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Review

The capillary dysfunction hypothesis of Alzheimer's disease

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ABSTRACT

It is widely accepted that hypoperfusion and changes in capillary morphology are involved in the etiopathogenesis of Alzheimer's disease (AD). This is difficult to reconcile with the hyperperfusion observed in young high-risk subjects. Differences in the way cerebral blood flow (CBF) is coupled with the local metabolic needs during different phases of the disease can explain this apparent paradox. This review describes this coupling in terms of a model of cerebral oxygen availability that takes into consideration the heterogeneity of capillary blood flow patterns. The model predicts that moderate increases in heterogeneity requires elevated CBF in order to maintain adequate oxygenation. However, with progressive increases in heterogeneity, the resulting low tissue oxygen tension will require a suppression of CBF in order to maintain tissue metabolism. The observed biphasic nature of CBF responses in preclinical AD and AD is therefore consistent with progressive disturbances of capillary flow patterns. Salient features of the model are discussed in the context of AD pathology along with potential sources of increased capillary flow heterogeneity.

1. Introduction

There is accumulating evidence of a link between cerebral vascular dysfunction and Alzheimer's disease (AD) (Iadecola, 2010; Kalaria, 2010; Pantoni, 2010; Zlokovic, 2011). This includes disruptions in the normal regulation of cerebral blood flow (CBF) by arterioles, also called neurovascular dysfunction (Girouard and Iadecola, 2006), and disturbances in the morphology and function of the capillary wall. The latter involve endothelial atrophy and collapse, thickened and irregular basement membranes, pericapillary fibrosis, swelling of the surrounding astrocytic end-feet, and increased permeability of the blood-brain barrier (BBB) (Bell and Zlokovic, 2009; Bell et al., 2012; Farkas and Luiten, 2001; Kalaria, 1996; Perlmutter and Chui, 1990). Capillary disturbances have been observed as antecedents to neurodegenerative changes associated with dementia in animal models (Bell et al., 2010, 2012). Neurovascular dysfunction is a common feature of hypertension and stroke, both of which are major risk factors for AD (Girouard and Iadecola, 2006), and hypoperfusion has been shown to precede the development of AD symptoms (Hirao et al., 2005; Ruitenberg et al., 2005). These observations suggest that vascular changes and hypoperfusion are intimately involved in the etiopathogenesis of the disease.

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However, it is difficult to reconcile this view with the observation of abnormally high CBF levels in asymptomatic carriers of the apolipoprotein E (APOE) ε4 AD risk gene, which is believed to be an important factor in the etiology of more than half of all AD cases (Corder et al., 1993). In asymptomatic APOE ε4 carriers, brain regions that are vulnerable to AD pathology have elevated resting CBF (Fleisher et al., 2009; Scarmeas et al., 2003; Thambisetty et al., 2010) and increased CBF responses during functional activation (Scarmeas et al., 2005), compared with control subjects. In addition, several functional magnetic resonance imaging studies reveal elevated blood oxygen level-dependent (BOLD) amplitudes in the mediotemporal cortex during memory encoding tasks in asymptomatic APOE ε4 carriers (Bookheimer et al., 2000; Braskie et al., 2010; Filippini et al., 2009; Fleisher et al., 2009; Trachtenberg et al., 2012). The biphasic nature of the CBF and BOLD changes during the course of the disease are illustrated in Fig. 1. The initial hemodynamic abnormalities can be detected in high-risk subjects decades before the typical onset of symptoms (Filippini et al., 2009; Scarmeas et al., 2003, 2005). This implies that there is either or both an increase in the CBF response and a decrease in oxygen extraction fraction (OEF) during periods with increased metabolic demands. Although APOE ε4 carriers and AD patients develop hypoperfusion before the onset of symptoms (Hirao et al., 2005; Ruitenberg et al., 2005) the observation of early hyperperfusion contradicts the idea that hypoperfusion is the initial event in the development of AD. Differences in the way in which CBF is coupled with the metabolic needs during the different phases of the disease can explain this apparent paradox in terms of factors that disturb the pattern of erythrocyte flow through capillary networks. Accordingly, the presymptomatic hyperperfusion and the subsequent hypoperfusion can both be viewed as neurovascular adjustments that attempt to maintain the availability of oxygen for the tissue.

2. Metabolic effects of capillary flow patterns

The local availability of diffusible substances, such as oxygen, is traditionally described by the Bohr-Kety-Crone-Renkin (BKCR) equation (Renkin, 1985) in terms of 3 hemodynamic parameters. Accordingly, net extraction is thought to be limited by (1) regional CBF; (2) capillary permeability; and (3) the capillary surface area. Capillary surface area is determined by capillary density, length, and blood volume per unit volume. Under normal conditions, regional CBF is the main factor that determines local oxygen availability. In contrast, capillary permeability is not thought to be a limiting factor, because of the high diffusibility of oxygen molecules across the BBB (Abbott et al., 2010). Capillary surface area also does not appear to play a role, because there is no evidence in brain tissue of capillary recruitment, that is, the opening of additional capillaries in response to increased metabolic demands (Kuschinsky and Paulson, 1992). Capillary surface area is therefore considered to be constant and proportional to the square root of the capillary density under normal circumstances. It can only be expected to change in response to a long-term reduction in oxygenation that results in angiogenesis. As a consequence, hypoperfusion and reductions in capillary density would appear to be the only hemodynamic factors in the original BKCR relationship that could lead to decreased oxygen supply, neuronal dysfunction, and neurodegeneration.

