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TOPICAL REVIEW

Integrative regulation of human brain blood flow

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Abstract Herein, we review mechanisms regulating cerebral blood flow (CBF), with specific focus on humans. We revisit important concepts from the older literature and describe the interaction of various mechanisms of cerebrovascular control. We amalgamate this broad scope of information into a brief review, rather than detailing any one mechanism or area of research. The relationship between regulatory mechanisms is emphasized, but the following three broad categories of control are explicated: (1) the effect of blood gases and neuronal metabolism on CBF; (2) buffering of CBF with changes in blood pressure, termed cerebral autoregulation; and (3) the role of the autonomic nervous system in CBF regulation. With respect to these control mechanisms, we provide evidence against several canonized paradigms of CBF control. Specifically, we corroborate the following four key theses: (1) that cerebral autoregulation does not maintain constant perfusion through a mean arterial pressure range of 60–150 mmHg; (2) that there is important stimulatory synergism and regulatory interdependence of arterial blood gases and blood pressure on CBF regulation; (3) that cerebral autoregulation and cerebrovascular sensitivity to changes in arterial blood gases are not modulated solely at the pial arterioles; and (4) that neurogenic control of the cerebral vasculature is an important player in autoregulatory function and, crucially, acts to buffer surges in perfusion pressure. Finally, we summarize the state of our knowledge with respect to these areas, outline important gaps in the literature and suggest avenues for future research.

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Abbreviations BP, blood pressure; CA, cerebral autoregulation; CBF, cerebral blood flow; CSF, cerebrospinal fluid; ICA, internal carotid artery; L-NMMA, N^G-monomethyl-L-arginine; MAP, mean arterial pressure; MRI, magnetic resonance imaging; P_{aCO_2}, arterial partial pressure of carbon dioxide; P_{aO_2}, arterial partial pressure of oxygen; PET, positron emission tomography; SNS, sympathetic nervous system; VA, vertebral artery.

Christopher Willie discovered physiology as an undergraduate student in the laboratory of Dr. Richard Wilson while working toward his Bachelors of Health Science degree at the University of Calgary. He met Dr Philip Ainslie at the same time and five years later began his PhD under Dr Ainslie's supervision. Mr. Willie's interests are studying human integrative physiology, with focus on cerebrovascular responses to changes in blood gases and blood pressure. To keep balanced, he enjoys rock, ice and alpine climbing around the world. In the future, Mr Willie plans to continue both his scientific and adventurous pursuits. Philip Ainslie is currently a Professor in the School of Health and Exercise Sciences at the University of British Columbia- Okanagan and holds a Canada Research Chair in Cerebrovascular Physiology. His main research focus attempts to examine the fundamental mechanisms that regulate human cerebral blood flow in health and in disease. He has a particular interest in how environmental stress – especially in the context of hypoxia, temperature, pressure and exercise – may impact on cerebral blood flow regulation.

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Introduction

Due to limited capacity for substrate storage (Brown & Ransom, 2007) and the high metabolic rate of brain tissue, the precise regulation of cerebral blood flow (CBF) is critical for maintenance of constant nutrient and oxygen supply to the brain. Substantial reductions in CBF quickly lead to unconsciousness (Van Lieshout *et al.* 2003) and, if maintained, brain damage and death ensues (Smith *et al.* 2011). Fastidious control of CBF involves a wide spectrum of overlapping regulatory mechanisms that together work to ensure optimal oxygen and nutrient delivery (Fig. 1). The fact that these mechanisms are present and largely unique to the cerebrovasculature does not obviate the importance of maintained systemic cardiovascular control. Yet, as will be explicated in this review, CBF regulation is often assumed to be so efficacious that it is treated separately, instead of as an integral component of the cardiovascular system.

The partial pressure of arterial carbon dioxide (P_{aCO_2}), mean arterial pressure (MAP), cerebral metabolism and the autonomic nervous system are the principal regulators of CBF. The regulation of CBF should not, therefore, be viewed as being limited to mechanisms within the cranium. Rather, the regulation of CBF should be noted as an integrative process that involves the marked influence of pulmonary gas exchange and cardiovascular function in addition to intracranial mediators of cerebral vessel resistance (and therefore flow). Despite over a century of study (Mosso, 1880; Roy & Sherrington, 1890), establishing an integrative understanding of these mechanisms in humans has been difficult (if not impossible) to achieve for a number of reasons. Over the past 50 years, a reductionist approach to cerebrovascular physiology has dominated the field, largely because of the difficulty of *in vivo* brain vascular assessment. The prevailing use of transcranial Doppler ultrasound in human CBF research since the late 1980s introduced assumptions of intracerebral vessel characteristics that are increasingly being shown to be incorrect. Finally, there has been limited study of CBF regulatory mechanisms in humans in the literature of the past decade.

This review aims to concentrate on human cerebrovascular control from an integrative standpoint in the hope of stimulating resurgent interest in a field of study that lags behind those of other systems of the body. We endeavour to synthesize an expansive scope of information into a brief review rather than detail specific areas or mechanisms of cerebrovascular control; there are specific reviews on many of the topics we cover herein, to which the reader will be referred throughout.

Four broad sections, each focusing on an important facet of cerebrovascular control, are delineated below. The first section discusses the metabolic control of CBF, from systemic metabolism and the consequent coupling of arterial blood gases and CBF to the effect of local neuronal metabolism on local CBF. The second section provides an overview of how the cerebrovasculature buffers changes in blood pressure (BP), termed cerebral autoregulation (CA), and how systemic and local metabolism might, in turn, affect CA. The third section covers the role of the autonomic nervous system in CBF regulation and, finally, the fourth section summarizes the state of our knowledge on cerebrovascular regulation, reiterating key gaps in our understanding and suggesting avenues for future research.

Metabolic regulation of cerebral blood flow

Regulation by arterial blood gases. Brain perfusion is highly sensitive to changes in changes in P_{aCO_2}. Studies using transcranial Doppler ultrasound of the middle (Ide *et al.* 2003; Battisti-Charbonney *et al.* 2011) and posterior cerebral arteries and the basilar artery (Skow *et al.* 2013), and Duplex ultrasound of the internal carotid artery (ICA) and vertebral artery (VA; Sato *et al.* 2012; Willie *et al.* 2012) all show an approximate 3–6% increase and/or 1–3% decrease in flow per millimetre of mercury change in CO_2 above and below eupnoeic P_{aCO_2}, respectively (see Figure 2, left). Imaging studies show broadly comparable results (Kemna *et al.* 2001; Mandell *et al.* 2008; Piechnik *et al.* 2008). It is important to recognize that methodological differences make comparison between studies difficult. These differences include the following factors: steady-state *versus* rebreathing methods of CO_2 manipulation; linear *versus* non-linear analyses of the cerebrovascular response to hypocapnia, hypercapnia or the entire manipulated range of CO_2; whether arterial partial pressure of O_2 (P_{aO_2}) is maintained during CO_2 manipulation; and the method of CBF measurement. All these factors influence the values of CBF reactivity to changes in P_{CO_2} (extensively reviewed by Ainslie & Duffin, 2009; Fierstra *et al.* 2013). Regardless, this high vascular sensitivity to CO_2 is unique to the cerebrovasculature (Ainslie *et al.* 2005) and is manifest throughout, from the large arteries of the neck (Willie *et al.* 2012) through the large intracranial arteries (Giller *et al.* 1993; Wilson *et al.* 2011; Willie *et al.* 2013b) to the smallest pial arterioles (Wolff & Lennox, 1930) and parenchymal vessels (Binks *et al.* 2008; Mandell *et al.* 2008; Nöth *et al.* 2008; Piechnik *et al.* 2008). This sensitivity appears to be similar between brain regions in the hypercapnic range, but dissimilar with hypocapnia (Sato *et al.* 2012; Willie *et al.* 2012), as assessed by flow through the arteries of the neck. Based on magnetic resonance imaging (MRI) data, CO_2 reactivity of the microvasculature in grey matter is greater than that of white matter, probably because of relatively less vascularization (Mandell *et al.* 2008; Nöth *et al.* 2008).

