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Role of orexin in pathogenesis of neurodegenerative parkinsonisms

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ABSTRACT

Introduction. The pathogenesis of parkinsonisms is not fully understood. Among possible factors which may influence the course of neurodegenerative diseases, endocrine abnormalities may be interpreted as having been underevaluated.

State of the art. Growing interest is associated with the role of neuropeptides such as orexin. Orexin is a neuropeptide produced by orexigenic neurons in the lateral parts of the hypothalamus and is linked with excitement, wakefulness and appetite. An extended analysis of this neuropeptide might answer whether changes in the metabolism of orexin is more likely to be a cause or a consequence of neurodegeneration.

Clinical significance. Orexin is a neuropeptide produced by orexigenic neurons in the lateral parts of the hypothalamus and is linked with excitement, wakefulness and appetite. The aim of this study was to discuss the role of this factor and its abnormalities in the pathogenesis and course of parkinsonian syndrome.

Future directions. Understanding the role of orexin in these diseases may be interpreted as an important feature in evolving therapeutical methods. Further evaluation based on larger groups of patients is required.

Key words: parkinsonism, orexin, Parkinson's Disease, hypothalamus, PSP

Introduction

Parkinsonisms are a relatively wide group of diseases of which Parkinson's Disease (PD) is the most common. Among other entities associated with this group, Dementia with Lewy Bodies (DLB) and atypical parkinsonisms such as Progressive Supranuclear Palsy (PSP), Corticobasal Syndrome (CBS) and Multiple System Atrophy (MSA) can be mentioned. The pathogenesis of these diseases is not fully verified [1–3]. However, growing interest is associated with the impact of endocrine abnormalities. Dopamine, of which a deficiency is characteristic for Parkinson's Disease (PD), is an important neurotransmitter that regulates hormone secretion. Due to the fact that both normal hormonal cells and tumour cells have receptors for dopamine, it can be assumed that abnormal levels of dopamine associated with Parkinson's Disease, as well as with its treatment, could potentially cause endocrine disorders.

Endocrine abnormalities in parkinsonisms

Currently, there are few prospective publications on long-term treatment with dopamine agonists and its effect on hormonal balance [4–7]. Based on the literature, in untreated patients diagnosed with Parkinson's Disease, there are no

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significant disorders in the basal secretion of anterior pituitary hormones- prolactin [8], thyroid-stimulating hormone [8], luteinsing hormone [9], and follicle-stimulating hormone [9]. The role of hormones contributing to non-motor PD symptoms is not fully understood, although a study has indicated cortisol and melatonin to be possible factors impacting upon these elements of clinical manifestation of PD [10]. In the context of melatonin, sleep disturbances and gastrointestinal dysfunction have been described as features negatively correlated with plasma melatonin concentrations [11].

Furthermore, Aziz et al. [8] found normal levels of growth hormone and IGF-1 in untreated patients with Parkinson's Disease in morning tests. However, in the testing of the nocturnal secretion of growth hormone, Bruno et al. observed its lower values, which could be more related to age and concomitant diseases than to PD [12]. Secondarily, hormonal imbalance in patients with PD may result from treatment with dopamine agonists rather than prior disease pathology. A significant decrease in prolactin concentration and increased secretion of growth hormone have been observed with unchanged concentrations of insulin-like growth factor (IGF-1), suggesting peripheral resistance to growth hormone in PD patients on dopaminergic medication [7]. Not all dopaminergic drugs cause endocrine abnormalities to the same extent. Among the drugs having the least effect on hormones are the non-ergoline dopaminergic agents, e.g. pramipexole, ropinirole, and rotigotine [13]. Currently, the significance of the hormonal disorders described above in patients with PD is unclear. However, it cannot be ruled out that they have an impact on the occurrence or intensification of non-motor symptoms of this disease, such as autonomic, neuropsychiatric, cognitive disorders, sleep disorders or weight loss.

Orexin in parkinsonisms

Growing interest is associated with the role of neuropeptides such as orexin. Orexin is a neuropeptide linked with excitement, wakefulness and appetite [14]. It is produced by orexigenic neurons located in the hypothalamus. It is a group of neuropeptides of two main types — orexin-A (OXA) and orexin-B (OXB) [14], which are derived from the same prepro-orexin precursor by proteolytic processing [15]. Preproorexin is composed of 130 amino acids and the first beginning of OXA and OXB. Mature OXA is a peptide with 33 amino acids ~3.5kDa, having two disulfide bonds [16], while OXB is a 28 amino acid peptide with mass of 2.9 kDa, and contains two α-helices which are connected by an elastic loop [17]. Orexin receptors, including orexin 1 receptor (OX_1R) and orexin 2 receptor (OX_2R), belong to G protein-coupled receptors (GPCR) [18–20].

