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Review article

Cerebral vasomotor reactivity in neurodegenerative diseases

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ABSTRACT

Small-caliber cerebral vessels change their diameters in response to alterations of key metabolite concentrations such as carbon dioxide or oxygen. This phenomenon, termed the cerebral vasomotor reactivity (CVMR), is the basis for blood flow regulation in the brain in accordance with its metabolic status. Typically, CVMR is determined as the amount of change in cerebral blood flow in response to a vasodilating stimulus, which can be measured by various neuroimaging methods or by transcranial Doppler. It has been shown that CVMR is impaired in cerebrovascular diseases, but there is also evidence of a similar dysfunction in neurodegenerative disorders. Here, we review studies that have investigated CVMR in the common neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and multiple sclerosis. Moreover, we discuss potential neurodegenerative mechanisms responsible for the impairment of CVMR.

1. Introduction

Cerebral blood flow (CBF) is controlled by three principle mechanisms – pressure regulation, neurogenic regulation, and metabolic regulation [1]. Pressure regulation, also referred to as the cerebral autoregulation, is a mechanism responsible for maintaining a constant CBF within a certain range of arterial blood pressure, whereas neurogenic regulation is the control of the vascular tone by both peripheral nervous system as well as central nervous system (CNS). Metabolic regulation is a mechanism responsible for keeping balance between energy supply and demand in the CNS. At the cellular level, these three mechanisms interact within a functional unit, termed the neurovascular unit (NVU), consisting of vascular cells, glial cells and perivascular nerves [2] (Fig. 1).

1.1. Metabolic regulation of CBF and cerebral vasomotor reactivity

It has been shown that CBF rises in response to an increasing arterial carbon dioxide concentration and decreasing arterial pH, whereas oxygen has the opposite effect [3]. These effects are mediated by changes in diameters of cerebral arterioles, and therefore, this phenomenon is described as the cerebral vasomotor reactivity (CVMR). It should be noted that CVMR is

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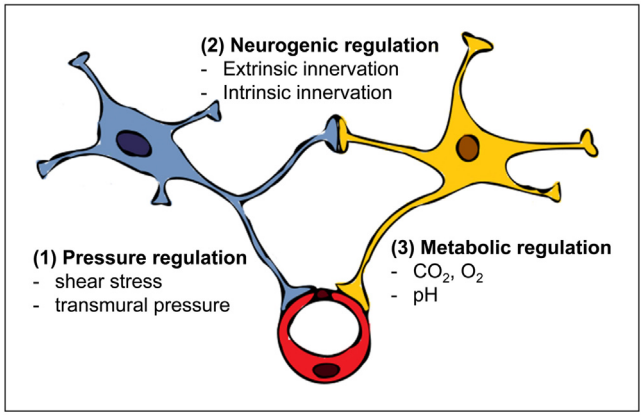

Fig. 1 – Control of cerebral blood flow and the neurovascular unit. At the cellular level, CBF is controlled by the NVU – a tripartite unit consisting of neurons (blue), vascular cells (red), and glial cells (yellow). (1) Pressure regulation is achieved by a reflex constriction of vascular cells in response to increased flow velocity (shear stress) and increased transmural pressure. (2) Neurogenic regulation is the control of vascular tone by both autonomic neurons (extrinsic innervation) and CNS neurons/interneurons (intrinsic innervation), (3) Metabolic regulation is responsible for maintaining appropriate levels of e.g. oxygen, carbon dioxide. CBF–cerebral blood flow, CVMR, cerebral vasomotor reactivity; NVU, neurovascular unit. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

different from the notion of neurovascular coupling (functional hyperemia), whereby changes in CBF occur in accordance, temporally and spatially, with local brain activity.

1.2. *Measurement of CVMR*

In principle, CVMR is determined by measuring CBF changes following a vasoactive challenge. CBF can be determined directly by neuroimaging methods (e.g. single photon emission computed tomography – SPECT, positron emission tomography – PET, functional magnetic resonance imaging – fMRI) or indirectly through the measurement of blood flow velocity (FV) in major cerebral arteries by transcranial Doppler (TCD). This latter approach is based on the assumption that vasoactive substances exert their effects by acting on small cerebral arterioles, whereas the effect on the major cerebral arteries, in which measurements are made, is negligible [4]. Among all the stimuli used for the assessment of CVMR, CO_2 is regarded as the most reliable [5]. However, other vasodilating stimuli such as intravenous acetazolamide and breath-holding are also commonly used. Lastly, several CVMR indexes have been used so far. Earlier studies used a qualitative approach and classified CVMR in individuals as either present (observable increase in CBF after vasoactive challenge) or absent (no observable change in CBF). More recent studies have used quantitative indexes such as a relative increase in CBF or FV following a vasoactive challenge, which is sometimes additionally normalized per each mm Hg of the increase in end-tidal partial pressure of CO_2 ($ETpCO_2$) that approximates arterial pCO_2. Finally, in the breath-holding test, CVMR is expressed as the breath-hold index (BHI), which is a relative change in FV upon apena divided by the time of breath holding in seconds (usually 30 s).

2. CVMR in neurodegenerative diseases

Below, we review studies that have assessed CVMR in the common neurodegenerative diseases – Alzheimer's disease (AD), Parkinson's disease (PD), and multiple sclerosis (MS).

2.1. *Alzheimer's disease*

Alzheimer's disease (AD) is a neurodegenerative disease that accounts for approximately 70% of dementia cases [6]. Although amyloid beta deposition in the CNS is considered as the central pathological feature of AD, the importance of vascular mechanisms has also been underscored [7]. There have been numerous studies investigating CVMR in AD, and they have been reviewed elsewhere [8,9]. Therefore, they are not described here in detail but are presented in Table 1. In summary, the evidence, especially that coming from more recent studies with appropriate control groups, indicates an impaired CVMR in AD. The clinical significance of CVMR is reflected by the fact that its impairment is associated with an increased risk of both conversion from mild cognitive impairment to AD [10,11] and cognitive decline in AD [12]. However, it remains less clear whether CVMR is affected differentially in AD and vascular dementia (VD).

2.2. *Parkinson's disease*

Parkinson's disease (PD) is a common neurodegenerative disease resulting primarily from the degeneration of dopaminergic neurons of the substatia nigra, which leads to the development of motor symptoms such as tremor, rigidity, and bradykinesia. Moreover, non-motor symptoms such neuropsychiatric symptoms (e.g. depression, dementia, psychotic disturbances) and autonomic symptoms can be present as well [34]. Autonomic dysfunction in PD manifests for instance as orthostatic hypotension [35] and can affect CBF and CVMR as well (see Table 2) [36,37].

Two out of three studies using TCD and breath-hold as a vasoactive stimulus reported significantly impaired BHI in PD patients in comparison to healthy controls [38–40]. In contrast, studies using fMRI for the assessment of CVMR did not show significant differences between PD patients and controls [41,42]. Similarly, the change in FV induced by hyperventilation was normal in PD patients [43]. Moreover, studies without control groups also indicated that CVMR in PD patients might be normal [44,45]. Because of the inconsistency of results between studies and a low number of studies that typically enrolled small samples, no definite conclusion as to a possible CVMR impairment in PD can be made. However, it seems that CVMR is not affected by dopaminergic treatment [38,39,41,45].