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Review / Derleme

Neuroanatomy of Postural Stability: Links to Parkinson's Disease

Postüral Stabilitenin Nöroanatomisi: Parkinson Hastalığı ile Bağlantıları

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Abstract

Postural stability is a complex task that requires the integration of many sensory inputs to produce an appropriate response for every environmental situation. The balance systems employ both reactive and anticipatory strategies to maintain the body's center of mass. The body's ability to maintain stability is limited by biomechanical constraints, such as the bodies' internal representation of position in space. The balance system has multiple internal representations of verticality including those in the vestibular and somatosensory cortexes that serve to orient the body and help to maintain balance. Moreover, the balance system uses cognitive resources to integrate sensory inputs. These cognitive resources are used to produce the appropriate motor responses in situations when the balance system is malfunctioning. Parkinson's disease (PD) is characterized by many motor symptoms, such as resting tremors, bradykinesia, and rigidity. PD is generally characterized by two subcategories of symptoms: the tremor type and the postural instability gait difficulties type (PIGD). Previous studies showed that the PIGD type is less responsive to current treatments, which include L-dopa. Thus, a better understanding of the balance system and how it affects the production of postural deficits is needed to better treat individuals suffering from the PIGD type of PD. Here, we review the candidate neural mechanism involved in balance, and inferences are made on how these balance networks may be affected by PD.

Keywords: Balance, postural stability, dopamine, acetylcholine, Parkinson's disease

Öz

Postüral stabilite çevresel koşullara uygun tepki verebilmek için farklı duyumsal girdilerin entegre edilmesini gerektiren karmaşık bir denge görevidir. Vücudun stabiliteyi koruma becerisi bedenin içsel temsilinin mekandaki konumu gibi biyomekanik kısıtlamalar ile sınırlandırılmıştır. Postürel stabilite, bedeni yönlendirmeye yarayan ve dengeyi korumaya yardım eden birden farklı beyin bölgesinin etkileşimini gerektirir, örneğin düşeyliğin vestibüler kortekste ve somatosensori kortekstеki etkileşimi buna bir örnektir. Dahası, denge sistemi duyumsal girdileri entegre etmek için bilişsel kaynakları kullanır. Bradikinezi, rijidite, istirahat halinde izlenen tremor gibi birçok motor semptom ile karakterize edilen Parkinson hastalığı (PH) genellikle tremor tipi ve postüral instabilite yürüyüş güçlükleri (PİYG) tipi olmak üzere iki alt kategoride sınıflandırılır. Önceki çalışmalar PİYG tipinin L-dopa içeren güncel tedavilere daha az yanıt verdiğini göstermiştir. Dolayısıyla PİYG tipi Parkinson hastalarını daha iyi tedavi etmek için denge sisteminin ve postüral eksikliklere neden olan etkilerinin daha iyi anlaşılmasına ihtiyaç vardır. Bu derleme makalede, dengenin korunmasına dahil olan nöral mekanizmalar gözden geçirilmekte ve bu denge ağlarının PH tarafından nasıl etkilenebileceğine ilişkin çıkarımlar sunulmuştur.

Anahtar Kelimeler: Denge, postüral stabilite, dopamin, asetilkolin, Parkinson hastalığı

Introduction

Postural stability is the ability to maintain balance with respect to ones' center of mass (CoM) within the cone of stability. The cone of stability is defined as the area within which the body can maintain its position without changing the base of support. Postural instability is one of the most debilitating symptoms of Parkinson's disease (PD), which leads to decreased quality of life (1,2). Maintaining postural stability is a complex skill that requires integration of different networks in the brain, and the progression of PD eventually leads to impairment of postural stability in certain patients with PD (3). A survey of mildly affected patients with PD during a six-month period found that 25.4% had multiple falls, and 50.8% had at least one fall during this time (4). The risk of falling in patients with PD is the highest in Hoehn and Yahr stage 3, and decreases in the later stages, as

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the patients become less mobile (4,5). Postural stability in PD can lead to severe disability as up to 40% of patients with postural instability have multiple falls (6).

Research in PD categorizes the symptoms in two subtypes: the tremor subtype and the postural instability gait difficulty type (PIGD), which differ in motor and cognitive symptoms (7). However, it is important to note that a mixed manifestation of the two subtypes can occur in some patients (7). In addition to the difference in symptomatology, there appears to be differences in functional connectivity and gray matter atrophy between the two subtypes of PD (8). The PIGD type is associated with gray matter degeneration and a related decrease in functional connectivity between cortical and subcortical motor areas (8).