The cerebrovasculature is sensitive to hypoxia, but only below a P_{aO_2} of ∼50 mmHg, (see Figure 2,

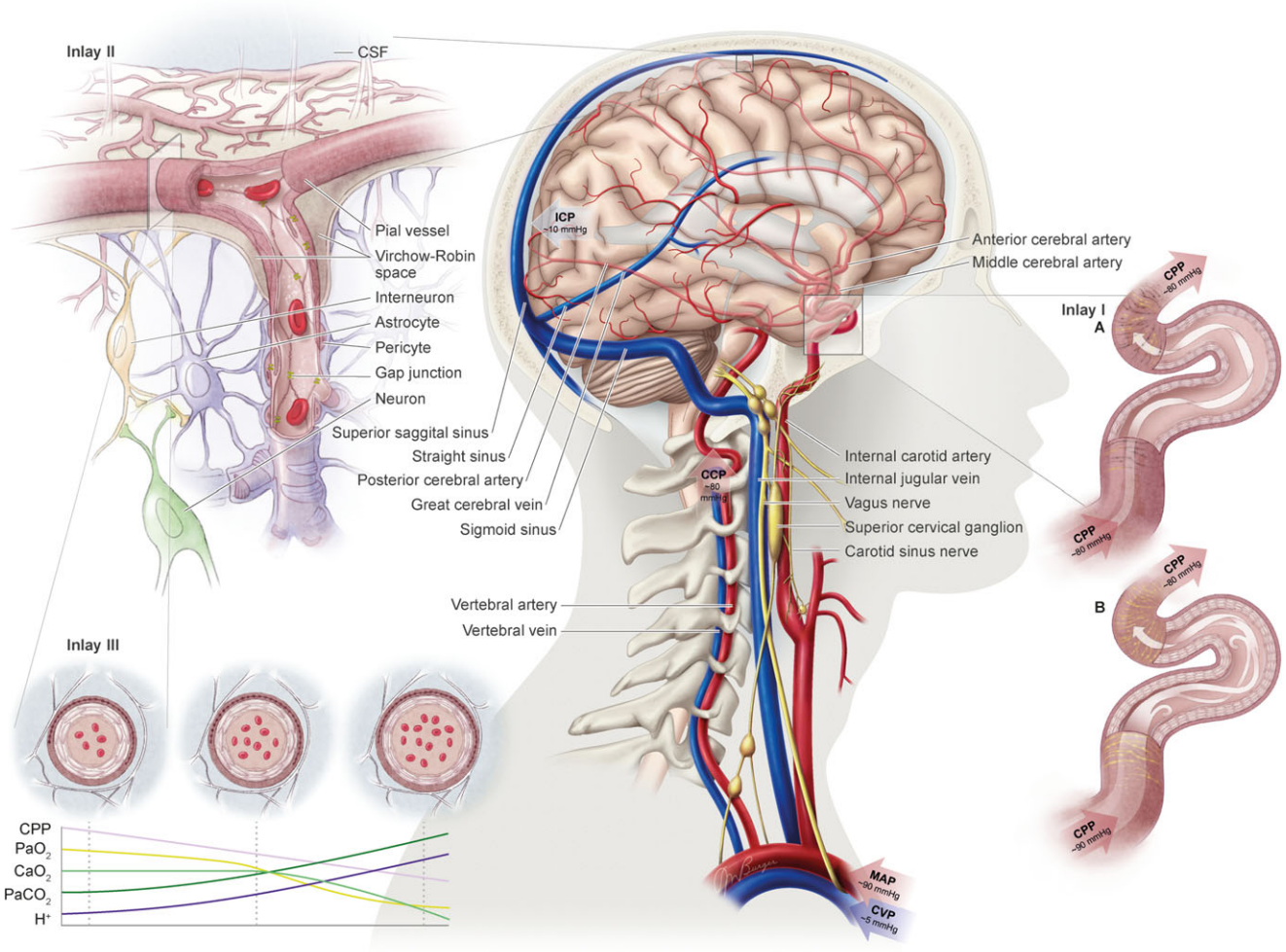

Figure 1. Schematic diagram illustrating the anatomy and key mechanisms of regulation in the cerebrovasculature

The central figure depicts the cerebrovasculature, comprised of two pairs of large arteries that branch from the sublavian arteries, i.e. the internal carotid arteries (ICAs) that carry ∼70% of total cerebral blood flow (CBF) and the vertebral arteries (VAs) that distribute ∼30% of total CBF to the brainstem, cerebellum and occipital cortex. Both the ICAs and VAs anastomose to form the circle of Willis before branching out into the main intracerebral arteries that ramify extensively en route to the brain surface. At the surface, the vessels form a dense network of highly vasoactive arterioles within the pia mater before they penetrate into the cortex (inlay II). The driving pressure in this system is the cerebral perfusion pressure (CPP) that is determined by the difference between mean arterial pressure (MAP) and intracranial pressure (ICP), in conditions where central venous pressure (CVP) is lower than ICP. In these conditions, MAP approximates CPP. Thus, it is important to note that the figure shows a schematic diagram of the cerebrovascular state in a resting supine human, and does not consider the myriad complex adjustments that take place with orthostatic stress (Gisolf *et al.* 2004; Hicks & Munis, 2005). As a result of the enclosed nature of the skull, ICP acts as a Starling resistor for cerebral venous outflow, a mechanism that is likely to be of greater importance with marked elevations in ICP or CVP, or both. The cerebral arteries (including the ICAs and VAs) are sensitive to changes in blood gases (Heistad *et al.* 1978*a*; Faraci *et al.* 1987*a*; Willie *et al.* 2012) and to changes in perfusion pressure, thus serving as a first-line defense in maintaining brain perfusion (Faraci *et al.* 1987*a*, *b*; inlay I). These arteries are also densely innervated with branches of the cranial nerves, the carotid sinus nerve and branches from the superior cervical ganglion. The role of these nerves is contentious, but evidence favours cerebral constriction in response to increased sympathetic outflow and/or increased MAP, particularly at the tortuous segments where the ICA and VA vessels enter the skull. Turbulent blood flow through these segments increases resistance for a given luminal diameter according to Poiseuille's law; constriction of the vessel in these sections in the face of increased MAP attenuates pressure increases distal to the tortuous segment (inlay I). Inlay II shows a neurovascular unit. The pial vessels respond to changes in CPP, arterial partial pressures of O_2 (P_{aO_2}) and CO_2 (P_{aCO_2}), oxygen content, and proton concentration (Wolff & Lennox, 1930; Kontos *et al.* 1978; inlay III). The pial arteriole penetrates the pia mater through the Virchow–Robin space, where it becomes encapsulated by glial processes termed end-feet and pericytes that release vasoactive substances and respond mechanically by constricting or dilating with changes in

right). The response is dependent on the prevailing P_{aCO_2}; hypercapnia increases and hypocapnia decreases cerebrovascular sensitivity to hypoxia (Mardimae *et al.* 2012). Studies of hypoxic cerebrovascular reactivity are thus confounded by the ventilatory response to hypoxia, which produces hypocapnia and results in cerebrovascular constriction (i.e. poikilocapnia). Studies incorporating a range of techniques that have assessed the CBF response to isocapnic hypoxia have reported CBF reactivities ranging from 0.5 to 2.5% increase in CBF per percentage point reduction in arterial saturation of O_2 (Cohen *et al.* 1967; Shapiro *et al.* 1970; Jensen *et al.* 1996; Querido *et al.* 2008, 2013; Reichmuth *et al.* 2009; Willie *et al.* 2012). Variability in the methods of blood gas manipulation, consequent changes in BP and degree of (or lack of) P_{aCO_2} clamping necessitated by the ventilatory response to hypoxia (Shapiro *et al.* 1970; Kolb *et al.* 2004; Willie *et al.* 2012) lead to variation in population norms, and values in the literature vary considerably, perhaps exacerbated by different sensitivities to hypoxia between brain regions. For a given severity of isocapnic hypoxia, blood flow to the brainstem increases more than that to the middle and anterior regions, as assessed by flow through the vertebral and internal carotid arteries, respectfully (Willie *et al.* 2012; Ogoh *et al.* 2013). Congruous positron emission tomography (PET) scan data collected during isocapnic hypoxia reveal that cortical blood flow is less responsive to hypoxia than phylogenetically older areas of the brain (Binks *et al.* 2008). Unlike the response to P_{aCO_2}, the CBF response to oxygen appears to be determined by oxygen content rather than P_{aO_2} *per se*, because a reduction in oxygen content resulting from carbon monoxide exposure, acute or chronic anaemia and haemodilution produces increased CBF (Paulson *et al.* 1973; Brown *et al.* 1985; Todd *et al.* 1994; Metry *et al.* 1999; Hare, 2004; Gottesman *et al.* 2012). Indeed, the limited data available suggest that the inverse relationship between blood haematocrit (ergo viscosity) and CBF (Muizelaar *et al.* 1986; Metry *et al.* 1999) is a function of oxygen delivery rather than viscosity *per se* (Todd *et al.* 1994; Tomiyama *et al.* 1999), but this remains to be studied explicitly in humans.