The use of the BKCR equation to describe oxygen extraction in tissue involves the implicit assumption that the flow of erythrocytes through individual capillaries is uniform. However, it is now well established that the flow velocities of erythrocytes through the individual capillaries during rest are not homogenous (Kleinfeld et al., 1998; Pawlik et al., 1981; Villringer et al., 1994). Capillary flow patterns are complex functions of capillary bed topology, blood viscosity, variable adhesion of blood cells to capillary walls, local capillary constrictions, and the relative number, deformability, and size of the blood cells (8–16 μm) relative to typical capillary diameters (6–8 μm) (Mazzoni and Schmid-Schonbein, 1996). Fig. 2 illustrates how the heterogeneity of capillary flows reduces the extraction of oxygen relative to that which would have been predicted from the BKCR paradigm (Østergaard et al., 2000). In view of this observation, we have recently extended the BKCR model to include the effects of capillary transit time heterogeneity (CTTH) on the oxygenation of tissue (Jespersen and Østergaard, 2012). According to the extended BKCR model, a reduction in CTTH is an integral part of the hemodynamic response to increased metabolic

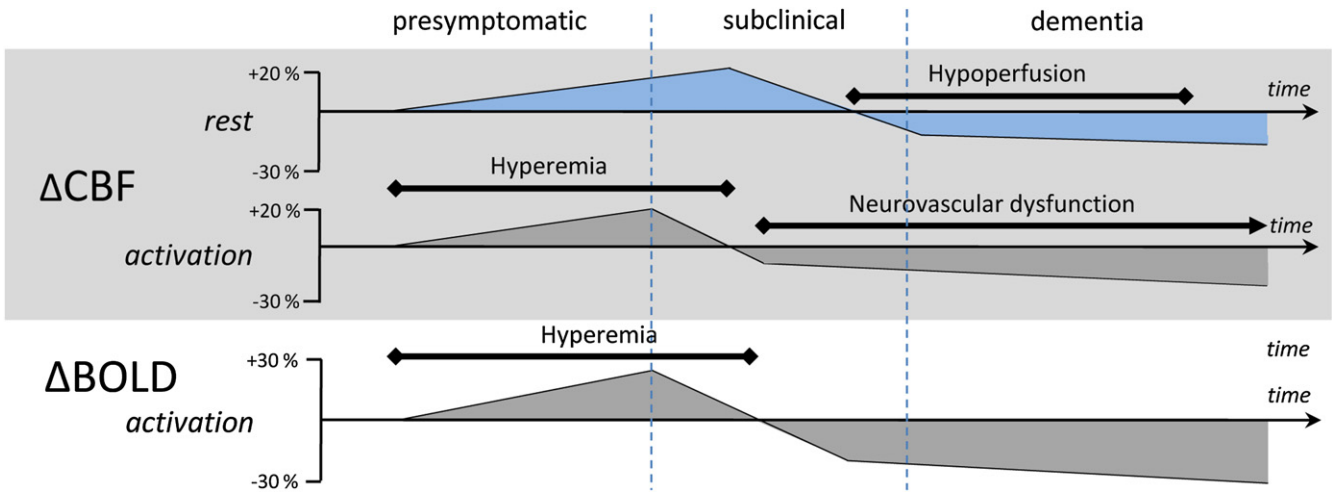

Fig. 1. Summary of neuroimaging studies of cerebral blood flow and blood oxygen level-dependent (BOLD) contrast changes in apolipoprotein E (APOE) ε4 carriers, in presymptomatic Alzheimer's disease (AD), and in AD. The graphs summarize reported measurements of resting cerebral blood flow (CBF) and activity-related changes in CBF and BOLD signal amplitude during the course of AD. The presymptomatic phase refers to measurements in young carriers of the APOE ε4 allele (Bookheimer et al., 2000; Filippini et al., 2009; Fleisher et al., 2009; Scarmeas et al., 2003, 2005; Trachtenberg et al., 2012). The subclinical phase refers to measurements made in the years preceding the diagnosis of AD (Hirao et al., 2005; Ruitenberg et al., 2005). The changes in CBF during rest and during activation (ΔCBF) are given as percent changes relative to normal controls. Therefore, y = 0 corresponds to normal CBF values at rest and normal CBF responses during activation. BOLD signal changes are measured relative to a resting condition. Accordingly, changes in BOLD signal amplitudes (ΔBOLD) are affected by changes in both CBF at rest and during activation and the oxygen extraction fraction (OEF) in the two conditions. Note the biphasic nature of all curves. Initially, subjects show increased CBF during rest, and elevated CBF and BOLD responses during activation. In contrast, a gradual decrease in CBF at rest is observed in the years preceding diagnosis of AD. Similarly, BOLD responses are attenuated in AD. Attenuated CBF responses are referred to as neurovascular dysfunction.