Zeitgebers'. These are environmental cues as light, motor activity and food intake (5) that influence the period and phase of the rhythm to phase-lock it to the external light-dark cycle.

Schematically, the circadian system consists of three elements: the Zeitgebers, the endogenous oscillator in the hypothalamic suprachiasmatic nuclei (SCN), and the pathways coupling the internal clock rhythm to physiology and behaviour (3). Human behaviour is strictly controlled by several clock systems, which are at the molecular level orchestrated by clock genes (6). As explained by Breen et al. clock genes form the molecular machinery of the circadian system (5). They operate via autoregulatory feedback loops, involving proteins BMAL1 and CLOCK (Figure 1 -(7)). These proteins form a heterodimer for regulating the expression of clock-controlled genes. Thereby these proteins drive circadian output. The BMAL1/CLOCK complex activates the expression of Period (*Per 1-2*) and Cryptochrome (*Cry 1-2*) genes by binding to their Enhancer box (E-box). The products of the genes (PER and CRY) act as the opposite factor in the feedback loop and inhibit the activity of BMAL1/CLOCK (5).

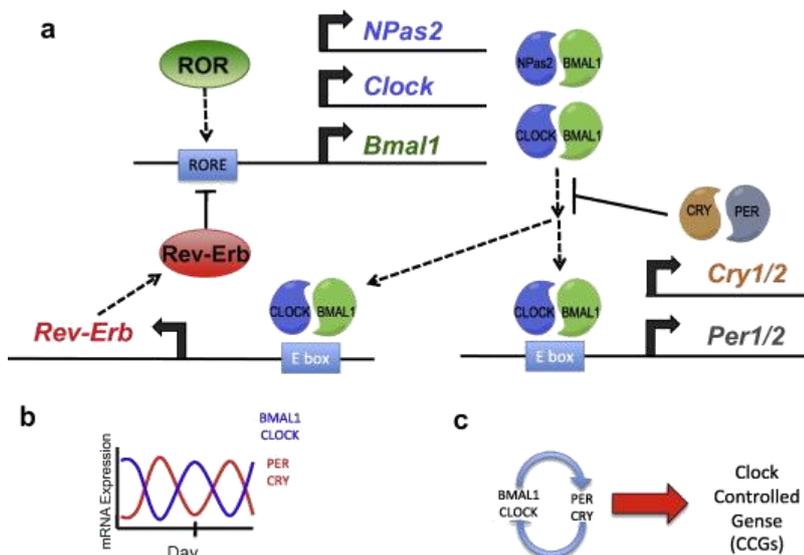


Figure 1 The circadian clock.
a= mechanism of the molecular clock. Illustration of the feedback loops for the maintenance of 24-h oscillations of BMAL1/CLOCK and PER/CRY.
b= antiphase of circadian oscillations of BMAL1/CLOCK and PER/CRY expression.
c= illustration of the relation between core clock and clock-controlled genes. (7)

The heterodimer BMAL1/CLOCK also drives the expression of Rev-Erb α , a nuclear receptor important for repressing *Bmal1* and *Clock* gene transcription by the direct binding to their promoters (7). Another nuclear receptor, ROR (retinoic acid receptor-related orphan receptor) plays a role in the activation of transcription of *Bmal1*. It binds to the same DNA elements as Rev-Erb α (7).

The circadian signals from the SCN reach the peripheral tissues via neural and hormonal mechanisms, and thereby they synchronize circadian oscillations in the entire body (5). Synchronization is necessary because there are several oscillators in the body. Though the SCN is the master clock, together with the other oscillators it forms the circadian timing system (7) (Figure 2 -(8)(7)). Such oscillators are found in many peripheral tissues, as the liver, intestine, heart, adipose tissue, retina and various brain areas (8). The synchronization of these peripheral rhythms is established by the SCN via neuronal connections and secretion of humoral factors, and indirectly by influencing behaviour and therefore rhythmic feeding, activity and body temperature, which coordinate rhythmic gene expression (8).

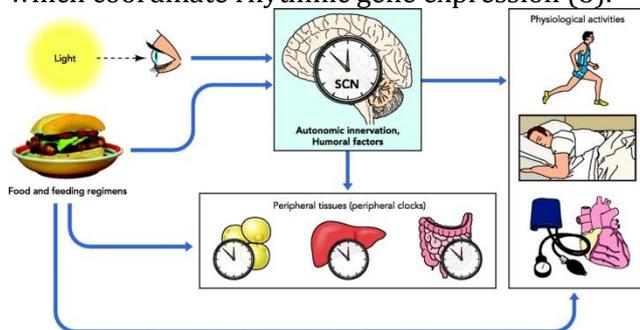


Figure 2 Entrainment of central and peripheral clocks. Light, food, and feeding regimens affect the central clock (SCN) or the peripheral clocks. The SCN synchronizes rhythms in peripheral tissues and physiological activities. (8)

The biological clock in older people is often advanced to an earlier time (9), which makes that they feel the urge to sleep earlier in the evening. Ageing leads to alterations in the output of the circadian clock, leading to a change in phase and decreased amplitude (8). Changes in rhythm are related to alterations in the output of the SCN: the neurochemical and electrophysiological output changes while cell number and size of the SCN stay the same (8). This altered functionality results in a less effective ability to reset peripheral oscillators. The conclusive fact that the aged SCN is the cause of the altered rhythms comes from research. Transplantation of a fetal SCN into aged animals restores diurnal rhythm of hormones and locomotor activity (8).

Melatonin

Melatonin is an important hormone of the circadian system. It is produced in the pineal gland, and the biosynthesis of melatonin is initiated by the uptake of the amino acid L-Tryptophan from the blood by the pineal cells (10). The cells each synthesize and secrete melatonin in the same significant rhythm exhibited by the entire pineal gland (11).

The nocturnal synthesis of melatonin is controlled by the SCN and is inhibited by light exposure (12). The pineal gland receives photic information from the retina transmitted through the SCN and the sympathetic nervous system (superior cervical ganglion) (13). Neural input is norepinephrine, output is melatonin. Since melatonin is under direct control of the circadian clock (SCN), it could be considered as an important efferent hormonal signal from the clock (14). Also because the rhythmic output of the pineal is controlled by the SCN, melatonin profiles can act as an endocrine reporter of the clock mechanisms (5).