Locations of CO_2 and O_2 sensitivity. Although the entire cerebrovasculature, from the large arteries of the neck to the penetrating cortical arterioles, is sensitive to changes in blood gases, the pial arterioles are generally considered to be the site of resistance modulation. The pial vessel response (dilatation) to asphyxia was observed ∼150 years ago in rabbits (Donders, 1851). Pial arteries dilate up to 40% in response to both increased P_{aCO_2} and increased cerebrospinal fluid (CSF) P_{CO_2} (Wolff & Lennox, 1930; Kontos *et al.* 1977*b*). Increased P_{aCO_2} produces smooth muscle relaxation, vessel dilatation and increased flow, whereas hypocapnia increases cerebrovascular resistance and decreases CBF (Kety & Schmidt, 1948; Wasserman & Patterson, 1961). Their anatomical position in the subarachnoid space, tethered to the abutting mater and surrounded by CSF (Fig. 1, inlays II and III), makes them readily exposed to local metabolic conditions. Thus, the tone of the pial vessels is a function of arterial blood gases, arterial pH and local CSF. As described below (see '*Neurovascular coupling*'), pial vessel resistance is also coupled to downstream metabolic activity via retrograde intramural propagation of vascular signals (Segal, 2000; Lagaud *et al.* 2002; Kawamura *et al.* 2003; Attwell *et al.* 2010; Itoh & Suzuki, 2012).

The cerebral arteries (including the internal carotid and vertebral arteries) are also sensitive to changes in blood gases (Heistad *et al.* 1978*a*; Faraci *et al.* 1987*a*; Willie *et al.* 2012) and perfusion pressure. While the pial arteriolar bed serves to modulate regional blood flow, the large vessels serve as a 'first-line' defense in maintaining brain perfusion (Faraci *et al.* 1987*a*,*b*; Fig. 1, inlay I). It has recently been demonstrated that the ICA and VA of humans are reactive to changes in arterial blood gases, with the ICA showing a ∼20% change in luminal diameter through a P_{aCO_2} range of 15–65 mmHg (Willie *et al.* 2012). The fact that the entire cerebrovascular arterial tree is vasoactive is a key feature of this system. Unified vasomotion allows microvascular pressure to remain relatively constant. For example, if constriction of only the large arteries were to occur, decreased pial artery pressure would result, whereas constriction along the entire cerebrovascular tree reduces flow with no changes in pial pressure (Baumbach & Heistad, 1983). Hypocapnia, for example, therefore produces no changes in small arteriole pressure despite attenuated flow, because small and large arteries both constrict in response to reduced P_{CO_2} (Faraci *et al.* 1987*a*).

Mechanisms of cerebrovascular sensitivity to arterial blood gases. The cellular mechanisms responsible for the cerebrovascular response to changes in P_{aCO_2} and

metabolic demand of the surrounding neural matrix. Gap junctions between the endothelial and vascular smooth muscle cells allow for retrograde conductance of intramural vascular signals such that vasodilatory or constrictive signals pass to the pial arterioles. Thus, the neurovascular unit titrates blood flow to the metabolism of discrete cortical areas. Inlay III shows a qualitative schematic diagram of pial cross-sections against a hypothetical metabolic milieu spectrum. Note the vessels are not only exposed to arterial conditions but also to that of the cerebrospinal fluid that completely surrounds the pial vessel, tethered on all sides by thin processes to the pia mater. The vessels dilate with decreases in perfusion pressure, PaO^2 and/or arterial O_2 content (C_{aO_2}) and increases in P_{aCO_2} and/or $[H^+]$.

P_{aO_2} have been subject of countless studies. Yet, the resulting diversity of conclusions serves largely to demonstrate a mechanistic redundancy inherent to the precise cerebrovascular regulation by arterial blood gases. Next, we will focus on human and select *in vivo* animal studies. Studies employing various *in vitro* vessel preparations are difficult to compare and apply to *in vivo* physiology; for detailed reviews of the *in vivo* literature see Faraci & Heistad, 1998; Yoon *et al.* 2012.

An alteration in alveolar gas exchange (either by changes in alveolar ventilation and/or metabolic CO_2 production) elicits concomitant changes in both P_{aCO_2} and pH. The latter is thus influenced by both respiratory alkalosis and acidosis in the short term and over longer periods by the degree of renal compensation. However, a long-standing question has been which of these (P_{aCO_2} or pH), or both, are responsible for the resultant change in CBF. Direct manipulation of arterial pH does not alter CBF in conditions of maintained P_{aCO_2} (Lambertsen *et al.* 1961; Harper & Bell, 1963). In contrast, manipulation of extravascular pH induces changes in arteriolar diameter (Wahl *et al.* 1970; Kontos *et al.* 1977*a*,*b*). These observations suggest that the CO_2 mechanism is independent of arterial pH and is therefore likely to be dependent on the diffusion of non-polar CO_2 molecules across the cerebrovascular blood–brain barrier that can induce a change in pH in the extracellular space of the vessel, and thus alter vascular smooth muscle tone (Lambertsen *et al.* 1961; Lassen, 1968). This model is supported by animal work using *in vivo* cranial windows and superficial application of solutions with varying P_{CO_2} and pH (Wolff & Lennox, 1930; Kontos *et al.* 1977*b*). For example, hypercapnic and hypocapnic solutions, respectively, cause pial arteriolar dilatation and constriction, providing the superfusate pH is correspondingly acidic or alkaline. In contrast, application of solutions of neutral pH elicits no vasomotion regardless of superfusate P_{CO_2} (Wahl *et al.* 1970; Kontos *et al.* 1977*a*,*b*). Moreover, the effect of arterial hypercapnia is nullified with external (i.e. around the pial vessel) application of alkaline superfusate in rats (Liu *et al.* 2012), dogs (Koehler & Traystman, 1982) and cats (Kontos *et al.* 1977*b*). Likewise, cerebral vascular smooth muscle cells contract with increased pH and relax with decreased pH (Apkon *et al.* 1997; Peng *et al.* 1998). Such evidence for the importance of extracellular pH has been corroborated more recently by *in vivo* vascular preparations as well (e.g. Toda & Okamura, 1998; Dabertrand *et al.* 2012). The net CBF response is thus a balance between the effects of CO_2 *per se* and endothelial signals in response to changes in flow.

Unlike the cerebrovascular response to changes in P_{aCO_2}, hypoxaemia causes little change in CBF until a threshold at the steep portion of the oxyhaemoglobin dissociation curve (~80% arterial saturation of O_2). Hypoxia appears to reduce cerebrovascular smooth muscle tone through activation of membrane potassium channels (Bonnet *et al.* 1991; Gebremedhin *et al.* 2008) and interference with transmembrane calcium flux (Vinall & Simeone, 1986; Pearce *et al.* 1992; reviewed by Pearce, 1995). Studies in baboons (James *et al.* 1969) and dogs (McDowall, 1966; Kogure *et al.* 1970) showed CBF to begin increasing at a P_{aO_2} of ~50 mmHg. Similar data have been published for humans (Ainslie & Poulin, 2004; Willie *et al.* 2012). The processes involved in the hypoxaemia-induced increase in CBF are multifaceted, probably comprising the following: (1) a retrograde stimulus arising at the neurons/glia of the neurovascular unit, i.e. neurovascular coupling, in response to local decreases in tissue oxygen (Pelligrino *et al.* 1995; Thompson *et al.* 2003; Iadecola & Nedergaard, 2007; Gordon *et al.* 2008; Leithner & Royl, 2014); (2) brain extracellular acidosis due to increased neuronal/glial anaerobic metabolism eliciting vascular dilatation (Kogure *et al.* 1970; Nolan *et al.* 1982); and (3) direct vascular mechanisms (see next paragraph). The relative contribution and importance of these processes remain unknown. Particularly with respect to the direct neuronal/glial contribution to hypoxic cerebrovascular dilatation there are few data (Gordon *et al.* 2008), but a direct CNS effect of hypoxia in ventilatory regulation has been described (reviewed by Powell *et al.* 2000; Joseph & Pequignot, 2009). In humans, however, there have been surprisingly few studies that have attempted to examine potential mechanisms by which hypoxia leads to cerebral vasodilatation. Those that have been done in humans have focused principally on the role of adenosine and NO and are considered in detail next.

