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Myogenic and metabolic feedback in cerebral autoregulation: Putative involvement of arachidonic acid-dependent pathways

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ABSTRACT

The present paper presents a mechanistic model of cerebral autoregulation, in which the dual effects of the arachidonic acid metabolites 20-hydroxyeicosatetraenoic acid (20-HETE) and epoxyeicosatrienoic acids (EETs) on vascular smooth muscle mediate the cerebrovascular adjustments to a change in cerebral perfusion pressure (CPP). 20-HETE signalling in vascular smooth muscle mediates myogenic feedback to changes in vessel wall stretch, which may be modulated by metabolic feedback through EETs released from astrocytes and endothelial cells in response to changes in brain tissue oxygen tension. The metabolic feedback pathway is much faster than 20-HETE-dependent myogenic feedback, and the former thus initiates the cerebral autoregulatory response, while myogenic feedback comprises a relatively slower mechanism that functions to set the basal cerebrovascular tone. Therefore, assessments of dynamic cerebral autoregulation, which may provide information on the response time of the cerebrovasculature, may specifically be used to yield information on metabolic feedback mechanisms, while data based on assessments of static cerebral autoregulation represent the integrated functionality of myogenic and metabolic feedback.

Introduction

Cerebral autoregulation functions to keep cerebral blood flow (CBF) relatively constant across a wide range of cerebral perfusion pressures (CPP; mean arterial blood pressure [MAP] – intracranial pressure [ICP]), by causing cerebral vasoconstriction when CPP increases, and cerebral vasodilation when CPP decreases [1–4]. Both myogenic and metabolic feedback mechanisms are critical to this response [4–7], and probably act in synergy. The basis of myogenic feedback is the intrinsic myogenic response in the cerebral vessels; hence, as the CPP is elevated by an increase in MAP, the concomitant increase in vessel wall stretch will induce vasoconstriction so that CBF is maintained, and *vice versa* when MAP is reduced [5,6,8]. In contrast, metabolic feedback involves the build-up of vasodilatory metabolites in the brain tissue, due to the instantaneous decrease in flow that occurs upon a reduction in CPP, which then causes cerebral vasodilation and normalises CBF; the opposite occurs because the release of these metabolites is reduced when CPP increases [4,8]. In terms of the temporal course of the cerebral autoregulatory response, it has previously been asserted that myogenic mechanisms are faster and thus initiate the response, while metabolic mechanisms mediate the slower components of the response [9,10]. In the present paper, I conversely propose that metabolic feedback mechanisms specifically mediate the rapid component, while myogenic feedback is relatively slower and functions to set the basal cerebrovascular tone. I furthermore provide putative cellular mechanisms that may account for this interplay between myogenic and metabolic feedback, which notably involve arachidonic acid-dependent pathways.

Relationship between myogenic and metabolic feedback

The presence of myogenic feedback in the cerebrovasculature has been documented in numerous studies, which have reported that a parallel increase in CPP and vessel wall stretch causes cerebral vasoconstriction, regardless of whether this is achieved by an increase in MAP or a decrease in ICP [11–14]; moreover, a corresponding reduction in CPP and vessel wall stretch by either a decrease in MAP or an increase in ICP causes vasodilation [15–22]. However, several studies have concluded that myogenic mechanisms responses cannot account for cerebral autoregulation alone. Hence, an increase in intravascular cerebral venous pressure, which reduces CPP while *increasing* vessel wall stretch, induces

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cerebral vasodilation [20,21,23–27]. If myogenic feedback were the sole mechanism responsible for cerebral autoregulation, an increase in intravascular cerebral venous pressure would cause vasoconstriction, and thus reduce CBF in response to the consequent reduction in CPP. These findings thus stress that the myogenic response is modulated by a complementary feedback mechanism in accordance with the brain's metabolic needs.

While the exact mediator of metabolic feedback in cerebral autoregulation is currently unknown [4,7,28], there is a lot to suggest that changes in brain oxygen tension act as an upstream 'trigger' of its release [29]. Accordingly, brain tissue oxygen tension has been reported to exhibit oscillations with a period of about 10 s, comprising so-called "oxygen cycles" [30], which are probably caused by instantaneous changes in CBF due to fluctuations in CPP, since their frequency coincides with that of similar spontaneous oscillations in arterial blood pressure [31]. They are accompanied by concurrent changes in cerebrovascular resistance, which are likely to represent autoregulatory adjustment triggered by the changes in brain oxygen tension [30]. Accordingly, the changes in vasomotor tone cease at MAP values where maximal autoregulatory vasodilation or vasoconstriction has been reached [30]. Other studies have demonstrated that the cerebral vasodilatory response to a reduction in MAP is eliminated when the instantaneous reduction in brain tissue oxygen tension that occurs upon a reduction in CPP is prevented by keeping the brain tissue hyperoxic [32,33]. Brain tissue hyperoxia furthermore converts the cerebral vasodilatory response to an increase in intravascular cerebral venous pressure to vasoconstriction [26], thus unmasking the underlying myogenic response, and stressing that myogenic and metabolic feedback do indeed interact to mediate cerebral autoregulation. Furthermore, the extent of the change in cerebrovascular resistance that may be induced by metabolic feedback at a given CPP is probably limited by myogenic feedback, since the CPP associated with maximal autoregulatory vasodilation, is higher when the CPP is reduced by an increase in cerebral venous pressure compared to a decrease in MAP or an increase in ICP [25].