Environmental light has a direct influence on the melatonin rhythm. However, it does not cause it, it entrains the rhythm. Day and night light cycles modify the secretion rhythms, pulses of light can abruptly suppress its production (13). The duration of nocturnal melatonin production is proportional to the length of the night (dark period). Changes in duration provide the brain with photoperiodic information (14). In fact, melatonin serves as an endocrine translator of the environmental light-dark cycle. It acts through (for now identified) three different G protein-coupled receptors, MT1-2-3 in different brain areas and organs (11). A high density of melatonin receptors is found in the SCN (11).

Melatonin and dopamine play opposite roles in the regulation of retinal physiology and visual processing (15). Melatonin synthesis in the retina primarily occurs during night, dopamine synthesis during day. Dopamine is important for light adaptation, whereas melatonin has dark-adaptive effects. This mutual feedback loop is probably an important component of the regulation of circadian rhythms in the eye (15).

The timing of endogenous melatonin secretion can be altered by exogenous administration, agonism of specific melatonin receptors in the SCN, and suppression by light and sleep deprivation (16). Resynchronization via manipulating melatonin secretion is an approach in treating depression, for disturbances in circadian rhythms have been associated with it

(16). Furthermore, melatonin has been reported to induce sleep (10,17). Exogenous administration of it, even in a low dose (18), could induce sleep when the homeostatic drive to sleep is insufficient. Melatonin can inhibit the drive for wakefulness and it can induce phase-shifts in the circadian clock (17).

Besides clock genes, melatonin is also responsible for the molecular organization of the internal clock systems at a neuro-humoral level, produced by the neurons of the SCN (6). Research in rats demonstrated the effect of exogenous melatonin on the output of several clock genes in the SCN. Administration of melatonin at dusk leads to up-regulation of ROR β and phase-advancement of Rev-Erba (Figure 3 -(12)) (12). This illustrates the effect of melatonin on clock genes and indicates a possible mechanism of the effect of melatonin on clock genes in humans. Because of the effect of melatonin on the SCN, melatonin can be used for altering the internal rhythm.

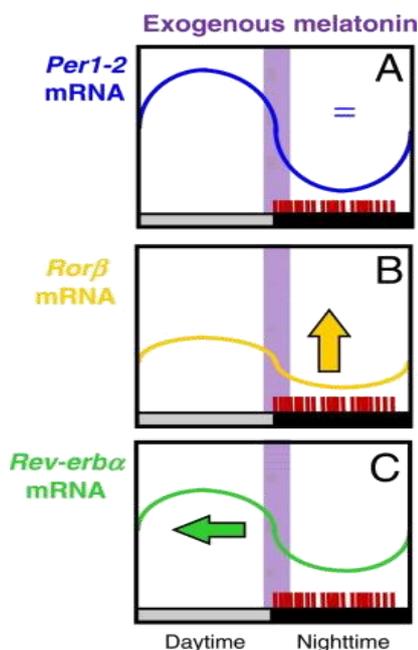


Figure 3 Exogenous administration of melatonin at dusk in rats. Exogenous melatonin affects clock gene expression in the SCN in rats. (12)

Chronotherapy

In all psychiatric disorders chronobiological problems are considered to be the greatest contributors to mood and sleep problems (6). Altering the internal rhythm for therapeutic purposes is called 'chronotherapy'. It is the controlled exposure to environmental stimuli that act on biological rhythms (19). Chronotherapy is based on changing internal rhythms of psychiatric patients. Melatonin can be used as an altering agent. Non-pharmacological chronobiological interventions are sleep deprivation, social rhythm therapies and light exposure (6).

Sleep deprivation therapy

It has been reported that patients with major mood disorders have abnormal circadian rhythms, modulated by the clock gene machinery (20). Chronotherapeutic treatments that alter clock gene processes can rapidly improve the symptoms of the major mood disorder.

Manipulation of the sleep-wake cycle has a rapid effect for depressed mood in approximately 60% of the patients with affective disorders (9,21,22). This manipulation is accomplished by altering the duration of sleep by total or partial sleep deprivation, or changing the timing of sleep via partial sleep deprivation or phase advance (21). The effect of sleep deprivation therapy (SDT) is rapid, but transient (19). SDT probably resets the machinery, however, a recovery night should reactivate the abnormal clock gene machinery (20). By combining this therapy with other chronobiological interventions and drug treatments the effect can be sustained (19), for example by treating bipolar depression by combining sleep deprivation with lithium and light therapy (23).

Light therapy

Bright light therapy (BLT) is used as a first line treatment for seasonal affective disorder, but its possible use in other neuropsychiatric conditions rises according to literature (24). Patients have to sit in front of a 'light box' with a high light intensity for a specific duration, for example light of 10000 lux for 30 minutes. Bright light is supposed to be the strongest entraining agent of circadian rhythms (25). With proper timing a phase-shift of the rhythm can be accomplished. Light in the morning is responsible for a phase-advance, in the evening light administration results in a phase-delay (20). This proper timing of light is strongly related to the endogenous melatonin onset, a proper indicator of the circadian rhythm (26).

As explained in the previous part, the biological clock influences melatonin secretion in such a way that it is rhythmic. Personal specific rhythms can tell something about a persons' chronotype, for instance if the person has evening preference or prefers mornings. The timing of melatonin onset can differ between people by up to six hours. To estimate the time of melatonin onset sometimes the MEQ (Morningness-Eveningness Questionnaire) score is used (26), which is less invasive than taking blood or saliva samples. With the MEQ score the chronotype and therefore the proper timing of light can be determined. Besides the MEQ also the MCTQ

(Munich Chronotype Questionnaire) can be used, which is slightly different than the MEQ, but also effective for determining chronotypes (27). BLT is supposed to be most effective when administered at a time that takes individual chronotype into account (28).

Many elderly are poor sleepers and have probably a disrupted cycle of their circadian rhythms (29). Therefore the disruption of biological rhythms could be the cause of sleep disorders. This could be due to age-dependent functional changes or organic degeneration of the central nervous system, in particular the SCN (29). To sleep problems due to abnormal timing or sleep phase BLT offers a treatment (29). The most common treatment, however, is pharmacological. Efficacy of non-drug interventions has been suggested to be slower, nevertheless, with no risk of drug-related tolerance or dependency (29).