This article briefly describes the neurotransmitter systems supporting postural control, and summarizes the neural infrastructure and effects of PD on these systems, and details the remedies used to maintain postural control of patients with PD. Accordingly, the remainder of the article focuses only on patients with PIGD-type PD.

Sensory Integration and Postural Stability

One of the most important resources available to the balance system is the ability to orient the body with respect to gravity. It is known that healthy individuals can identify gravitational verticality within 0.5° and that there are multiple regions of the brain that are responsible for proprioceptive verticality (9). The vestibular cortex is thought to be responsible for the perception of verticality. However, individuals with a lesion to the vestibular cortex (the posterior insula) do not necessarily have a tilted posture or a loss of lateral balance (10). This suggests that there is more than one internal representation of verticality in the brain, and that different verticality centers of the brain may compensate for one another in the event of lesions or neurodegeneration. As stated earlier, patients with PD exhibit a diminished ability to process vestibular input where the deterioration of the processing of vestibular input does not depend on the stage of the disease (11). It may therefore be inferred that the vestibular cortex of patients with PD may receive an inaccurate image of the body position relative to gravity, leading to postural instability, which contributes to diminished-stability (12).

There are two major categories of postural behavior (i) postural orientation and (ii) postural stability. Postural orientation uses sensory inputs from the somatosensory system, the visual system and the vestibular system, through using higher-level integrative process and effector component by the motor cortex. In order to maintain postural orientation, sensory inputs from the vestibular and somatosensory system are all used as compensatory mechanisms (9). For example, when placed in a dark room with diminished visual input, the weight on the visual system decreases, and the weight on the somatosensory and vestibular system increases to maintain postural stability. Similarly, when on an unstable surface, somatosensory input is devalued and dependence on visual and vestibular input increases. Accordingly, in a well-lit room with a firm, level base for a person's feet to engage, a healthy person relies 70% on the somatosensory inputs, 10% on visual inputs, and 20% on vestibular inputs (12). The ability to re-weight these inputs is vital to maintaining postural orientation, when changing between environments (10). The loss of the ability to quickly re-weight sensory inputs can lead to more frequent falls.

PD is one such disease in which the ability to re-weight sensory inputs may be compromised. The hallmark symptoms of PD are rest tremors with a frequency of 3-5 Hz, rigidity, bradykinesia and postural stability (13). However, postural stability is considered to be a nonspecific symptom, and is usually not prominent in the early stages of PD (13). In addition, although PD is traditionally thought of as a motor disorder, many non-motor symptoms are also present, which include cognitive deficits and psychiatric changes, sensory symptoms, and sleep disturbances, which might affect the compensatory systems (13).

Currently, most research on the balance of patients with PD relies on the use of the Berg Balance Scale (BBS) (14). The BBS is commonly used to test balance impairments, and these impairments were correlated with the Unified Parkinson's Rating Scale (15). However, the BBS has limitations and once the cut-off score is achieved, lower scores were not found to correlate with an increase in falls (16,17). The Mini-Balance Evaluation System Test (BESTest) has been developed, which avoids the ceiling effect of the BBS and therefore is an important tool for discerning the deficits in the different balance control systems (14). The BESTest can be used to evaluate the six different balance control systems: biomechanical, verticality, anticipatory, reactive, sensory orientation, and stability in gait (14).

PD is characterized by motor impairments and vestibular and somatosensory impairments (18,19). For example, some patients with PD display reduced or absent vestibular function (20). Moreover, the somatosensory system may have impairments' in patients with PD, through reduced sensitivity in the extremities (21). Diminished somatosensory and vestibular inputs may limit the ability of an individual with PD to re-weight somatosensory and vestibular inputs in response to changing environmental inputs. Thus, patients with PD are advised to pay close attention to changing environmental conditions. A good example for this is low light conditions; patients with PD cannot rely on compensatory systems as normal healthy individuals can, the compensatory mechanism might also be dysfunctional, for example due to peripheral neuropathy (22).