Ox_1R and Ox_2R are found in the brain and central nervous system [21] but OXA is more lipophilic and stable than OXB. OXA is also detectable in the cerebrospinal fluid (CSF) as it crosses the blood-brain barrier and rapidly enters the brain by simple diffusion. In contrast, OXB is rapidly degraded in the serum before entering the CNS [22, 23].

The distribution of these two receptors overlaps, but certain regional differences can be observed. For example, OX_1R is more intensively expressed in the ventromedial nucleus of the hypothalamus, cortical areas, and the nucleus of the bed of the striatum terminal and hippocampus, while OX_2R expression is more pronounced in the cerebral cortex, anterior pretectal nucleus, and the nucleus accumbens (NAc) [24, 25]. The NAc is the projection area of dopaminergic neurons that are present in the VTA. Both receptors are conserved in mammals. Human OX_1R and OX_2R have 94% and 95% resemblance to rat OX_1R and OX_2R, respectively. Both human receptors consist of 425 and 444 amino acids, respectively [26].

The affinity to orexigenic receptors varies depending on the type of orexin [27]. Its impact is based on inducing orexin 1 and orexin 2 receptors. Orexin-A is generally associated with stimulating orexin 1 receptor, Orexin-B is not linked with a majorly affected receptor [28].

Orexin is evaluated in various entities. Its deviated levels may be observed in physiological conditions such as pregnancy and various pathological states [29]. Narcolepsy is among the main entities associated with the abnormalities within orexin neurons [30]. Orexin abnormalities are associated with multiple pathologies, although the mechanism of deterioration varies. In the most common tauopathy, Alzheimer's Disease (AD), the progressive deterioration of orexin neurons is associated with developing sleep abnormalities. It is hypothesised that in AD sleep may be affected by abnormalities in orexin regulations, which may be linked with tau and beta-amyloid secretion, accumulation and clearance [31]. Orexin is related with abnormalities in parkinsonisms, although it is not known whether the factor is one of the causes of, or rather a consequence of, the pathological pathways observed in the diseases [32, 33]. In diseases affected by Lewy Bodies such as PD or DLB, the pathology selectively affects the regions of the hypothalamus, among which can be mentioned orexin/hypocretin neurons, tuberomammillary nucleus and lateral tuberal nucleus [34, 35]. Among neurological diseases with abnormalities in the orexinergic system can be mentioned PD, atypical parkinsonisms, Huntington's Disease, AD and multiple sclerosis [36]. In some of these diseases, as with PD, abnormalities of the levels of orexin are associated with disease severity [37]. The role of orexin in parkinsonism has been studied for more than 20 years (Tab. 1).

Orexin in synuleinopathic parkinsonian syndromes

From previous studies, it is known that orexinergic neurons are significantly affected by Parkinson's Disease (PD). Fronczek et al. [38] showed that in patients with PD, the number of orexinergic neurons is decreased in the hypothalamus, while the concentration of OXA in the CSF and the frontal cortex is reduced. In addition, studies in animal models have shown that

Table 1. Abnormalities associated with orexin in parkinsonisms*

Disease	Clinical features
Synucleinopathic parkinsonian syndromes	– excessive daytime sleepiness – anxiety – cognitive deterioration** – dysautonomia – inverse correlation between levels of orexin and duration of morbidity
Tauopathic parkinsonian syndrome	– inverse correlation between levels of orexin and duration of morbidity

*Based on literature summarised in paragraph "endocrine abnormalities in parkinsonisms"
**Questionable data concerning Dementia with Lewy Bodies

the greater the damage to orexinergic neurons, the greater the decrease in the level of orexin in the cerebrospinal fluid [39].

Orexin as possible neuroprotective agent

Studies on PD animal and cell models have provided data suggesting a neuroprotective effect of orexin on dopaminergic neurons; orexin-A reduced MPP+-induced damage by increasing the expression of hypoxia-inducible factor 1α. Feng et al. [40] showed that hypoxia-inducible factor 1 alpha (HIF1-α) is deficient in PD as a result of mitochondrial dysfunction, while administration of orexin-A leads to a significant neuroprotective effect on dopaminergic neurons through activation of HIF-α. Orexin-A attenuated 6-hydroxydopamine toxicity [41] and lowered MPTP-induced loss of dopaminergic neurons in the substantia nigra in mice [42]. Therefore, it can be hypothesised that neurodegeneration of orexigenic neurons observed in PD may accelerate further damage of other brain structures.