The exact mechanism of action of BLT is unclear. It is almost certainly mediated through the eyes (30), and melanopsin plays a major role. Melanopsin is a short-wavelength light sensitive G-protein-coupled receptor and is situated in a subset of retinal ganglion cells of the eyes. It transduces short-wavelength light signals into neural signals and is primarily responsible for resetting the timing of the SCN, influencing alertness (31) and suppressing pineal melatonin secretion (30).

Chronopharmacology

Besides the use of chronotherapy, patients often also take drugs for their particular disease. Since almost all components of our body exert a certain rhythm, it appears logical to think that pharmacological treatments also need a chronotherapeutic approach. Chronopharmacology is not a therapy like chronotherapy. It does not intentionally alter the internal rhythm, but takes it into account in the current pharmacological treatment.

Response to a drug or a toxic agent depends on the time of its administration (32). Circadian rhythms influence how drugs are absorbed, distributed, metabolized, and eliminated from the body (7). This is schematically visualised in *Figure 4* -(7). To achieve the most optimal pharmacological treatment, circadian rhythms should also be addressed. Circadian-controlled release or delivery of therapeutics could enhance the efficacy of the treatment (7).

Parkinson's Disease

Before discussing chronotherapeutic aspects in Parkinson's Disease (PD), it is necessary to introduce the major symptomatology of PD. PD is an age-related neurodegenerative disorder. There are two forms of the disease, an inherited form and a sporadic or idiopathic form. In general, onset before an age of 20 years is considered juvenile-onset PD, before the age of 50 years early-onset PD, and after the age of 50 years is late-onset PD (33).

Motor symptoms

PD is characterized by tremor at rest, rigidity, bradykinesia (slowed movement) and in a more severe state postural instability (33). The onset of PD is classically unilateral. Involuntary abnormal movements as postural or action tremor and limb dystonia can also occur (33). The diagnosis of PD is made based on the patient history and physical examination (34). There is variability between patients, for approximately 20% of the patients do not exhibit a typical rest tremor (34). A very conclusive fact for the diagnosis of PD is the significant clinical response to dopaminergic therapy, if this response lacks, another diagnosis should be found. For diagnosing PD also PET and SPECT imaging can be used (34). Motor complaints can be experienced by the patient, while the neurological exam is still normal (35).

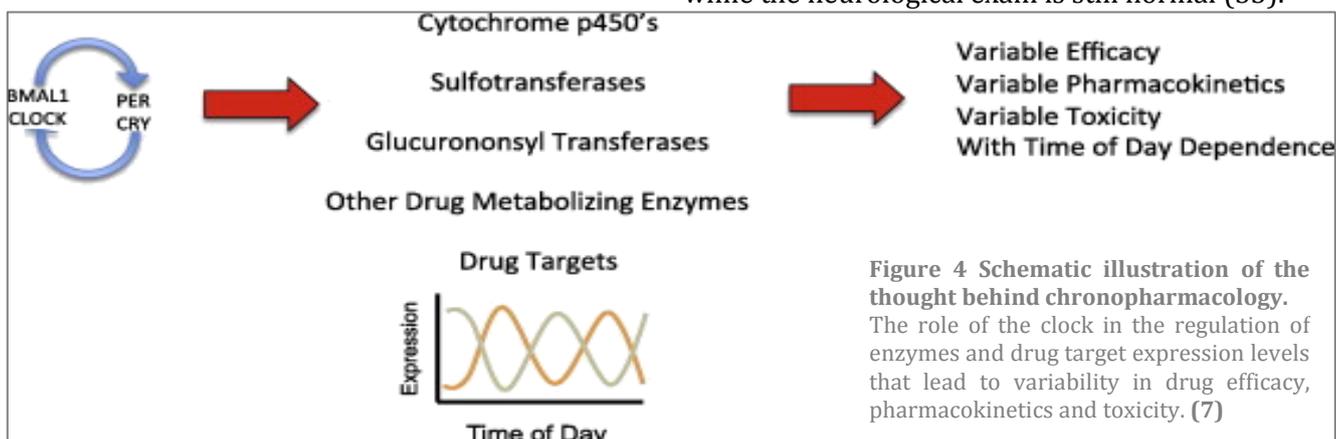


Figure 4 Schematic illustration of the thought behind chronopharmacology. The role of the clock in the regulation of enzymes and drug target expression levels that lead to variability in drug efficacy, pharmacokinetics and toxicity. (7)

Non-motor symptoms

Besides the typical motor effects of PD, non-motor symptoms are also important (36). There is a variety of existing non-motor symptoms in PD. Neuropsychiatric symptoms as depression, psychosis and dementia, autonomic features as orthostatic hypotension, excessive salivation, bladder dysfunction, gastrointestinal disturbances, somatic and sensory problems, and sleep disorders occur (37). About 90% of all PD patients experience non-motor problems because of their disease (36). These problems have a huge impact on the quality of life of PD patients, maybe even stronger than the typical motor symptoms.

The effect of PD on non-dopaminergic neurons can account for many non-motor symptoms (35). The antiparkinsonian pharmacotherapy can have side effects which also can induce non-motor symptoms, for example hallucinations, daytime sleepiness and leg oedema (36). Non-motor symptoms could show even before motor complaints arise (35).

Sleep problems

Sleep problems are very common among PD patients, research states that 60-90% of all patients report having problems with sleep in a particular way (3,5). Increased sleep latency, reduced sleep efficiency, sleep fragmentation, restless leg syndrome, reduced rapid eye movement sleep, excessive daytime sleepiness and insomnia are all problems PD patients can have (5). These problems even can precede the onset of PD by years (3). It has also been reported that PD patients can have a sustained elevation of serum cortisol levels, reduced melatonin levels, and altered *Bmal1* expression (5). The abnormal sleep in PD patients could relate to alterations in the circulation of relevant proteins and hormones. The origin of these sleep problems varies: the association with dopaminergic dysfunction could form the basis, but problems also can arise because of non-dopaminergic PD pathology or because of the treatment patients get (38).

Depression

Depression in various forms (major-minor) is common in PD (36). Approximately 30-40% of the patients have significant depressive symptoms (39). Since features of depression are very similar with certain symptoms of PD, such as psychomotor retardation, anhedonia and sleep disturbance, it is hard to know whether these features can be attributed to an intrinsic depression or whether it is connected to PD (36). Conversely, depressive symptoms could precede

the onset of motor symptoms in PD and would present itself as a clinical depression, therefore screening for PD in depressive patients could be advantageous (36).