Finally, somatosensory information also plays a role in verticality representation, and may even serve as a compensatory mechanism for vestibular inputs if vestibular loss is experienced (23). The brain appears to synthesize both the somatosensory and vestibular representation of verticality, but this process highly depends on the availability of somatosensory information (23). However, there is little information on how PD affects somatosensory processing. There is therefore a need for more information on internal models for somatosensory and vestibular vertically and how PD affects them.

Resources and Constraints of Postural Stability: Links to Parkinson's Disease

Reactive and Anticipatory Movement Strategies

There are three major reactive strategies that individuals employ to maintain their CoM. Two of these strategies are

accomplished without movements, which are known as the ankle strategy and the hip strategy (24). The ankle strategy entails the body moving at the ankle to try to maintain stability, whereas the hip strategy entails the body moving at the hip to quickly shift the body's CoM, and thus gain stability. In the third reactive strategy, patients usually take a step forward or backward in an attempt to move their CoM, in order to regain stability. It has been noted that people who have a fear of falling or an increased risk of falling use the hip strategy and the stepping strategy more often than the ankle strategy to maintain their equilibrium (25). Anticipatory strategies are also used before voluntary movements to help to maintain stability during movement because movements inertly destabilize the body. In that case, in response to an external perturbation, a subject with PD would be able to maintain stability. However, patients with PD show poorly coordinated anticipatory postural adjustments, and as a result, show postural instability during self-initiated movements (9). This is because patients with PD may not be able to produce the necessary force to restore their CoM to equilibrium (26).

Moreover, postural deficits in PD were not only observed in response latency, but also in generating the needed force to maintain posture, and in the ability to modulate background tonic stiffness and respond to perturbations (26). It has been argued that the decrease in the dopamine system seen in patients with PD may be responsible for the lack of modulation of background muscle tone and the diminished generation of force needed to maintain postural control (26). Additionally, Levodopa treatments have been shown to significantly lower muscle tone (i.e., decrease rigidity) in patients with PD, but did not increase the patients' ability to respond to perturbations (26). Thus, levodopa did not alleviate all of the PD-related symptoms associated with postural control, hinting that multiple neurotransmitter pathways may be involved in PD-related symptoms.

Recent studies suggested that pulsatile dopamine release may play an important role in the symptoms of dyskinesia during the late phases of PD, when tonic levels of dopamine are depleted and dopamine release becomes almost entirely dependent on the pulsatility following each dose (27). Accordingly, it may suggest that there is a need for new pharmacologic agents for balance control and that longer acting dopamine agonist (DA) or other pharmacologic agents that prevent the depletion of dopamine are needed to prevent the occurrence of dykinesias in the long term in order to increase motor control in patients with PD (27).

Biomechanical Constraint of Postural Control

One of the most important aspects of postural stability is the ability to control the body's CoM relative to the base of support: the feet. Here, the standing equilibrium is defined as the area in CoM at the base of support. The CNS has an internal representation of this cone of stability, producing a working model used in reactive and anticipatory strategies to maintain equilibrium (9). It is a combination of both physical and psychological constraints that ultimately determine an individual's cone of stability (Figure 1). In people with PD, the basal ganglia are affected, and it is hypothesized that PD leads to an inaccurate representation of the cone of stability (9), which leads to postural instability.

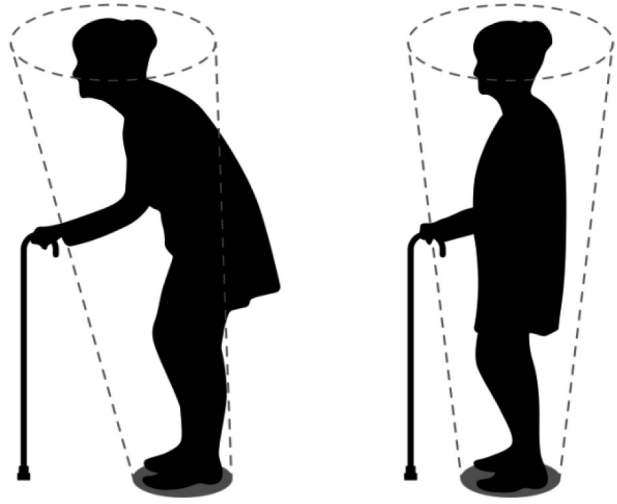

Figure 1. Cone of stability is represented by the area in which a person moves their center of mass. The left figure shows unstable and unbalanced cones of stability where the center of mass falls outside the base of support. The cone of stability on the right is unstable but balanced.