Brain-derived neurotrophic factor (BDNF) promotes neuroprotection and neuroregeneration [43]. In animal models of PD, BDNF enhances the survival of dopaminergic neurons, and improves dopaminergic neurotransmission and motor performance. OXA increases BDNF protein levels in dopaminergic neurons in PD by reducing tyrosine hydroxylase (TH) and upregulating BDNF in the substantia nigra. This is mainly mediated by OX_1R [44, 45].

Research has shown that mRNA expression of BDNF is downregulated in the substantia nigra, and inhibition of BDNF expression leads to loss of dopaminergic neurons in the substantia nigra of PD patients [46–48]. Epidemiological studies have shown that lower levels of BDNF in serum were associated with cognitive and motor impairments in PD patients [49–51].

These studies may suggest a role for orexin-A deficiency in the progression of PD, as well as explaining the link between narcolepsy-like symptoms in PD as both dopamine and orexin influence the regulation of the sleep pattern by activating the midbrain and thalamocortical pathways [52].

Orexin in context of narcolepsy-like symptoms

Ylikoski et al. [53] reported a high correlation between the occurrence of symptoms of narcolepsy and REM sleep behaviour disorder (RBD) among PD patients. Interestingly, many symptoms of PD and narcolepsy are shared: excessive daytime sleepiness, REM sleep abnormalities, sleep paralysis, hypnagogic hallucinations, and cataplexy. This phenomenon could be, at least partially, explained by progressive loss of orexigenic neurons in the process of neurodegeneration which causes orexin deficiency similar to that in narcolepsy with cataplexy. Ylikoski et al. concluded that narcolepsy-like symptoms in PD patients are secondary to PD itself as there is no evidence suggesting that patients with narcolepsy have a higher risk of developing PD. Genetic analysis revealed the existence of 38 genes shared in PD and narcolepsy gene sets [54] mainly associated with locomotion, circadian circle, sleep, learning and memory. The correlation of narcolepsy-like symptoms with orexin deficiency could potentially have a therapeutic impact in the future; currently animal studies indicate the usefulness of orally administered TAK-994 (OX2R agonist) in ameliorating narcolepsy-like symptoms in narcolepsy mouse models [55].

Orexin in context of body metabolism

Further studies on animal models have shown that orexin is an important link between sleep and body metabolism, as sleep deprivation leads to increased food intake and induction of catabolism [56]. It is known that orexin is responsible for stimulating food intake as a result of inhibiting autonomic digestive reactions. Orexigenic neurons are inhibited by leptin and food intake, while ghrelin and hypoglycaemia activate these neurons. The use of a high-protein and amino acids diet may affect the hyperpolarisation of orexigenic neurons and block glucose-induced activations of orexigenic neurons [57]. The association between the impact of food intake, the role of orexin and PD has not yet been explored. One study indicated links between reward functions and orexin, as the abnormalities within this mechanism may be linked with drug-craving, which is commonly described as a feature of dopaminergic dysregulation [58]. On the other hand, food intake by be affected by the dysregulation of striatal dopamine D2/D3 receptors. In this mechanism, the impact of orexin was found to be inducing depressive behaviours in animal models [59]. These mechanisms show examples of possible and indirect pathways leading to food intake disruptions.

Orexin in context of other neurotransmitters

Both orexin receptors are involved in stimulating various neurotransmitters that are associated with the activation of the central nervous system such as monoamine neurons (serotonin, histamine, norepinephrine and dopamine), and cholinergic neurons in the basal forebrain [60]. Therefore, orexin receptor mutations lead to sleep disorders. Yamanaka et al. [61] showed that activation of OX_2R by orexin leads to wakefulness mediated by the neurotransmitter histamine, as antihistamine blocks the excitatory effects of orexin, while activation of OX_1R by orexin leads to wakefulness through the neurotransmitter norepinephrine. Decreased CSF orexin levels have been documented in

patients with narcolepsy, and are indeed now considered one diagnostic criterion for diagnosing narcolepsy.