The depression feature of PD could be endogenous or exogenous (40). Exogenous as a subjective reaction to being diagnosed with PD, a chronic disease without a cure, or endogenous caused by the disease process via neurological changes and underlying brain dysfunctions. Depression in PD as a result of neurodegeneration involves changes in three pathways: dopamine (D₂), noradrenalin, and serotonin (40). A specific loss of dopamine and noradrenaline innervation in the limbic system is associated with depression and anxiety in PD (41). Another explanation for the depression can be the treatment of PD, antiparkinsonian medication (40). Late stage fluctuation in response to Levodopa are accompanied by changes in mood, called "on-off" phenomena, and at least two thirds of the patients with PD experience these symptoms. During off-periods patients even could be diagnosed with a major depression. The highest frequencies of depression in PD are in the early and late stages, suggesting that the depression is due to a combination of exogenous (diagnosed with PD) and endogenous (progress of brain dysfunctions) reactions in PD (40).

Location

Patients suffer from their symptoms because of neurodegeneration in the brain. This degeneration does not occur randomly in the brain, but specific locations are preferred. The 'basal ganglia' refers to a group of subcortical nuclei in the brain (striatum: caudate nucleus and putamen, globus pallidus, substantia nigra, nucleus accumbens, subthalamic nucleus). They are primarily responsible for motor control, but also for motor learning, executive functions and behaviours, and emotions. Disruption of the basal ganglia network is the basis of several movement disorders (42).

PD is the primarily result of death of dopaminergic neurons in the substantia nigra (35). Neuronal dysfunction and cell death lead to the depletion of the neurotransmitter dopamine in the striatum, a central component of the basal ganglia, consisting of the putamen and the caudate nucleus. This region is responsible for the initiation of control of movements (1).

Hallmarks of PD are the loss of the nigrostriatal dopaminergic neurons and the presence of intraneuronal proteinaceous cytoplasmic inclusions, named Lewy Bodies (35).

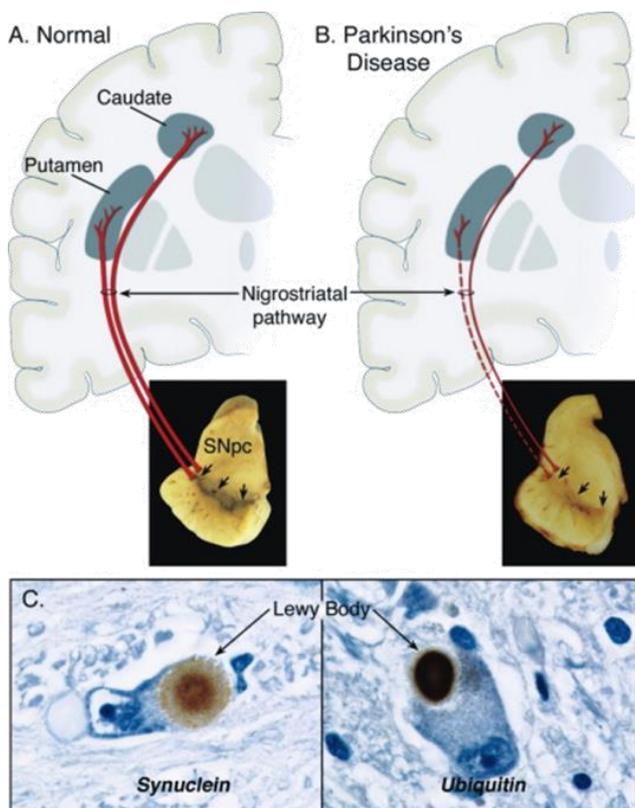


Figure 5 Affected location in PD.

A= normal nigrostriatal dopaminergic projection from the substantia nigra pars compacta (SNpc) to the striatum.

B= impaired projection in PD. Loss of these neurons (which contain neuromelanin) results in depigmentation.

C= staining of Lewy Body components. (35)

In the substantia nigra pars compacta (SNpc) are the cell bodies of nigrostriatal neurons which primarily project to the putamen (Figure 5 -(35)). Mesolimbic neurons arising from cell bodies adjacent to the SNpc in the ventral tegmental area (VTA) are much less affected in PD. Therefore the depletion of dopamine is much less in the caudate (35). PD is an age-related disease. However, the pattern of neural loss is different from the pattern seen in normal aging (35). In PD, cell loss is concentrated in ventrolateral and caudal portions of the SNpc. During normal aging the dorsomedial part of the SNpc is affected. Ageing is the most important risk factor for PD (43). Biochemical changes because of aging aggravate the abnormalities in a PD brain.

PD is characterized by loss of dopaminergic neurons, though neurodegeneration extends beyond dopaminergic neurons (35). Neurodegeneration and Lewy Body formation are found in noradrenergic (locus coeruleus), serotonergic (raphe nuclei), cholinergic (nucleus basalis of Meynert, dorsal motor nucleus of vagus nerve) systems, cerebral cortex (cingulate and entorhinal cortices), olfactory bulb, and the autonomic nerves system. The high rate of

dementia among PD patients can be explained by degeneration of hippocampal structures and cholinergic cortical inputs (35). Patients can develop depression months or years before the onset of PD motor symptoms, this can be related to early involvement of non-dopaminergic pathways, which are clearly also important pathways in PD.

Dopamine

The synthesis and degradation of dopamine (DA) in the brain takes place where it is present as a neurotransmitter. For instance, in the nigrostriatal system, mesolimbic system and retina (10). The DA-catabolic enzymes as MAO (monoamine oxidase) and COMT (catechol-O-methyl transferase), are logically in the same regions.

DA is stored in presynaptic vesicles and is released by an action potential in the nerve. The neurotransmitter has an effect on different receptors, though specific for DA. Effects of DA stop when it is transferred with uptake mechanisms or when it is metabolically degraded (10).