Adenosine is popularly held to mediate hypoxic cerebral vasodilatation. This is based on the following evidence: (1) adenosine is released with hypoxaemia (Winn *et al.* 1981; Meno *et al.* 1993); (2) in most animal studies adenosine receptor antagonists attenuate the increase in CBF during hypoxaemia (Haller & Kuschinsky, 1987; Morii *et al.* 1987; Pinard *et al.* 1989; Laudignon *et al.* 1990; Coney & Marshall, 1998; Miekisiak *et al.* 2008); and (3) *in vitro* data indicate that adenosine blocks vasoconstrictive signals within the parenchyma (Gordon *et al.* 2008). The few studies assessing the role of adenosine on the human cerebrovasculature have reported a 20–30% decrease in CBF and cerebral oxygen delivery in normoxia (Wechsler *et al.* 1950; Gottstein & Paulson, 1972; Magnussen & Hoedt-Rasmussen, 1977), during competitive adenosine receptor antagonism with aminophylline. Nevertheless, following adenosine receptor blockade, the cerebral hypoxic vasodilatory response in fact remains intact; CBF decreases with aminophylline administration in normoxia but increases with hypoxic exposure, albeit to values approximately equal to normoxic control conditions (Bowton *et al.* 1988; Nishimura *et al.* 1992, 1993). Thus, while the release of adenosine during hypoxia

certainly implicates it in the normal hypoxic cerebral vasodilatory response, it cannot be the sole mediator of the hypoxaemia-induced increase in CBF in humans.

There is similar confusion concerning the role of nitric oxide in mediating hypoxic cerebrovascular dilatation. Studies in animals have reported substantial effects of nitric oxide synthase inhibition on the CBF response to moderate hypoxia (Hudetz *et al.* 1998; Santizo *et al.* 2000; Bauser-Heaton & Bohlen, 2007), whereas others have reported little effect (Pelligrino *et al.* 1993, 1995). Only two studies in humans have assessed nitric oxide synthase inhibition [both via N^G-monomethyl-L-arginine (L-LMMA) infusion] on the cerebrovascular response to 20 min hypoxaemia. Using phase-contrast MRI to measure CBF in healthy young men, Van Mil *et al.* (2002) reported that CBF returned to near-normoxic values following L-NMMA administration during hypoxia (Oxygen saturation (SpO_2) = 80%). Conversely, Ide *et al.* (2007) found L-NMMA to have no effect on the increased CBF with slightly less severe hypoxia (end-tidal P_{O_2} = 50 mmHg; SpO_2 not reported) as assessed with transcranial Doppler ultrasound of the middle cerebral artery. Aside from a larger L-NMMA dose used by Ide *et al.* (2007) and the slightly more severe hypoxia used by Van Mil *et al.* (2002) there was no apparent difference in either the methodology or the reported physiological response of the subjects in these studies (except for CBF), including end-tidal P_{CO_2}. A speculative explanation for these discrepant findings is a change in middle cerebral artery diameter following hypoxia and/or L-NMMA infusion that would confound the estimations of CBF by Ide *et al.* (2007); indeed, middle cerebral artery dilatation in hypoxia is now well documented (Wilson *et al.* 2011; Willie *et al.* 2012, 2013b), as well as after glycerol trinitrate administration (Hansen *et al.* 2007).

Local CBF is tightly coupled to neural metabolism, which is a function of the exquisite physical association between neurons, glia and the microvasculature, together termed the neurovascular unit (see '*Neurovascular coupling*', below). Excitation of astrocytes by hypoxia *in vitro* stimulates the direct and indirect production arachidonic acid metabolites associated with local vasodilatation (Liu & Alkayed, 2005; Yamaura *et al.* 2006). It is difficult to identify in humans the mechanisms of neurovascular coupling involved in the hypoxic vasodilatory response. Given that transient local hypoxia following increased local metabolism is thought to mediate in part the blood oxygen level dependent (BOLD) MRI response during cognitive activation (Vanzetta & Grinvald, 1999; Thompson *et al.* 2003; Offenhauser *et al.* 2005), it is likely that the neurovascular unit is only one of the mechanisms involved in cerebral vasodilatation in hypoxia. This finding suggests both mechanistic redundancy of mediators of hypoxic vasodilatation and synergism between the neurovascular unit and the larger arteries and arterioles of the cerebrovasculature due to their similar responses to hypoxia.

Neurovascular coupling. The fact that local cerebral metabolism is tightly coupled to local brain perfusion has been known, although not understood, for over a century (Donders, 1851; Mosso, 1880; Roy & Sherrington, 1890). This coupling is a product of the anatomical and metabolic relationship between neurons, glial cells and cortical penetrating arterioles (Fig. 1, inlay II) that together comprise the neurovascular unit. Excitatory and inhibitory neurons synapse on both astrocytes and GABAergic interneurons, these interneurons being in close association with astrocytes having processes that terminate in end-feet enveloping cortex-penetrating arterioles. By way of gap junctions between adjacent vascular smooth muscle cells, intramural propagation of vascular signals produces remote vasodilatation of upstream pial arterioles (Fig. 1, inlay II; Lagaud *et al.* 2002; Kawamura *et al.* 2003; Iadecola, 2004). The result is a robust coupling of neuronal activation to regional CBF that can be observed easily with transcranial Doppler ultrasound, for example, by activation of the occipital cortex by visual stimulation that elicits an immediate ~20–30% increase in the blood velocity through the posterior cerebral artery feeding the posterior lobe (Rosengarten *et al.* 2001, 2003; Boms *et al.* 2010; Willie *et al.* 2011). This signalling between the local neuronal metabolic state and the vasculature that feeds it is involved in the response to systemic stimuli, such as hypoxaemia (Liu & Alkayed, 2005; Yamaura *et al.* 2006). There is a rich body of literature based on *in vitro* experimental data devoted to the mechanisms of communication within the neurovascular unit. Numerous excellent reviews have been written on the topic which, being beyond the purview of this review, will not be detailed here (Iadecola, 2004; Girouard & Iadecola, 2006; Hamel, 2006; Iadecola & Nedergaard, 2007; Jakovcevic & Harder, 2007). Despite this extensive knowledge of the molecular mechanisms based on numerous *in vivo* studies, it should be noted that, to the best of our knowledge, no studies to date have attempted to delineate the mechanisms of neurovascular coupling in humans.

Cerebral autoregulation

In 1895, Bayliss, Hill and Gulland concluded in *The Journal of Physiology* that 'In all physiological conditions a rise in arterial pressure accelerates the flow of blood through the brain, and a fall slackens it' (Bayliss *et al.* 1895). This concept prevailed until, in a review paper published in 1959, Lassen constructed a plot of average BP and total brain blood flow from seven studies involving 11 different patient groups having a range of drug- and/or pathology-induced BP levels (Lassen, 1959); see Fig. 3, left panel). The plot revealed a

plateau region wherein cerebral blood flow appears to be completely stable across a relatively wide range of blood pressures (~60–150 mmHg). Such a physiological relationship requires reflex adjustments in cerebrovascular resistance concomitant with changes in BP, and was termed static cerebral autoregulation. Lassen's curve continues to be cited and illustrated in numerous high-impact publications and textbooks (Dagal & Lam, 2009; Barret *et al.* 2010); the potential consequences of such a parochial view in fields such as anaesthesiology are obvious, as stated previously (Drummond, 1997).