Orexin in contest of daytime sleepiness

A work based on the examination of three patients did not show abnormalities in the level of orexin-A among patients with PD and excessive daytime sleepiness. The group was affected by several limitations apart from the number of patients, among which could be mentioned the diverse ages of the patients — 52 to 69, and the fact that treatment duration varied from 0.5 to 5 years. All of the patients received dopamine agonists – pramipexole and pergolide, factors increasing their vulnerability to daytime sleepiness [62]. On the other hand, a study based on a larger group of patients revealed an association between reduced orexin levels in ventricular CSF and daytime sleepiness in advanced PD [63]. The impact of orexin in parkinsonian syndromes is not limited to sleep disturbances. The lack of an effect between orexin levels and daytime sleepiness in PD patients is still unclear, but many factors may be at play. Firstly, it may be a discrepancy between the measurements of the CSF of the spinal cord and the ventricular CSF [64]. The next explanation could be a deficiency in other neurotransmitters besides orexin. PD and parkinsonian syndromes are neurodegenerative diseases in which broad neuronal systems are impaired, including not only orexin fibres, but also acetylcholine, serotonin, and norepinephrine neurons. These neurotransmitters also play an important role in sleep/wake mechanisms [30, 65]. Confirmation of this thesis came from a paper by Rey et al., which showed the possible involvement of midbrain noradrenergic and dopaminergic neurons on the sleep/wake state via thalamocortical pathways [66]. In addition, the arrangement of orexin fibres in the hypothalamic and brainstem nuclei that are damaged in PD may contribute to the dysfunction of the orexin system. Therefore, CSF orexin levels are poorly correlated with clinical sleep disturbance in PD [30].

Orexin in context of dementia

Orexin-B transferred intracerebroventricularly in MPTP parkinsonian mice resulted in the reduction of dopaminergic neuron degeneration. Orexin B application was correlated with improvements in spontaneous activity and motor coordination [67]. Additionally, the impact of Orexin-A is different in dementias. In Dementia with Lewy Bodies (DLB), the cognitive function is not correlated with its levels in the cerebrospinal fluid, whereas the correlation is maintained in AD [68–70]. In parkinsonian syndromes it is considered as a factor affecting sleep abnormalities [71]. In a study examining PD patients with REM Behaviour Disorder (RBD), PD without RBD and idiopathic RBD, no significant decrease in the levels of orexin compared to healthy controls was observed [72]. The lack of differences between the groups was accompanied by similar results of Tumour Necrosis Factor alpha in the serum and cerebrospinal fluid.

Increased levels of plasma orexin-A have been detected in entities preceding neurodegenerative disease, as in mild cognitive impairment with Lewy Bodies [73]. In PD, increased levels of orexin-A have been correlated with anxiety, cognitive and non-motor symptom scales [74]. Similar results have been observed in DLB, although in DLB with cognitive fluctuation or parkinsonisms the levels of orexin-A were decreased when contrasted with healthy controls. Plasma orexin-A was found to be correlated with cognitive and motor features in MCI-Lewy Bodies and DLB [73]. The abnormalities regarding orexin in DLB were also interpreted as a differentiating feature in AD and DLB in females, as its levels were decreased in this synucleinopathy when compared to tauopathy [75].

Role of orexin in autonomic nervous system

Orexin neurons are connected with multiple structures involved in autonomic functions such as presympathetic neural cells inter alia in rostral ventrolateral and ventromedial medulla, raphe nuclei, noradrenergic cells in the pons, paraventricular nucleus of the hypothalamus, nucleus ambiguus, dorsal motor nucleus of the vagus nerve, and solitary tract nucleus [76]. Orexin has an impact on the sympathetic cardiovascular system causing an increase of blood pressure (BP), heart rate (HR) and renal sympathetic nerve activity [76]. Animal studies have indicated that orexin is involved in the cardiovascular stress response that is sympathetic excitation and in baroreflex and chemoreflex responses [76], although this is a rather minor role focused on potentiating and controlling other inputs, as HR and BP variability are preserved in animals with orexin signalling dysfunction [76].

It is possible that a similar mechanism may be involved in orthostatic hypotension observed in patients with PD and especially multiple system atrophy (MSA). Animal studies suggest orexin signalling is necessary in cardiovascular regulation during sleep [77]. Although the impact of orexin on cardiovascular system and sympathetic regulation is evident in animal studies, it is unwise to extend these results to humans as there are no methods enabling a direct assessment of orexin activity applicable for human participants. Another animal study indicates that transgenic rats with a minimal number of orexigenic neurons have decreased response to B-blockers, impaired R-R interval regulation, and heart hypotrophy [78].

Some data supports a hypothesis concerning the role of orexin in the fight-or-flight response — e.g: orexin administration causes an increase in cardiovascular and respiratory activity and analgesia [79]. Interestingly, in a mouse model, the suppression of baroreceptor reflex was visible only during the defence response, while it remained normal at rest [80]. Orexigenic neurons, but not orexin peptides, are involved in stress-induced hyperthermia in a mouse model, which indicates the role of other neurotransmitters in this process [81]. Orexin neurons are sensitive to changes in pH and CO_2 concentration; acidosis causes its excitation and an

increase in autonomic respiration rate regulation, whereas alkalosis reduces their firing rate and causes a decrease in respiratory activity [82].