Cerebrovascular response times

Between the 1960s and 1980s, a number of authors asserted that the autoregulatory response to a steady state change in CPP is initiated within three to eight seconds, and complete within a minute. This was based on both theoretical predictions and direct observations of cerebral vessels during various experiments [13,15,34–36]. As the transcranial Doppler ultrasound technique was developed in the 1980s, it became possible to study the cerebrovascular response times with an unprecedented temporal solution [37], and it was thus shown that the cerebrovascular response to a sudden drop in MAP induced by thigh cuff deflation is initiated within approximately two seconds, and complete after ten to fifteen seconds [38]. Of note, findings from both classical and recent transcranial Doppler ultrasound-based studies furthermore imply that cerebral autoregulatory responses times are asymmetric, since the vasodilatory response to a reduction in CPP tends to be faster than the vasoconstrictor response to an increase in CPP [13,39].

How well do the observed cerebrovascular response times fit with the assertion that the myogenic response accounts for the faster component of a cerebral autoregulatory response [9,10]? Surprisingly, the response times of cerebrovascular myogenic responses vary considerably, but do not appear to set in until after about six seconds, and although most of the diameter adjustments occur within the first thirty seconds, the response may not be complete till after four to five minutes [40]. Furthermore, the response time appears to be slightly faster to an increase rather than a decrease in cerebral vessel wall stretch, which is the opposite of cerebral autoregulatory responses [40]. In contrast to cerebral myogenic responses, metabolic stimuli, such as seizures, functional activation, and hypoxia, do indeed evoke cerebrovascular responses within a few seconds [13,33,37].

While it is clear that both myogenic and metabolic mechanisms are involved in cerebral autoregulation, the above points towards metabolic feedback as the most attractive explanation of the fast component of the cerebral autoregulatory response, while intrinsic myogenic feedback mechanisms are probably slower, and primarily function to set the basal cerebrovascular tone, and perhaps to limit the extent of cerebrovascular vasodilation and -constriction in response to metabolic feedback. In the following section, I describe the putative signalling pathways that may account for this interplay between myogenic and metabolic feedback.

Cellular pathways of the myogenic response

It is well established that the cerebral myogenic response involves the formation of the vasoconstrictor 20-hydroxyeicosatetraenoic acid (20-HETE) [41]. 20-HETE is the major arachidonic acid hydroxylase metabolite of the cytochrome P-450 4A in cerebral arterial smooth muscle [42,43]. Elevations in transmural pressure increases the intracellular concentration of 20-HETE and induces vasoconstriction of rat cerebral arterial vessels *in vitro*, and this is blocked by cytochrome P-450 inhibition [44]. Cytochrome P-450 inhibition furthermore impairs cerebral autoregulation in rats *in vivo* [44].

The pathways that are believed to link increased vessel wall stretch to enhanced 20-HETE formation and subsequent vascular smooth muscle cell contraction involves inhibition of calcium-dependent potassium channels, and will briefly be outlined here (Fig. 1). As the transmural pressure is increased, stretch of the vascular smooth muscle cell activates a mechano-sensitive G-coupled protein (G_{st}), which probably belongs to the group of P_{2Y} pyrimidine receptors [42], and a so-called stretch-activated cation channel (SAC). G_{st} activates phospholipase C (PLC) [45,46], so that intracellular levels of 1,4,5-trisphosphate (IP_3) are increased, and calcium is released from the sarcoplasmic reticulum (SR). SAC depolarises the cell membrane [47], which then activates L-type calcium (L_{Ca}) channels and causes a calcium influx from the extracellular space.

The increased intracellular calcium levels have two main effects: (1) activation of transient receptor potential (TRP) channels which are monovalent selective cation channels that cause further depolarisation of the cell membrane [48,49], thus promoting further calcium influx through L_{Ca}; (2) activation of the contractile machinery of the vascular smooth muscle cell. However, TRP is only briefly sensitive to calcium, and calcium simultaneously activates the calcium-activated potassium channel, which causes cell membrane hyperpolarisation through potassium efflux, thus antagonising any activation of the contractile machinery. This is where 20-HETE becomes critical. Apart from IP_3, PLC also increases the intracellular levels of diacylglycerol (DAG) [50], while the raised intracellular calcium levels activates the calcium-dependent phospholipase A_2 (PLA_2), and these act in concert to release arachidonic acid from membrane-bound phospholipid pools. Cytochrome P-450 4A then forms 20-HETE from arachidonic acid [43,51], which then translocates protein kinase C (PKC) to the cytosol [52]. PKC phosphorylates TRP and the calcium-activated potassium channel [52,53], while 20-HETE furthermore directly increases L_{Ca} activity [42]. TRP thereby maintains its calcium sensitivity, so that it can depolarise the membrane, while the hyperpolarising effect of the calcium-activated potassium channel is attenuated. Calcium influx through L_{Ca} may then ensue with a pronounced increase in intracellular calcium, activation of the contractile machinery, and consequently vascular smooth muscle cell contraction [43].