Unfortunately, very few attempts have been made to characterize the normal within-subject relationship between pressure and flow across the brain. The major challenge is that normal baroreflex function limits the effective range of blood pressures, necessitating the use of vasoactive drugs or physical manipulation of central blood volume, both of which confound interpretation of cerebrovascular reflexes *per se*. Although recent studies have shown a more pressure-passive relationship between MAP and CBF in healthy individuals, this is not a universal finding (e.g. Liu *et al.* 2013). However, limitations of the majority of these studies are threefold. First, CBF velocity quantified by transcranial Doppler ultrasound represents CBF only if the diameter of the insonated vessel remains constant. This assumption has been evidenced to be violated in conditions of very high P_{aCO_2} (Willie *et al.* 2012) or hypoxia (Wilson *et al.* 2011; Willie *et al.* 2013*a*)

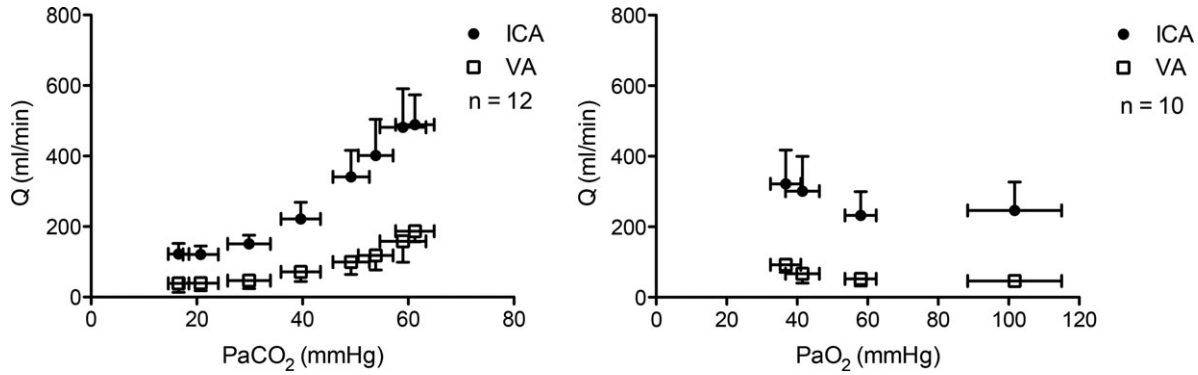

Figure 2. Blood flow ($\dot{Q}$) through the internal carotid (ICA) and vertebral arteries (VA) during steady-state changes in arterial CO_2 (left) and oxygen (right)
Cerebrovascular reactivity to changes in CO_2 and to hypoxia (%ΔCBF / mmHg CO_2) and %ΔCBF / %SaO_2) was found to be similar between vessels in the hypercapnic range, ~10% greater for the VA than the ICA in the hypocapnic range, and 50% greater for the VA with extreme hypoxia.

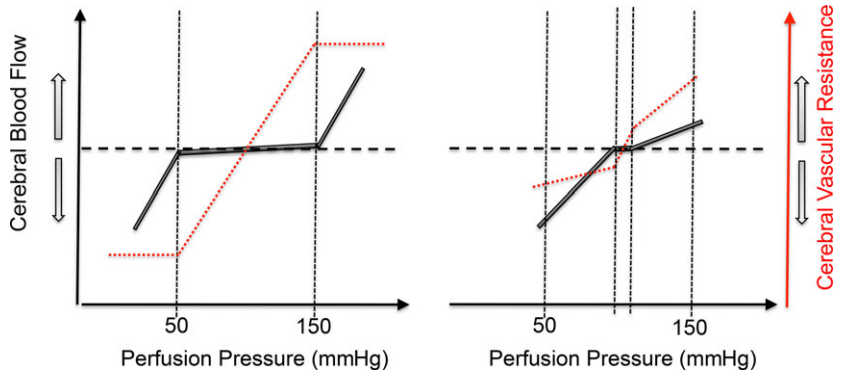

Figure 3. Stylized representation of the classical (left) and contemporary (right) relationships between mean arterial pressure and cerebral blood flow – i.e., autoregulation
Left panel is a stylized representation of the classical view of the relationships between mean arterial pressure (MAP) and cerebral blood flow (CBF), i.e. autoregulation, put forward by Lassen *et al.* (1959) based on the between-subject analysis of patients during various pharmacological interventions or pathologies. Right panel is a schematic diagram based on contemporary data indicating a small plateau region (Tan, 2012) and cerebral autoregulation hysteresis. Based on the within-subject reanalysis of 41 studies that reported concomitantly measured CBF and MAP during increases or decreases in blood pressure, the slope of the %ΔCBF *versus* %ΔMAP relationship was determined to be 0.81 ± 0.77 in the hypotensive range and 0.21 ± 0.47 in the hypertensive range. This indicates a far more pressure-passive CBF than is conventionally believed, and that more efficacious buffering capacity against increases than decreases in perfusion pressure (unpublished observations). See main text for details.

and may be violated when MAP is changed dramatically (based on animal data showing that the large intracranial vessels react to changes in perfusion pressure; Mchedlishvili, 1964; Mchedlishvili *et al.* 1973; Faraci & Heistad, 1990). Second, many studies have manipulated CBF pharmacologically with anaesthetics (McCulloch *et al.* 2005; Ogawa *et al.* 2008, 2010), angiotensin (Krejcy *et al.* 1997) and α-adrenergic receptor agonists and/or nitric oxide donors (Zhang *et al.* 2009; Lucas *et al.* 2010; Liu *et al.* 2013; Willie *et al.* 2013*a*), the influence of which on cerebrovascular tone is not well understood and is the subject of controversy (e.g. Drummond, 2012; Stewart *et al.* 2013). Finally, although P_{aCO_2} is markedly altered during pharmacological manipulation of BP (Liu *et al.* 2013), only a few studies have attempted to control for this confounding effect (e.g. Lucas *et al.* 2010; Chan *et al.* 2011; Gelinas *et al.* 2012). Static autoregulation is thus likely to be a function of the experimental conditions in which is it assessed, and its definitive efficacy in healthy humans remains uncertain. Despite this caveat, however, the available within-subject human data indicate that the CBF–MAP relationship is not flat through a broad range of MAP (Fig. 3). We recently reanalysed 41 studies in healthy humans reporting concurrently steady-steady state changes in MAP and CBF for the slope of the $\%\Delta$CBF/$\%\Delta$MAP relationship above and below resting MAP, which was found to be 0.81 ± 0.77 in the hypotensive range and 0.21 ± 0.47 in the hypertensive range (Unpublished observations: Numan T, Smirl JD, Bain AR, Lewis NC, Hoiland RL & Ainslie PN). Of the 41 studies, 33 estimated CBF by transcranial Doppler ultrasound; however, separate analysis of the studies using other modalities (e.g. MRI, PET or ^{133}Xenon technique) yielded similar CA values. These data indicate that the cerebrovasculature does have autoregulatory capacity, but that its efficacy is not perfect and is dependent on the severity and direction of change in perfusion pressure, as outlined next.

The study of the human cerebrovascular response to rapid changes in MAP has evolved in the last two decades following the introduction of BP and CBF quantification techniques that afford a high temporal resolution. Static *versus* dynamic CA is an experimental not physiological distinction, where 'static CA' refers to the steady-state relationship between MAP and CBF and 'dynamic CA' to the cerebral pressure–flow relationship during transient changes in MAP, such as during changes in posture, for example. There are no data, however, that explicitly indicate that short- and long-term regulation of CBF (dynamic and static CA, respectively) are separate mechanistic entities (Tan & Taylor, 2014). Early methods of CBF quantification lacking sufficient temporal resolution to assess the CBF response to rapid changes in MAP were subsequently referred to as static CA, with the inception of the dynamic CA concept arising out of the ability to measure beat-to-beat CBF and MAP concomitantly. Indeed, frequency-domain analysis of CBF was born out of a single technique (transcranial Doppler ultrasound) that allows beat-to-beat analysis of blood velocity in the intracerebral vessels, typically the middle cerebral artery. Two seminal studies in particular have provided a foundation for our understanding of dynamic CA. Aaslid *et al.* (1989) were the first to study the temporal relationships between middle cerebral artery blood velocity and MAP during the release of inflated thigh-occlusion cuffs that induces rapid transient hypotension. The finding that cerebral blood velocity tracked the drop in MAP but recovered more quickly demonstrated clearly the conceptual inadequacies of the classical view that autoregulation was nearly perfect by showing that CA yielded relative, not absolute, flow buffering. Further characterization of CA as a relative flow buffer followed when Birch *et al.* (1995) showed that the transfer function characteristics between BP and cerebral blood velocity fluctuations resemble a high-pass filter wherein higher frequency BP fluctuations are more linearly transferred to the cerebral circulation than lower frequency fluctuations.