Orexin in tauopathic parkinsonian syndromes

A study evaluating orexin in PD, DLB, CBS and PSP revealed an inverse correlation between levels of orexin and duration of morbidity in PSP and its lack in other examined diseases [83]. The authors hypothesised that orexin may be a feature of neurodegeneration in PSP [83]. Information concerning the role of orexin in PSP has been relatively briefly described. One of the cases revealed orexin-A in undetectable levels in the CSF in a 74-year-old patient with probable PSP [84]. The authors assessed the neuropathological changes in PSP as neurofibrillary tangles in the hypothalamus as being associated with deviated orexin neurotransmission.

Orexin in other entities

The role of orexin-A has also been evaluated in MPTP parkinsonian mice. This work showed an association between BDNF and impacting OX1R receptors [85]. Orexin-A was found to have a neuroprotective role. Apart from sleep disorders, orexin has been found to be a factor decreasing the severity of motor impairments and deficits in memory updating [86]. The recent development of pharmacological orexin antagonists provides a good avenue for therapy in this field, which also has potential in neurodegeneration [87, 88]. The mechanism of orexin inhibition is associated with beta-amyloid accumulation [89]. Dual orexin antagonists block the association of the wakefulness-promoting neuropeptides orexin A and orexin B, with their location and receptor sites. Currently, two orexin receptor antagonists (suvorexant and lemborexant) are approved for the treatment of insomnia.

These drugs bind reversibly to both receptors (OX1R and OX2R) and inhibit the activation of the arousal system; thereby facilitating the induction and maintenance of sleep [90–92], although lemborexant has a stronger inhibitory effect on OX2R than OX1R compared to suvorexant which could increase non-REM sleep. Lemborexant binds to and rapidly dissociates from orexin receptors, unlike other orexin receptor antagonists which usually dissociate slowly, which will make it easier to fall asleep and reduce the risk of drowsiness the next day.

Suvorexant is generally well tolerated, but it has a lesser effect on the neurophysiology of sleep compared to benzodiazepines (traditional hypnotics). However its efficacy requires additional validation [93, 94]. A few studies have reported rare, but significant, side-effects of suvorexant in the treatment of insomnia disorder in Parkinson's patients. These include sleep paralysis, abnormal dreams, over-sedation, the acute worsening of depressive symptoms, REM sleep behavioural disorder and suicidal thoughts [95–97]. Confirmation of the above comes from a paper by Tabota et al., which presented a 72-year-old patient with PD in whom administration of 15 mg suvorexant induced both nightmares and abnormal behaviour during sleep, whereas he did not exhibit such dream enactment behaviour when not taking suvorexant [98].

However, no papers have yet addressed the therapeutic potential of lemborexant in PD patients.

Orexin antagonists are among the methods of therapy in this field. The mechanism of orexin inhibition is associated with decreased beta-amyloid plaque formation [89]. A study has shown that physiological levels of orexin A in the CSF are linked with excessive daytime sleepiness [99]. This study revealed that the level of orexin-A in CSF was similar to the one observed among geriatric patients, decreased in comparison with AD, and increased in comparison with Frontotemporal Lobe Dementia [99].

Orexin as a factor in anti-parkinsonian medication

Interestingly, the orexinergic neurons may be reduced as an effect of anti-parkinsonian medication. The role of ropinirole is not fully understood, however the authors of one study suggested a possible association between impacting dopaminergic receptors and inhibiting excitatory activities of the neurons correlated with orexin [100]. The impact of anti-parkinsonian drugs on orexigenic receptors is not fully understood. A work on the role of levodopa revealed its antinoceptive function in colonic distension by stimulating D2 dopamine receptor and inducing endogenous brain orexin [101].

Conclusions

The main question regarding abnormalities of orexin levels in the context of parkinsonisms is whether the factor is more of an inductor, a consequence of neurodegeneration, or simply a neutral feature.

In the context of vigilance and sleep deviations in this group of diseases, the possible interference of orexin may play a role. The ambiguous results of analyses of orexin levels in parkinsonian entities may suggest that the role is diverse, possibly depending more on the stage of the disease than the type of parkinsonism.

The often contradictory outcomes of studies may suggest an undetectable feature or that the significance of orexin in parkinsonisms may be questionable. Moreover, the majority of studies have been affected by a lack of sleep-specific data as well as of polysomnographic data, a sleep questionnaire, and circadian rhythm data. Such detailed analysis would be helpful in obtaining possibly more effective methods of treatments. The findings concerning orexin in parkinsonisms lacking evidence-based treatment as atypical parkinsonisms seem additionally striking. More research in this field is required.

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