The control of posture during dynamic movement is comprised of forward and lateral control of stability. There are many complex balance pathways involved in both types of control, and different pathways may respond to different types of treatment. People with PD have both forward and lateral balance control deficits (28).

In gait, the forward control of stability comes from placing the swinging limbs under the falling CoM (9). Gait forward control of stability largely comes from the passive dynamics of the limbs in the sagittal plane. However, rhythmic stepping behavior is also needed to maintain forward balance. This rhythmic stepping pattern is produced in the mesencephalic locomotor region, which contains the pedunculopontine nucleus (PPN). The PPN nucleus is the major cholinergic nuclei that is adjacent to the midbrain reticular formation (29,30). PD-related neurotoxication, such as MTMP neurotoxication, is correlated with the loss of the PPN cholinergic neurons (30). Post mortem findings showed that patients with PIGD-type PD, specifically with the falling type, had reduced PPN acetylcholinesterase (AchE)-containing neurons compared with patients with non-falling-type PD (30). Moreover, it has been found that subcortical cholinergic denervation of PPN neurons may be related with PIGD-type PD, which is not responsive to dopamine (29). PPN-DBS was shown to be particularly effective in the amelioration of postural and gait symptoms of PD (31). A better understanding of the interaction between striatal cholinergic neurons and striatal dopaminergic neurons is crucial, because both types of neural projections have a dense concentration of interneurons in the striatum and both are affected by the progression of PD (29,30).

Control of the lateral plane is the result of lateral trunk movement and the lateral placement of the feet. Lateral control requires significant active control to stabilize the body's CoM and to prevent falling (28). Individuals with PD may have less ability to actively control lateral movement due to restricted lateral movements and thus may not be able to prevent falling to the

side. The reasons for restricted lateral movements, disregarding age-related factors, seem to be related to the basal ganglia's role in maintaining postural tone. Patients with PD display rigid postural tone without the flexibility needed to compensate for the CoM in lateral movements (9). Current L-dopa treatments appear to return appropriate muscle tone to normal levels in individuals with PD (9).

Neurobiologic Constraint of Postural Control During Dynamic Movement

Although the role of cerebellum in motor control and learning is well understood in healthy people (32,33), its role in PD and balance is less clear (34). Recent studies suggested that cerebellum played a crucial role in balance and dynamic postural control in patients with PD (34), which is due to anatomic connectivity between the cerebellum and basal ganglia (35). It has been suggested that cerebellar connections between the subthalamic nucleus and cerebellum via the pontine nuclei (PN) may account for the resting tremors in patients with PD (36). However, the role of the cerebellum in balance and gait is more complicated (37).

The flocculonodular lobe, known as the vestibulocerebellum, located at the dorsal part of cerebellum, is involved in vestibular processing, and its major function is to control balance and eye movements (38). Moreover, the vermis receives the most input from visual, auditory, vestibular, and somatic sensory regions, and sends outputs indirectly to the proximal muscles of the body and limbs (37). Recently, the neural mechanism for performing self-initiated and externally triggered movements in PD has been determined (39). Taniwaki et al. (39) showed that during externally triggered finger movements, connectivity of cortico-striatal processing was weakened, but cortico-cerebellar neural circuits remained unaffected. In addition, functional connectivity analysis of brain networks in PD shows that the striato-cortical connections are weakened and the connections between cerebello-thalamo-cortical motor regions are strengthened during self-initiated movement (40), a finding supported by resting state connectivity studies in PD (41).

Early on in PD, this observed strengthening of the cortico-thalamo-cerebellar connection might serve to compensate for basal ganglia dysfunction and also mask symptoms of severe postural instability seen in the middle stages of PD (34). Additionally, a weakening of functional connectivity between cortical-striatal areas in L-dopa ON patients and an increase in connectivity between cortico-striatal regions in L-dopa OFF patients were observed (41). Supporting these previous findings, Festini et al. (42) showed that OFF-medication PD patients had increased cerebellar-whole connectivity, whereas ON-medication PD patients had decreased levels of cerebellar-whole brain connectivity. These changes in functional connectivity are thought to be a related to L-dopa compensation. An understanding of how these networks of brain regions work together may lead to more effective long-term treatment of patients with PD, and decrease their chance of falling.