The above inferences on the nature of dynamic CA are based on the implicit assumption that active and linear changes in cerebrovascular resistance are the primary determinants of dynamic pressure–flow relationships. However, recent studies employing the Windkessel model suggest that the compliant nature of intracranial blood vessels may play an important role in mechanically buffering against dynamic BP fluctuations and that this ability of vessels transiently to 'store' blood through a cardiac cycle depends on the speed of MAP change (Zhang *et al.* 2009; Chan *et al.* 2011; Tzeng *et al.* 2011). Transfer function analysis also assumes that the cerebrovascular response to changing MAP is identical whether MAP is rising or falling, but there is clear evidence of hysteresis in CA, i.e. the brain defends more effectively against acute hypertension than hypotension (Aaslid *et al.* 2007; Schmidt *et al.* 2009, 2012; Tzeng *et al.* 2011). At a practical level, the above findings suggest that metrics of CA derived from pressure–flow recordings need to consider not only absolute BP as an input to the cerebral circulation, but also whether BP is accelerating or decelerating and rising or falling (Chan *et al.* 2011; Tzeng *et al.* 2011). Such a comprehensive and universal metric does not yet exist, but there is a need to consider important non-stationary components (Panerai, 2013). Recently, Tan (2012), using projection pursuit regression, purported to circumvent some of these linear limitations and reported a small autoregulatory plateau of only $\sim$10 mmHg when BP oscillations were induced at 0.03 Hz. If the autoregulatory range is in fact so limited, characterization of static CA through incremental changes in MAP may miss the autoregulatory region altogether (e.g. Zhang *et al.* 2009; Lucas

et al. 2010; Liu *et al.* 2013). It is important to recognize that there remain numerous methods of quantification of CA, each with inherent assumptions and caveats and each specific to some experimental model, and that no one method is considered a 'gold-standard' measure. Indeed, the available metrics of CA have been evidenced to yield largely divergent results for the same data (Tzeng *et al.* 2012) and should thus be scrutinized carefully. There is, however, enough data to support the contention that CA does not maintain constant perfusion through a MAP range of 60–150 mmHg as is so often cited in the literature.

Mechanisms of cerebral autoregulation. Changes in cerebrovascular resistance must necessarily underlie CA, whether static or dynamic, yet there remains little consensus, especially in humans, on the mechanisms and location of this cerebral resistance modulation. Most of the attention paid to CA in the last two decades has aimed to characterize CA, to deduce a role of neural regulation of CA and to study the effects of stimuli ranging from exercise to pathology on CA. These studies almost universally ignore the question of where exactly this regulation takes place (e.g. Claassen & Zhang, 2011; Jordan & Powers, 2012). The pial arterioles are dogmatically accepted to serve in this capacity (Fog, 1938; Lassen, 1959). But there are data to the contrary indicating that only the largest of these vessels respond to physiological ranges of MAP and that the large intracranial arteries as well as the even larger vessels of the neck contribute to a substantial portion of cerebrovascular resistance (Heistad *et al.* 1978*a*; Kontos *et al.* 1978; Faraci *et al.* 1987*a*). Notwithstanding the exact site(s) where CA is modulated, there seems to be inbuilt mechanistic redundancy. For example, in addition to the apparent roles for the autonomic nervous system (see '*Autonomic regulation of cerebral blood flow*', below) there is a myogenic role in the regulation of CA. Only two studies in humans have addressed CA following myogenic 'block' using Ca^{2+} channel inhibitors; Tzeng *et al.* (2011) used the cerebrovascular-specific Ca^{2+} antagonist (nimodipine), and Tan *et al.* (2013) used the systemically acting vascular smooth muscle cell Ca^{2+} channel blocker (nicardipine). Both studies demonstrated altered CA, but only during low-frequency (∼20–30 s) oscillations of MAP as driven by oscillating lower-body negative pressure. Given that buffering of CBF against changes in perfusion pressure must necessarily entail changes in vascular resistance somewhere within the cerebrovasculature, it is perhaps not surprising that compromising the vascular smooth muscle cells alters CA. Equally, however, alterations of CA by Ca^{2+} channel blockers must not be of elemental importance, because widespread orthostatic intolerance is not necessarily observed in patients prescribed these drugs (Grünig *et al.* 2013). The relative importance and relationships between myogenic, autonomic and local neuronal mechanisms in CA remains to be understood holistically and will certainly require innovative study design and may necessitate methods of CBF assessment that directly consider cerebral vasomotion (such as Duplex ultrasound or MRI, rather than transcranial Doppler ultrasound alone).

Large conduit arteries and cerebral autoregulation. There is a convincing body of evidence demonstrating that the large arteries of the brain play a much larger and more important role in the regulation of CBF than generally ascribed to them (Mchedlishvili, 1964; Mchedlishvili *et al.* 1973; Faraci & Heistad, 1990). Indeed, using a canine *in situ* ICA where the inlet pressure could be controlled, ICA constriction maintained pressure at the circle of Willis nearly constant in the face of increasing perfusion pressure (Mchedlishvili *et al.* 1973); the feline VA, in contrast, does not buffer increases in MAP (Faraci *et al.* 1987*a*). Another group, using a different *in vivo* technique that allowed calculation of the lumped resistance for all the large arteries in dogs and cats (Heistad *et al.* 1978*a*; Faraci *et al.* 1987*a*), found similar results, concluding that the large arteries were responsible for a quarter to half of the total cerebrovascular resistance during resting conditions.

Perhaps because these larger arteries of the neck are generally considered to be 'conduit' arteries, the idea that they can actively participate in CBF regulation has not been embraced. However, in rabbits and dogs the internal geometry of the ICA and VA was found to change considerably where the vessels bend, at the cavernous sinus for the ICA (the carotid siphon) and at the V3 segment of the VA at the entrance of the foramen magnum (Mchedlishvili, 1964). The turbulent flow resulting from such luminal diameter changes within tortuous segments must dramatically increase resistance compared with non-tortuous segments. That is to say that a smaller decrease in lumen diameter would be required to produce a given increase in resistance within the carotid siphon and V3 segment of the VA (Fig. 1, inlay I).

Recent human MRI data showing complex non-Newtonian flow and attenuated pulsatility along the carotid siphon support this theory (Takeuchi & Karino, 2010; Schubert *et al.* 2011). In humans, these vessels change diameter in response to changes in P_{aCO_2} and P_{aO_2} (Wilson *et al.* 2011; Willie *et al.* 2012); future studies using such advanced imaging techniques should assess whether they are also involved in the cerebrovascular response to acute changes in MAP.

Interaction between arterial blood gases and cerebral autoregulation. Traditional tests to assess cerebrovascular CO_2 reactivity or CA treat these concepts as separate entities. Clearly they are not; there are

persuasive data that both CA and CO_2 responses may use the same vascular reserve. In a landmark study, Harper & Glass (1965) examined the brain vascular reactivity to changes in P_{aCO_2} in dogs at various blood pressures (see Fig. 4). Severely hypotensive animals (approximately −60% MAP) showed no change in cerebral vessel diameter in response to increases or decreases in P_{aCO_2} (i.e. CBF reactivity was abolished), because the vessels were already maximally dilated (Harper & Glass, 1965). The reciprocal instance was also demonstrated where, in hypocapnia, CBF was well maintained in the face of controlled haemorrhage-induced hypotension (Iwabuchi *et al.* 1973). In contrast, with hypercapnia, CBF fell linearly with MAP (Iwabuchi *et al.* 1973).