At several levels of the circadian system dopaminergic neurotransmission is represented (44). The first level is that of the photic input pathway to the clock. DA plays an important role in light adaptation in the retina, and it regulates the rhythmic expression of melanopsin, related to circadian entrainment. Dopaminergic amacrine cells in the retina express circadian rhythms in clock genes as *Per*, *Cry*, *Clock* and *Bmal1* to anticipate changes in environmental illumination and adapt the tissue for the most optimal photic response (44). DA also has an effect on the phase and amplitude of clock genes. In return, clock genes also play a role in dopaminergic metabolism, for example the *Clock* gene regulates its activity in the VTA. In the promoter regions of the dopamine active transporter (DAT), D1a receptor, and tyrosine hydroxylase (TH) genes an E-Box element is situated as the target of the molecular clock (44). Dopaminergic activity and metabolism can be considered to be an output of the circadian clock, for DA metabolism exhibits a diurnal rhythm in striatal regions partially due to cyclic variations of DAT, DA receptors and TH. SCN lesions demonstrate that the SCN is at least partially responsible for cyclic day/night differences in DAT and TH expression in several regions in the brain (44).

Etiology

For the etiology of PD environmental factors and genetic factors could contribute, however, the specific etiology is not known. A number of toxins have been associated with the development of parkinsonism (clinical state referring to motor complaints as seen in PD). However, no specific toxin has been found in the brain of PD patients. Evidence for an environmental factor in PD relates to the toxin MPTP (1,2,3,6-methyl-phenyl-tetrahydropyridine) (2). It is a by-product of a synthetic meperidine derivative. Drug addicts who took MPTP developed a syndrome what resembled PD in the clinical and pathological way. Neurotoxin based models (MPTP) helped elucidate the molecular cascade of cell death in dopaminergic neurons (35). Epidemiological research indicates that rural living, pesticide use, well-water consumption, mining and welding, are associated with an increased risk of PD. However, no specific agent has been identified for causing PD (1). Night shift work seems to be protective against PD, and habitual longer sleep an early marker of PD (45). Males are more affected than females, but whether this reflects workplace exposure, sex-linked genetic variability or perhaps a protective effect of oestrogen, is not known (1).

It took a long time to unravel the genetic basis for PD. Now multiple mutations in at least seven genes have been described in families with a Mendelian pattern of PD inheritance (1). Mendelian forms of PD are inherited as autosomal dominant, autosomal recessive, or rarely, X-linked. However, also the non-Mendelian manner could play a role in the emergence of PD (33). In this manner, effects of genes and environmental risk factors could both be accounted for. The discovery of PD genes has led to the hypothesis that misfolding of proteins and the dysfunction of the ubiquitin-proteasome pathway are a key in the PD pathogenesis. Another hypothesis states that mitochondrial dysfunction and oxidative stress (including toxic oxidized DA species) are the key for the pathogenesis. However, it probably would be an interaction between both (35). For example oxidative damage to α -synuclein can enhance the misfolding and accumulation of misfolded proteins.

Misfolding and aggregation of proteins

Aggregated or soluble misfolded proteins can be neurotoxic in various ways (35). They could cause direct damage, for example via deforming the cell or interfering with intracellular processes. Also they could affect proteins important for cell survival, however, no correlation in PD between

Lewy Bodies and cell death is reported. Pathogenic mutations probably directly induce abnormal toxic protein conformations or indirectly interfere with processes that recognize or process misfolded proteins (35). This is seen in patients with inherited PD. In sporadic PD direct protein-damaging modifications and the indirect contribution of dysfunctions of chaperones or the proteasome to the accumulation of misfolded proteins is probably the cause of PD. Oxidative stress could be a trigger for this process (35).

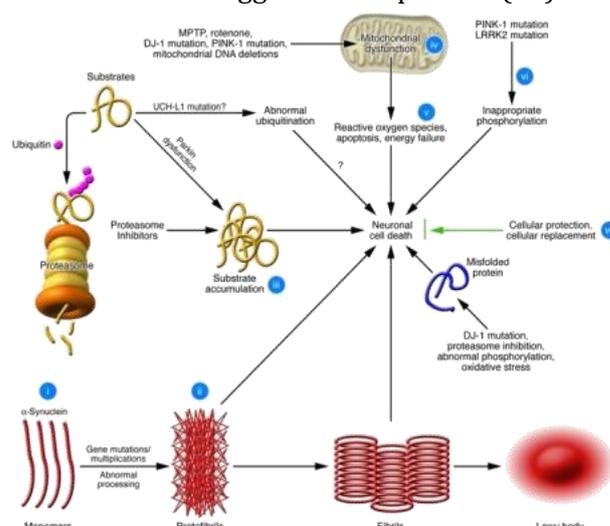


Figure 6 Pathways leading to neuronal cell death in PD. (34)

Pathways leading to neuronal cell death in PD are visualized in Figure 6 -(34). Lewy Bodies contain oxidatively modified α -synuclein which has a greater propensity to aggregate. Chaperones should refold the misfolded proteins, but when the desired structure cannot be accomplished, proteins are targeted for proteasomal degradation by polyubiquitination (35). Besides α -synuclein in Lewy Bodies also parkin plays an important role in PD. It is an E3 ligase with the function of adding ubiquitin molecules to target proteins for proteasomal degradation (34). Loss of parkin results in the abnormal accumulation of toxic substrates and eventually cell death. Therefore mutations in the *parkin* gene cause an autosomal-recessive form of early-onset PD. Important to take into account is the age-related diminished ability of cells to handle misfolded proteins. The activity of the proteasome is decreased and the ability of cells to induce various chaperones is impaired. Excess of misfolded proteins inhibit the proteasome even more, creating a vicious cycle (35).

α -Synuclein is the prominent structural component of Lewy Bodies (34). It is present in aggregated and insoluble filaments that are hyperphosphorylated and ubiquitinated. A mutation for α -synuclein, oxidative stress,

phosphorylation, mitochondrial and proteasomal dysfunction and DA can affect the folding of α -synuclein into protofibrils, fibrils and filaments. The first two are the most toxic forms (34). However, the research of Xu et al. indicates that soluble 54-83-kD α -synuclein protein complexes mediate neurotoxicity, not aggregated α -synuclein corresponding to fibrillar or protofibrillar forms (46). According to their research α -synuclein rather has neuroprotective properties, but in dopaminergic neurons it is toxic. The accumulation of α -synuclein requires endogenous DA production and is mediated by reactive oxygen species. Their research indicates that the selectively lost dopaminergic neurons in PD can be associated with this soluble protein complex with α -synuclein and '14-3-3 protein', which is elevated in the substantia nigra.