Cognitive Constraints

A higher level cognitive processing is required for non-reflexive balance tasks, and it is known that several areas of the cortex are impaired in patients with PD. These cortical impairments may be the cause of these postural deficits (43). There is an accumulation of studies suggesting that cognitive resources (e.g., working memory) are required to achieve postural stability (44,45). It is also known that increasing the difficulty of the postural task by temporarily impairing one of the sensory inputs needed for balance requires greater cognitive resources (46). In the healthy aging normal population, this increased cognitive demand may be adequately met, and no effective loss of balance may be observed (47). However, the increased cognitive demand may overload shared cognitive resources in the elderly and for those with impairments in these cognitive functions (48,49). It is reported that the simultaneous performance of a cognitive task while walking changes the gait pattern, decreasing average stride time, and increasing stride time variability, especially in patients with PD (50). Interestingly, patients with PD also showed significantly more variability in average stride time and average variability of stride time compared with healthy controls (50). As a result of this lower cognitive capacity, individuals with neurologic diseases such as PD may suffer falls as a result of insufficient cognitive resources to complete two tasks simultaneously.

It is known that the performance of highly practiced skills such as walking may be affected by cognitive loading (51). Patients with PD may use more cognitive resources to complete procedural tasks normally, such as walking, which explains their susceptibility to dual task decrement (50). A semi-redundant postural stability system may exist, and be brought in to operation during gait and other movement tasks. The semi-redundant nature of these systems lies in the fact that one system may have an internal model of gait based on previous experiences that is used to make movement decisions before the complete sensory picture is available (e.g., a forward model), and another balance system may be able to integrate sensory inputs and update these internal models of the movement based on changing environmental inputs. The cortico-cerebellum system may have this internal model of gait system and may be able to serve as a compensatory system (41).

In PD patients, the semi-redundant nature of cortical-cerebellum systems may serve as a compensatory modulator for postural stability and the gait system, in early to mid PD, when the striatal-cortico connections are affected by the progression of PD (41). The cortico-cerebellar pathways could be used as a compensatory modulator for postural stability, but it would be in a diminished fashion because the ability to update this internal model based on new environmental conditions is limited in patients with PD, resulting in their being more susceptible to falls. Also, it should be noted that the cerebellum is susceptible to the pathologic effects of the progression of PD, which is the result of dopaminergic denervation (34). It is hypothesized that the compensatory role that the cerebellum plays may strengthen in the early stages of PD, but eventually diminishes as it is overcome by the pathologic role of the cerebellum (7).

It is known that instability is not very visible in the early stages of PD (13). The most prevalent model of cell death in patients with PD is the Lewy body model, in which protein accumulates. Lewy bodies first appear in the olfactory bulb, and then progress into areas such as the midbrain and finally to the cortex (52). The

progression of Lewy bodies from the lower levels of the brain to the higher centers may dictate the appearance of balance-related symptoms.

Discussion and Future Research

Many fundamental questions relating to PD and postural stability remain to be answered. Important among these unresolved issues are, how the progression of PD affects the vestibular, somatosensory, and visual cortexes, and how these cortical regions can serve as compensatory centers in patients with PD to maintain balance.

Another issue is the role of DA treatment in PIGD-type PD. Postural stability-related symptoms are not completely responsive to current treatments (4). For example, L-dopa treatments for PIGD-type PD seem to be less effective for PIGD-type PD, and it may be inferred that different neurotransmitter pathways may be involved. Further studies are needed to determine the effect of the cholinergic system in PD because previous studies suggest that the cholinergic system is also impaired in PD, and this effect may be specific to the PIGD subtype of PD (29). For example, in recent positron emission tomography study, Bohnen et al. (53) showed no significant difference in the nigrostriatal dopamine system between patients with PD with a history of falls and those with no history of falls; however, they showed that patients with a history of falls had reduced thalamo-cortical AchE levels. Based on this argument, several studies showed a reduction in falls with cholinergic treatments in patients with PD (54,55).

More research into classifying and understanding different subtypes of PD may lead to more specific PD treatment that targets the specific neurologic deficits seen in the different subtypes of PD. Patients with PIGD-type PD may be able to overcome these impairments, resulting in minimal functional loss in the near future. Additionally, improving performance in compensatory mechanisms should be studied to help individuals with PD to avoid falls because shared cortical resources are thought to serve for compensation in PD.

Ethics

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Authorship Contributions

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