Broadly comparable findings in both healthy humans (Przybyłowski *et al.* 2003; Ainslie *et al.* 2012) and those with pathology (e.g. carotid stenosis; Nishimura *et al.* 1999) indicate that CBF reductions with transient hypotension lead to a blunting of the CBF response to hypercapnia; hypotension selectively attenuated cerebrovascular CO_2 reactivity to hypercapnia but not hypocapnia. Thus, the compromised capacity of the cerebral vessels to dilate in hypotensive conditions when P_{aCO_2} is elevated indicates that the maintenance of cerebral perfusion takes precedence over the maintenance of a normal tissue P_{CO_2} or that there is limited vasodilatory reserve regardless of the combined stimulus. Equally, the latter process may take place regionally. For instance, during times of decreased perfusion or global cerebral vasodilatory stimulus, vascular beds with reduced vasodilatory reserve may have limited ability to dilate sufficiently to compete for limited blood flow to the brain successfully (Mandell *et al.* 2008). As a result, despite global vasodilatation, regional CBF in these vessels may even decrease, resulting in a cerebrovascular 'steal' phenomenon (Faraci & Heistad, 1990; Mandell *et al.* 2008; Fierstra *et al.* 2010).

Moreover, given that the brain does not autoregulate perfectly (Fig. 4) and that hypoxia and elevations in P_{aCO_2} also 'impair' the capability of the brain to defend against BP changes (Tzeng *et al.* 2012), BP is clearly a critical component of CBF. Examples of these integrated changes in P_{aCO_2} and BP occur in a myriad of everyday activities, such as changing posture, laughing, exercise, straining, sexual activity and coughing, to name but a few.

Although there is extensive evidence in support of this proposed interaction between pressure and chemical regulation of the cerebrovasculature (Kety & Schmidt, 1946, 1948; Jordan *et al.* 2000; Przybyłowski *et al.* 2003; Ainslie & Tzeng, 2010; Ainslie & Smith, 2011; Tzeng *et al.* 2012; Willie *et al.* 2012), integrated consideration of these players is seldom incorporated into contemporary research design. The cerebrovascular conductance index is sometimes used for this reason, because it may provide for more precise estimation of CO_2 reactivity that considers the effect of arterial BP on CBF; however, this does not take into account factors that may be manifest during alterations in ventilation, such as large changes in intrathoracic, intracranial and central venous pressures that in turn affect cerebral perfusion pressure. It also assumes that the relationships of P_{aCO_2} and MAP *versus* CBF are linear, when this is probably not the case (Battisti-Charbonney *et al.* 2011). As such, cerebrovascular conductance may oversimplify the issue. In our view, expressing the effects of CO_2 and MAP individually (e.g. Willie *et al.* 2012) gives a better impression of the relative effects of each on CBF.

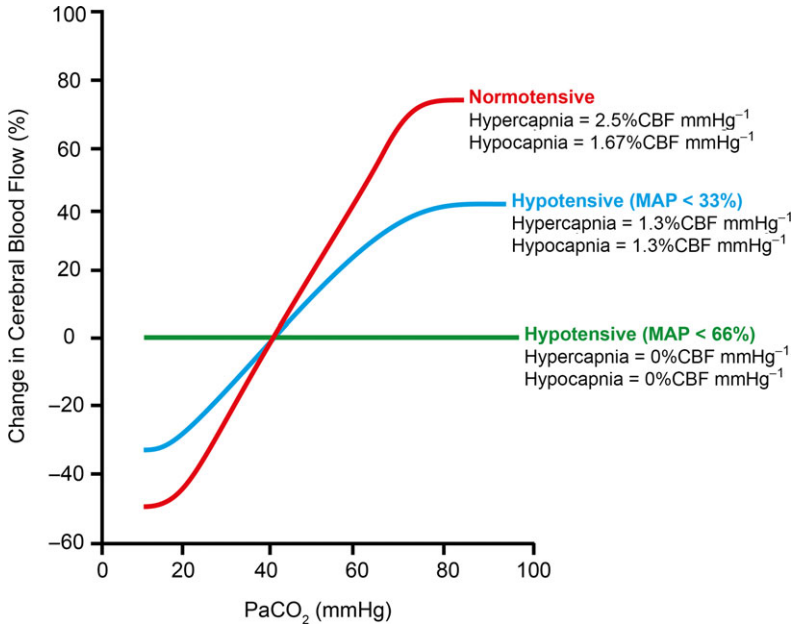

Figure 4. Schematic diagram of the effect of prevailing mean arterial pressure on cerebrovascular reactivity to changes in P_{aCO_2}
P_{aCO_2}
Note the abolishment of cerebrovascular reactivity with progressive hypotension. Values are calculated from the data of Harper & Glass (1965).

Autonomic regulation of cerebral blood flow

The entire cerebrovasculature is extensively innervated by adrenergic and cholinergic fibres of diverse extrinsic (e.g. cervical, sphenopalatine and trigeminal ganglia) and intrinsic origins (e.g. locus coeruleus, fastigial nucleus and dorsal raphe nucleus). Cerebral arteries show three layers of nerve plexi, as follows, with relative distribution varying with the vessel location: (1) the most superficial layer is a paravascular layer of nerve bundles longitudinally arranged superficially to the adventitia; (2) a dense perivascular plexus within the adventia; and (3) a deep perivascular plexus following a transverse course at the adventitial–medial border (Bleys *et al.* 1996). The extracranial arteries feature a higher proportion of longitudinally arranged paravascular nerve bundles, whereas intracranially there is a greater total density of perivascular nerve fibres, with more following a spiral or annular course, and far more neuron terminals, particularly at bifurcations, communicating arteries and the intracranial curvatures of the ICA and VA (Borodulya & Pletchkova, 1973, 1976; Mchedlishvili, 1986; Bleys *et al.* 1996). The ICA territory appears to possess denser sympathetic innervation than the vertebrobasilar system (Edvinsson & Hamel, 2002). The necessary anatomy is therefore extant for a neural role in the regulation of CBF.

Sympathetic nervous system (SNS) and CBF. Human studies assessing this role are broadly of two types, namely studies of patients with various diseases treated by ganglionectomy or studies in healthy humans employing local subcutaneous blockade of a ganglion(s) or oral pharmacological blockade of sympathetic ganglia or a systemic receptor group. Four studies have assessed CBF following ganglion excision and each showed increased CBF (Shenkin *et al.* 1951; Shenkin, 1969; Suzuki *et al.* 1975; Jeng *et al.* 1999). Following local cervical ganglion block, five studies reported increased CBF (Linden, 1955; Umeyama *et al.* 1995; Ide *et al.* 2000; Treggiari, 2003; Yokoyama *et al.* 2004), whereas three reported no change in CBF (Harmel *et al.* 1949; Scheinberg, 1950; Ohta *et al.* 1990), and in one study a decrease in CBF was found (Kang *et al.* 2010). Local anaesthesia can result in a partial block of the targeted ganglion, which could explain the lack of effect on CBF in three studies. Although the pathological conditions should be acknowledged, the finding that ganglionectomy universally increased CBF is convincing evidence for a role of sympathetic nerves in CBF regulation, although these data shed little light on the precise nature of such a role.

Invasive animal experiments suggest that the SNS is most important during changes in BP. Most well-controlled animal studies have observed some decrease in CBF at baseline, but especially during hypertension with stimulation of the superior cervical ganglion. This role of the SNS seems especially important in buffering surges in perfusion pressure (Mayhan *et al.* 1987; Cassaglia *et al.* 2008*a*,*b*, 2009; Ainslie, 2009; Tzeng *et al.* 2010). Unilateral resection of the superior cervical ganglion during induced hypertension produced ipsilateral disruption of cortical vessel integrity (Ponte & Purves, 1974; Heistad *et al.* 1978*b*). This apparent protective function of the SNS in response to increases in perfusion pressure seems to be a function principally of the larger arteries. For example, only the largest pial arterioles respond to sympathetic activation (Wei *et al.* 1975) and do so to a smaller degree than the large cerebral arteries (Baumbach & Heistad, 1983). The ability of these larger vessels to maintain flow during changes in perfusion pressure is dependent on their innervation, because the vessels become pressure passive once denervated; autoregulation in the large vessels is perhaps modulated, at least in part, neurogenically (Mchedlishvili *et al.* 1973; Tamaki & Heistad, 1986). Interpretation of studies using animal models to assess the role of the SNS in cerebrovascular function should be done with caution, because profound differences have been reported between species (Heistad *et al.* 1978*b*; Busija *et al.* 1980) and nothing is known of the corresponding relationship to human physiology.