Conventional therapy

Motor symptoms

For over 40 years Levodopa is the standard drug treatment of PD (47). It is associated with the largest improvement in motor function, compared to other dopaminergic therapies. The key in the treatment is DA replacement (2). Levodopa, or L-dopa, is the precursor for this neurotransmitter. Though L-dopa is the most effective drug for the treatment of PD, long-term use is complicated by highly disabling fluctuations and dyskinesias (48). Therefore, in the beginning of the disease practically all patients benefit from this medicine, but after 5-10 years it generates problems (2). The majority of the patients develop adverse Levodopa-related motor complications (LDRMCs) (49).

There are many existing therapies using, besides L-dopa, adjunct drugs to enhance the effect of it. For example: selective MAO-B inhibitors, which reduce the metabolic breakdown of L-dopa and therefore extend the duration of action, and COMT inhibitors, which enhance the bioavailability of L-dopa (50).

Before the rise of Levodopa as standard treatment for PD, surgical procedures were used (51). A common technique was the pallidotomy, but this technique was rapidly replaced in the late 90s by deep brain stimulation (DBS), mainly because of the adverse effects of the lesions and irreversible effects from poorly placed lesions (51). In DBS an electrode is placed in a certain brain region, and there it electrically stimulates this region. Possible regions are the subthalamic nucleus, pallidum and thalamus (50). The subthalamic nucleus is the most common location for DBS electrode placement (51).

Non-motor symptoms

Pharmacotherapy of non-motor symptoms in PD is complicated (37). This, because of possible drug interactions, side effects and changes in metabolism of the current antiparkinsonian treatment. Moreover, the antiparkinsonian drugs can contribute to the onset of non-motor symptoms in PD.

Sleep Problems

The initial treatment option for sleep disturbances is to avoid the use of alcohol, caffeine and nicotine (37). What kind of drugs can be used depends on the sort of sleep disturbance a patient suffers from (36). Various DA agonists can be effective in treating restless leg syndrome. Another problem patients can suffer from is rapid eye movement sleep behavioural disorder (RBD). An effective treatment for RBD is the drug Clonazepam (benzodiazepine). Also melatonin has been reported to be effective for RBD. The prevalence of excessive daytime sleepiness (EDS) in PD patients is 15 to 50% and is possibly related to the dose of dopaminergic medication (36). Therefore, usage of this drug should be reduced if possible. After reduction, modafinil (200 mg/day) can be an effective treatment for EDS (36). Depression, a frequent psychopathological feature of PD, can be accompanied by sleep disorders, and therefore treatment for the depression instead of the sleep problems is logical (37).

Depression

According to Veazey et al., three common suggestions are stated in literature for the best clinical practice in treating depression in PD (40). The first suggestion is to treat the patients PD symptoms optimally with antiparkinsonian medication before treating the actual depression, for that could be sufficient enough. After achieving the optimal treatment, a specific treatment for the depressive symptoms could be added (40). It could also be important to determine whether depression and anxiety symptoms occur solely in off-periods. If so, adjustment of antiparkinsonian medication is required and usually successful (39). If symptoms are not due to non-motor fluctuations, the severity should be determined to evaluate the need for treatment (39). The second suggestion is the immediate use of antidepressant medication like SSRIs and TCAs as a specific treatment for the depression (40). The third suggestion is psychosocial support and behavioral therapy, for it should minimize stress and increase the quality of life (40). Mostly when suffered from mild depression, non-pharmacological

interventions are used (39). Electroconvulsive therapy is a treatment of last resort (40).

There are some concerns about using medication to treat the depression in PD (40). These drugs could have adverse neurological side effects and interactions with the antiparkinsonian medication, inducing more motor effects, hallucinations, mental changes and other symptoms.

Circadian system

For almost two centuries the involvement of the circadian system of the body in various aspects of PD is recognized, however, never really charted, according to Willis et al. (4). Patients with PD often experience less motor symptoms in the morning, and they worsen during the afternoon and evening (32). Clinical and experimental studies demonstrated daily fluctuations of clinical (motor activity, autonomic dysfunctions, sleep disorders) and biological (catecholamines, cortisol, melatonin) factors in PD (32). These diurnal fluctuations of motor and non-motor symptoms and a high prevalence of sleep-wake disturbances suggests an influence of the circadian system in modulating these symptoms (44).

Besides, PD is also described as an endocrine disorder of melatonin hyperplasia. The RDMP (retino-diencephalic/mesencephalic-pineal) axis is suggested to be activated during the course of PD and during therapeutic interventions (4). Parts of the RDMP axis probably undergo neuropathological changes and neurotoxicity associated with melatonin is encountered. Melatonin tends to induce PD-like behavioural toxicity. It has adverse effects on motor function, induces hypotension, depression, insomnia, and has biochemical effects when administered. These are all important features for the proposal to introduce melatonin as an adjuvant in the treatment of PD (4).

Circadian fluctuations of symptoms in PD could be caused by fluctuations in pharmacokinetics of drugs used for the treatment (32). Fluctuations of L-dopa kinetics and its main metabolites, according to time of day of administration, have been documented in rats (32). Furthermore, DA replacement, the key in the current treatment for PD, probably is effective because of its effect upon the circadian system, rather than simply replacing deficient DA (4). Alterations of the biological rhythms observed in PD may be considered the cause or consequence of the disease (32).

Melatonin

A study of 20 patients with PD demonstrated that they have blunted circadian rhythms of melatonin secretion compared with controls (44). Also the amplitude of the melatonin rhythm and the overall circulating level was lower in PD patients. Patients also enduring EDS had an even lower amplitude and level of melatonin. Therefore, circadian dysfunction may underlie EDS in PD (44).

Another study demonstrated a significant phase advance in plasma melatonin secretion in patients receiving dopaminergic treatment compared with untreated patients (49). Patients with also LDRMCs had an increased level of melatonin during the day, and a decreased level during the night, suggesting that the pattern of melatonin secretion was altered in these patients (49). A phase advance of the nocturnal elevation of the melatonin level has been demonstrated in L-dopa treated patients, but not in 'new' untreated patients (49). Therefore, L-dopa could modify melatonin secretion. LDRMCs may be influenced by changes in melatonin secretion, for melatonin also exerts direct motor effects through interactions with DA and serotonin pathways (49). Melatonin administration increases dopamine D₂ receptor sensitivity, therefore endogenous melatonin could be involved in altering D₂ receptor sensitivity (49). However, this involvement of melatonin in LDRMCs has not been investigated (49).

Chronotherapy and Parkinson's Disease

To find an answer to the main question if chronotherapy is effective for Parkinson's Disease, the therapeutic features in combination with PD characteristics should enlighten a lot. Therefore, the chronotherapeutic interventions are assessed again, but now in the context of PD.

Sleep deprivation therapy

Already in 1987, Bertolucci et al. performed a study with twelve PD patients subjected to one night of total sleep deprivation (52). An improvement of rigidity, bradykinesia, gait, posture disturbances, and functional disability remained for two weeks. Also in depressive symptoms an improvement was perceived, lasting for one week. They explain this by the possible change of dopaminergic receptors, induced by sleep deprivation.

Another pilot study with 35 patients with parkinsonism demonstrated a reduction of rigidity, bradykinesia, gait, and the total score of the patient's condition severity after one night of total sleep deprivation (53). Total sleep deprivation also proved to be antidepressant.

In 1993 Perry et al. deduced that SDT may be attributing to enhanced activity of DA in the dopamine-depleted VTA, and therefore SDT might be beneficial for a subpopulation of depressed patients (54). Since it is a well-tolerated and safe procedure, it does no harm using it (54).

From 1995 onwards, studies consequently show the positive effects of total sleep deprivation on motor functions, but merely focus on proving the mechanism behind it, for they already accept the positive relationship (55,56). It could be the suppression of cholinergic activity, which is thought to be excessive in depression and PD (56), or the light adaptive changes in the retinal pigment epithelium might have something to do with it, where SDT improved motor symptoms correlate with increases in light adaptive retinal epithelium potentials (55).

However, findings about the effect of sleep deprivation on motor symptoms are not consistent. Högl et al. (2001) only found that 4 of the 15 nondepressed patients improved their motor score after partial sleep deprivation, and none after total sleep deprivation (57). This indicates that there is not an overall positive influence of sleep deprivation on motor function, maybe that there are different responses to different types of SDT and that only a subgroup of patients could benefit of it (57).

The discussion about the effect of SDT on PD has been raised earlier, for in 1994 Lauterbach said that SDT aggravates the symptoms of PD, possibly via reducing DA synaptic availability (58). Sleep may improve PD symptoms by replenishing presynaptic DA stores, therefore sleep deprivation could aggravate symptoms by reducing DA availability. However, L-dopa related depression could be reduced by this hypodopaminergia, since it enhances synaptic DA availability (58), but only 3-4% of PD patients suffer from this form of depression (58). SDT-induced hypodopaminergia might increase the number of off-periods leading to more depressive episodes (58), and therefore caution is required in considering antidepressant SDT for PD patients (59).

Light therapy

Besides SDT, also several studies are performed to examine the effects of BLT on PD. Paus et al.

assessed the effects of BLT in 36 patients (60). Results indicate that BLT improves depression, sleep, tremor, and induces better results in the UPDRS (Unified Parkinson's Disease Rating Scale) I, II, and IV, respectively 'mentation, mood, behaviour', 'activities of daily living', and 'complications of therapy'. However, the better result on depression did not correlate with UPDRS I and II (60), therefore the effects of BLT on behaviour and daily functioning can be seen as independent of changes in mood (28).

BLT has a positive effect on the accompanied depression in PD (26). Furthermore, together with this antidepressant effect motor functions also improve (26). Because of the presumed advanced melatonin rhythm, late evening light exposure (1000-1500 lux), which phase-delays, proved helpful in a part of the patients with PD, with a reduction in bradykinesia and rigidity (26). This phase advancement could probably be related to the fact that PD is an age-related disease and ageing often leads to phase-advancement. Although patients are phase advanced, insomnia is prevalent. Surprisingly, evening light reduces sleep onset latency (26).

Mostly BLT aims to diminish a depressive disorder, but often improvement of sleep is accompanied with the antidepressant effect (29). Literature suggest that monotherapy of BLT is effective in improving sleep efficiency and quality, and in reducing daytime sleepiness in PD, however, sometimes exogenous melatonin administration is required to obtain the desired reaction (28). Melatonin administration has little improving effects on sleep time, but to what extent this is clinically helpful is not known (61). Subjective sleep improvement, however, may even occur without objective improvements (61). Yet, according to Zesiewicz et al., melatonin did not improve motor symptoms in patients with PD, and therefore cannot be recommended as a complementary therapy for motor symptoms in PD (61). In the context of melatonin being toxic, antagonizing it with BLT has a therapeutic value in treating the symptoms of PD (4). BLT in 60-90 minutes before bedtime suppresses night-time melatonin secretion and this could have improving effects on motor symptoms (61). Willis et al. made use of this technique in a study with twelve PD patients, where they found that patients improve the onset and continuity of sleep, have an elevated mood, have a reduced impotence, and an increased appetite (62).

In a retrospective study of Willis et al. monitoring 129 patients, the patients were divided by means of compliance (63). The most

adherent group reported the best results to BLT: significant improvement of bradykinesia, rigidity, balance, and motor tests. Overall depression improved, but in the compliance group the most. Nevertheless, the possible improvement in depressive symptoms could be assigned to the improved motor symptoms. For example, some motor symptoms as psychomotor retardation are also a component of depression (28). Besides, improved motor symptoms also can contribute to alleviation of the depression. Yet, Paus et al. demonstrated a lowered depression in patients without improvement in motor function (60). This indicates the positive influence of BLT on depression, independent of motor score.

Under BLT patients even can lower their dopaminergic medication and symptoms do not worsen (26). This is an important feature considering the long-term adverse reactions to L-dopa.

Chronopharmacology

Frequently diurnal differences in reaction to L-dopa have been described by PD patients (32). Duration and quality of motor response differs over the day. However, few studies have been devoted to find the influence of the moment of administration of antiparkinsonian drugs and their response.

A small study with 5 patients complaining about diurnal variations to L-dopa was executed by Frankel et al. in 1990 (64). Under controlled conditions, the response to L-dopa did not change with the moment of administration.

Bonuccelli et al. (2000) performed a study with 52 patients, administering standard medicine doses at 8:00 a.m., 12:00 noon, and 4:00 p.m. (65). Motor activity was measured in a period of 3 hours after each L-dopa dose. In newly diagnosed patients no diurnal changes in motor score occurred during the day. Stable patients and patients with off-periods experienced daytime worsening of motor symptoms. The suggestion, however, is that the diminished motor response to afternoon and evening doses of L-dopa in patients with long-term L-dopa therapy, does not relate to the pharmacokinetics of the drug. Possibly it is the occurrence of tolerance to repeated doses of L-dopa (65).