Sympathetic nervous system and CA. Studies employing pharmacological blockade benefit from being completed in healthy humans but are potentially confounded by the systemic effects of the drug. Nonetheless, a number of elegantly studies have reported similar findings, indicating impairment of CA following SNS blockade. Both sympathetic ganglion blockade with trimethaphan (Zhang *et al.* 2004) and α-adrenoreceptor block with phentolamine (Kimmerly *et al.* 2003) resulted in a greater rise in CBF for a given increase in MAP produced during a Valsalva manoeuvre or noradrenaline infusion, respectively. Likewise, both these pharmacological interventions increase transfer function gain and decrease phase lead at low frequencies (0.03 Hz), indicating impaired CA (Zhang *et al.* 2002; Hamner *et al.* 2010), and α_1-adrenoreceptor block with prazosin impairs CBF recovery from transient hypotension induced by thigh-cuff release (Ogoh *et al.* 2008). It is nonetheless difficult to dissociate the systemic effects of SNS blockade (ganglionic or receptor group) on the peripheral vascular system from direct effects on CA *per se*. The changes in MAP or the very reflexes responsible should MAP remain constant following SNS block cannot be ruled out from having a direct effect on cerebrovascular regulation.

Sympathetic nervous system and arterial blood gases. The relationship between the SNS and the cerebrovascular response to CO_2 and hypoxia also remains vague, because it is difficult to dissociate the peripheral (e.g. MAP) from direct cerebrovascular effects of SNS activity. A convincing study in baboons reported that hypoxaemic stimulation of the carotid bodies increased ipsilateral CBF

and that this response was abolished following resection of cranial nerve VII (Ponte & Purves, 1974). Human data are inconsistent. Carbon dioxide reactivity has been reported to be unchanged following augmentation of SNS by hand grip (Ainslie *et al.* 2005) and lower-body negative pressure (LeMarbre *et al.* 2003); but conversely, attenuated CO_2 reactivity was reported during lower-body negative pressure (Zhang *et al.* 2011) and following ganglionic blockade with trimethaphan (Jordan *et al.* 2000).

Systemic pharmacological manipulation of SNS activity is likely to be confounded, however, by the consequent blunted MAP response to increased P_{aCO_2} or P_{aO_2}. For example, given that MAP may influence CBF (see '*Metabolic regulation of cerebral blood flow*', above), lowering of reactivity is likely to be confounded by an attenuated hypercapnia-induced pressure response (Przybyłowski *et al.* 2003; Ainslie *et al.* 2012). Moreover, to our knowledge, no study has examined whether sympathetic blockade attenuates the hypoxia-induced CBF increase or, conversely, whether SNS activity might serve to restrain large increases in CBF observed in severe hypercapnia or hypoxia (Wilson *et al.* 2011; Willie *et al.* 2012).

Parasympathetic nervous system and CA. There are limited data available assessing the cholinergic control of CBF in humans, but again anatomical studies of cerebral vessels indicate rich distribution of cholinergic nerve terminals throughout the intracranial vessels proximal to the Virchow–Robin spaces (Florence & Bevan, 1979; Heistad *et al.* 1980; Sato *et al.* 2001; Hamel, 2004). As with the SNS, cholinergic control seems to be species specific, because petrosal nerve resection or stimulation does not affect baseline CBF in cats but does in dogs (D'Alecy & Rose, 1977) and rats (Pinard *et al.* 1979). Only one study has assessed cerebrovascular control at rest in healthy humans. Hamner *et al.* (2012) reported increased transfer function coherence between MAP and CBF (as estimated by transcranial Doppler ultrasound) following systemic cholinergic blockade with glycopyrrolate, suggesting impaired CA. As explained in the '*Cerebral autoregulation*' section above, the precise physiological meaning of transfer function metrics remains ambiguous and, while these data do indicate a cholinergic role in cerebrovasculature function, more work certainly needs be directed to this end.

Conclusions

Our aim in the present review is to call attention to dated concepts in the accepted understanding of cerebrovascular regulation. Despite ample data and past reviews in high-impact journals that have highlighted these erroneous views, they continue to be taught to medical professionals, neuroscientists and physiologists across the globe. Below, we outline four principal points that should be incorporated into contemporary knowledge of cerebrovascular physiology, as well as future directions of research pertaining to each.

(1) Cerebral autoregulation does not maintain constant perfusion through a MAP range of 60–150 mmHg. The cerebral circulation does have more effective autoregulatory ability in the range above baseline MAP, and to a lesser extent below baseline MAP; however, CBF is nonetheless directly affected by changes in perfusion pressure. A definitive, within-individual assessment of global and regional CBF across a range of non-pharmacologically and pharmacologically perturbed blood pressures with maintained P_{aCO_2} has yet to be completed. How this relationship may alter in pathological conditions is therefore also unknown.

(2) There is important stimulatory synergism and regulatory interdependence of arterial blood gases and BP on CBF regulation. The study of cerebrovascular regulation needs to consider this relationship; if BP and P_{aCO_2} or P_{aO_2} change simultaneously, interpretation of the relative impact of each becomes difficult. The relationship between MAP and cerebrovascular reactivity to P_{aCO_2} remains unknown in the hypertensive range. Moreover, advanced imaging techniques should facilitate study of the effects of vascular reactivity and resistance heterogeneity in the cerebral vascular bed on the distribution of CBF in response to vasoactive stimuli.

(3) Cerebral autoregulation and cerebrovascular sensitivity to changes in arterial blood gases are not modulated solely at the pial arterioles. The large arteries of the neck and cerebrum are critically involved, serving the first-line defense such that the pial and cortical vessels experience minimal changes in pressure and can respond principally to prevailing systemic and local neural metabolism. In order to understand better the role of these vessels in human CBF regulation, high-resolution MRI/magnetic resonance angiography (MRA) should be used to assess their responses to non-pharmacologically driven changes in BP and controlled dynamic and steady-state changes in arterial blood gases

(4) Neurogenic control of the cerebral vasculature is an important player in autoregulatory function, particularly in the large vessels, and acts to buffer surges in perfusion pressure. Although the precise role of cerebral vasomotor nerves is poorly understood after more than 80 years of study, it remains premature to dismiss their role. There are numerous studies yet to be completed in humans to determine precisely the capacity for sympathetic and cholinergic nervous input on the cerebrovasculature. Future studies in healthy humans should not rely solely on

transcranial Doppler ultrasound in assessing these questions. Newer imaging modalities, and direct modification of cerebral SNS outflow, rather than global perturbation of SNS receptors, will help to elucidate the role of the autonomic nervous system in cerebrovascular control. Particularly during transient bouts of hypertension, such as those commonly experienced during activity, strain (defaecation, lifting, etc.), pathology (autonomic dysreflexia, subarachnoid haemorrhage, etc.) and during rapid-eye movement sleep, the sympathetically mediated buffering of global CBF and constriction of large cerebral arteries should be assessed. One methodological possibility to this end would be to use a centrally acting α_2-adrenoreceptor agonist (e.g. clonidine) to diminish SNS outflow whilst quantifying regional (cerebral) noradrenaline spillover (Mitchell *et al.* 2009) during non-pharmacologically induced changes in MAP. Another approach would be to assess CBF and large artery vasomotion (by ultrasound or MRI) during transient hypotension and hypertension before and following cervical ganglion block.

Answering these questions in healthy humans will provide new insight into the fundamental mechanisms that regulate CBF. Only by first understanding these mechanisms can we subsequently decipher the role of CBF regulatory impairment in myriad cerebrovascular diseases, such as Alzheimer's disease and dementia (Faraci *et al.* 1987*b*; Qiu *et al.* 2003; Hebert *et al.* 2004) and even neurogenic hypertension (Waki *et al.* 2011).

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Additional Information

Competing interests

None declared.

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