According to Bruguerolle et al. (2002) several studies indicate that responses to drugs can be dependent on the hour of administration, but the current available chronopharmacological data on DA, kinetics of L-dopa, and diurnal differences in motor response to L-dopa are not

sufficient to support L-dopa administration according to a circadian profile (32).

Discussion

The previous chapter 'Chronotherapy and Parkinson's Disease' gave an overview of studies performed in the context of chronotherapy in PD. The general findings are outlined in the upcoming two paragraphs.

In the context of SDT and PD, Levin (53) and Bertolucci et al. (52) demonstrated improved motor symptoms and depressive symptoms, and Perry et al. (54) saw the importance for SDT in treating depressed PD patients. From 1995 onwards, studies no longer investigate the effect of SDT in PD motor symptoms, but they already focus on the mechanism behind it. However, Högl et al. (57) found no overall positive influence of SDT on motor function, only partial SDT and a subgroup of patients probably benefit of it. Lauterbach (58) is not positive at all, according to him SDT just aggravates PD symptoms.

The common view about the use of BLT for PD is that it is helpful in all symptomatic aspects of PD. Paus et al. (60) demonstrated success in motor symptoms, depression and sleep problems, Rutten et al. (28) showed the importance for EDS, Terman (26) for the depression, motor symptoms, and insomnia. According to Zesiewicz et al. (61) even exogenous melatonin has little improving effects for particular sleep problems accompanied in PD. However, he does not recommend it for motor symptoms. Willis et al. (62) showed improvement in every symptomatic aspect after BLT. In the retrospective study of Willis et al. (63) BLT proved important for motor symptoms and depression. The chronopharmacological approach in PD seems not to be relevant, because the moment of administration of L-dopa does not seem to make a difference in response to it. Bonuccelli et al. (65) reported a diminished response to it later the day, however, that probably is the result of tolerance to repeated doses of L-dopa.

Unfortunately, there are only few studies involving chronotherapy in PD, so a very conclusive answer to my main research question cannot be given. Based on the current literature I tend to answer 'Yes' to the question 'Is chronotherapy effective for PD?'. However, it is understandable that this answer is not as explicit as it seems. To start with, it is not clear if any form of chronotherapy slows the natural progression of PD. Since neurotransmitter secretion of DA is modified, it could be that this has a positive (or

negative) influence on the progression of PD, however, from research this not becomes clear. To find out to what extent chronotherapy is beneficial for PD, this is an important feature to examine. Probably longitudinal studies are necessary, but also quantitative experimental studies focussed on the brain and neurotransmitters would be useful to examine the long-term effects of chronotherapy on PD and for finding out if the natural progression slows.

Since research about sleep deprivation in PD is scarce and dates back many years, it is necessary to devote more studies to this topic. Lauterbach (58) is the only one in literature really stating that SDT in PD patients is not wise, other studies have demonstrated good results. Therefore, I tend to believe that SDT has above all a positive effect, at least on motor symptoms in PD, but also depression seems to attenuate. Still, I think no strong conclusions can be drawn from so few studies.

Even the most abundant non-motor features as depression and sleep problems are not currently targeted in the chronotherapeutic management of PD. At least, in literature it does not seem that handling the specific form of that accompanies PD, nor diminishing sleep problems, is the primarily target. Mostly, improvement of these features is seen as secondary to improvement in motor function.

Since depressive disorders are currently targeted with chronotherapeutic interventions as SDT and BLT, it is logical to think that these interventions could have positive effects for the depression in PD as well. Although such an effect has been shown, in the current literature no study seems to fully aim on treating the PD depression. The same applies for the sleep problems. In general, there are not many studies on the effect of BLT for sleep disorders, and even less for sleep disorders in PD, while this probably is an effective non-drug therapy. Therefore this effect should be investigated. The same goes for SDT, which does not seem to be researched in the context of sleep disorders, nor sleep disorders in PD.

Patients with LDRMCs probably have altered melatonin levels. L-dopa treatment changes melatonin secretion and LDMRCs could be influenced by these changes. Because this involvement of melatonin in LDRMCs has not been investigated and there is an indication of a relationship between both, it seems important to dedicate research to this possible feature of PD.

Besides Bruguierolle et al. (32) not many research groups seem to have investigated the importance of chronopharmacology in PD. Their

research is being cited, but not extended. Bonuccelli (65), Frankel (64), and Bruguierolle (32) et al. all state that the chronopharmacological approach of L-dopa in PD is not a relevant approach. However, I find this hard to believe. Since it is known that circadian rhythms influence how drugs are absorbed, distributed, metabolized, and eliminated from the body, this must also be the case for L-dopa. Besides, a conclusion made on so few studies cannot be called a significant conclusion. Further studies have to investigate the chronopharmacological approach in PD. It could indeed be that it is not very helpful for motor symptoms, but maybe non-motor symptoms could benefit of it. To even consider a chronopharmacological approach in PD, the exact rhythm of DA should be known. This must be examined in healthy people, PD patients, and newly diagnosed patients, for the rhythm of DA could be different between these groups. When the exact DA rhythm is known, the rhythm of administration in the 24-cycle can be determined in order to mimic the endogenous DA secretion.

Conclusion

The general answer to the question 'Is chronotherapy effective for PD?' is positive. The overall effect of BLT seems to be very good. To motor symptoms and non-motor symptoms in PD, studies concluded that BLT is helpful. Nobody really questions the positive effect of it in PD. About SDT is more discussion. Positive effects on depressive symptoms and motor symptoms have been reported, however, this is possibly only beneficial for a subgroup of patients. In contrast, it even could be that SDT aggravates PD symptoms. Although the effect of SDT is debatable, I think that this therapy is useful for motor symptoms and depression, and since it appears to be well-tolerated and safe, it does no harm using it. Furthermore, the only feature that does not really seem relevant in PD is the chronopharmacological approach. However, the current knowledge about drug metabolism in a circadian manner strongly suggests that this statement is incorrect.

It is clear that many aspects in PD are related to our circadian clock. The altered clock can be the consequence or cause of the disease. Antiparkinsonian medication also can influence the clock. Altering the circadian clock in such a way that it is beneficial in PD, is not a conventional therapy. However, the demonstrated relationship between the altered biological rhythms and PD indicates that chronotherapy could be helpful in patients with PD.

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