MINIREVIEW

Neurohumoral Regulation of the Cerebral Circulation (43340B)

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The cerebral circulation is regulated by chemical stimuli, metabolic factors, perfusion pressure, and nerves. However, the role of certain neurohumoral mechanisms in the regulation of cerebral blood flow remains rather controversial (1, 2). The unique characteristics of this regional circulation could provide a partial explanation for the previously reported divergent roles of neurohumoral control mechanisms. For instance, arteries and large arterioles are important resistance vessels, in contrast to most other circulations (2, 3). Second, most brain vessels possess a blood-brain barrier that limits access of circulating agents to the brain parenchyma (2). Third, neurotransmitters could escape from the synaptic region and accumulate in the cerebrospinal fluid (CSF), thereby providing a mechanism for the transport of these substances to distant cerebral targets. While there are many stimuli for the regulation of the cerebral circulation, the arterial PCO_2 is one of the most important (2). Hypocapnia results in arterial constriction and reduced cerebral blood flow, whereas hypercapnia causes profound arterial dilation and increased cerebral blood flow (2). However, this review will not describe the cerebrovascular effects of inorganic stimuli such as PCO_2, PO_2, or pH. This review will focus on local humoral control of a paracrine-autocrine nature and on selected novel (vasopressinergic, opioid) and classical (sympathetic, cholinergic) neural-humoral stimuli for the control of the cerebral circulation. Due to the voluminous literature on the subject and the intended nature of a minireview, local humoral control of cerebral hemodynamics, although of intense interest, can be presented in a general, overview fashion only.

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Paracrine-Autocrine Stimuli

The contributions of prostanoids to the regulation of cerebral hemodynamics in adult animals are the subject of considerable controversy. Indomethacin has been reported to reduce cerebral blood flow and abolish cerebrovascular dilation in response to hypercapnia in adult baboons and gerbils (4, 5). Conversely, others have found that indomethacin, at doses that block cerebral dilator responses to exogenous arachidonic acid, does not alter cerebral blood flow, pial arterial diameter, or responses of cerebral arterioles to hypercapnia in adult cats or rabbits (6, 7).

More consistent findings have been made in newborn animals. Prostanoids are prominent in the cerebrovascular physiology of the neonate and contribute to the maintenance of resting cerebral blood flow and cerebrovascular dilation in response to hypercapnia (8, 9). Topical prostaglandin (PG) I_2 and PGE_2 elicit potent pial arteriolar dilation in the piglet (9). The most abundant prostanoid present in the piglet periarachnoid cortical CSF is PGE_2, and this CSF concentration is in the vasoactive range (9). Prostanoids can modulate other vasoactive mechanisms in the cerebral circulation at several different levels of interaction. First, prostanoids can attenuate responses. For example, norepinephrine elicits pial arteriolar constriction accompanied by an increase in CSF prostanoid concentration in the piglet (10). Because indomethacin potentiates this constriction, prostanoids serve as inhibitors in this case. However, cerebral arteriolar constriction can occur without prostanoids. Topical platelet-activating factor produces potent pial arteriolar constriction that is unchanged after cyclooxygenase receptor inhibition in the newborn pig (11). Furthermore, platelet-activating

factor does not increase periarachnoid cortical CSF prostanoid levels (11). Second, prostanoids can mediate dilation to some vasoactive stimuli. For example, hypercapnia and methionine enkephalin dilate pial arterioles through prostanoid production (9, 12). Other stimuli, such as isoproterenol and vasopressin, elicit dilation independent of cyclooxygenase product formation (9, 13). Third, prostanoids can serve a permissive role in mediating responses to acetylcholine (14). Indomethacin blocks acetylcholine-induced cerebrovascular constriction, but subthreshold concentrations of thromboxane (TX) A_2 or PGH_2 restore acetylcholine-induced constriction to indomethacin-treated piglets (14), indicating that the presence of PGH_2/TXA_2 is necessary for the production of acetylcholine-induced vasoconstriction (see Cholinergic Stimuli, below).

Prostanoids can also contribute to the maintenance of cerebral blood flow during hemorrhagic hypotension. In the piglet, indomethacin produces a decrease in blood flow to the brain (8, 9, 15). Indomethacin treatment caused a uniform decrease in blood flow that cannot be explained by changes in cardiac output, arterial pressure, or blood gases. Since indomethacin decreases cerebral blood flow, and decreases in cerebral prostanoids are detected in conditions in which indomethacin decreases cerebral blood flow, prostanoids appear to be important in autoregulatory vasodilation of the cerebral circulation during hemorrhagic hypotension.

Recently, the importance of the endothelium in the control of the cerebral circulation has been recognized. The endothelium contributes to the regulation of cerebrovascular tone through the release of endothelium-derived relaxant factors and contractile factors. The absolute identity of endothelium-derived relaxant factor is not completely certain, but it is thought to be nitric oxide or a nitric oxide-containing species (16, 17). Examples of other types of endothelium-derived relaxant factors include PGI_2 (see above) and a hyperpolarizing factor of unknown identity that involves potassium channels (16). In the cat cerebral circulation, acetylcholine elicits dilation that is blocked by endothelium damage with a filtered mercury lamp-fluorescein dye technique or by inhibition of nitric oxide synthase (17). Nitric oxide has also recently been suggested to be co-stored with norepinephrine in adrenergic nerve terminals and to mediate the nonadrenergic, noncholinergic dilation observed with electrical stimulation of isolated cerebral arteries (18). Furthermore, nitric oxide has been suggested to function as a neuronal messenger in the brain (19). Purported types of endothelium-derived contractile factors include: a cyclooxygenase product of arachidonic acid metabolism (e.g., PGH_2/TXA_2); a polypeptide (endothelin); and a diffusible factor, formed in anoxia and hypoxia situations or in response to increases in perfusion pressure (20). Most of the recent work in this field has focused on endothelin. In the cerebral circulation, endothelin has been observed to produce vasoconstriction (20, 21) and to decrease cerebral blood flow (22). In the newborn pig, however, topical endothelin elicits dilation at low concentrations and constriction at higher concentrations (21). Both the dilation and the constriction are associated with an increase in periarachnoid cortical CSF prostanoid levels (21). Indomethacin blocks the dilation and attenuates the constriction. Therefore, prostanoids mediate endothelin-induced cerebrovascular dilation and contribute to endothelin-induced constriction.

Additionally, dilation of cerebral blood vessels could result from activation of central nervous system pathways. For example, electrical stimulation of the fastigial nucleus of the cerebellum in the rat results in profound increases in cerebral blood flow without comparable increases in cerebral metabolism (23). Cerebrovascular dilation during fastigial nucleus stimulation appears to involve muscarinic cholinergic receptor activation (24). However, others have noted the critical role of anesthesia and the fact that fastigial nucleus stimulation does not change cerebral blood flow in well-anesthetized cats and rats (25, 26). In the above studies, stimulation of the fastigial nucleus produced a delayed increase in cerebral blood flow that was blocked by α-chloralose anesthesia. The authors interpreted this delayed increase of cerebral blood flow to suggest that a metabolic mechanism, not a direct neurogenic vascular effect, could account for the increased cerebral blood flow observed with fastigial nucleus stimulation (26). Alternatively, sensory fibers arising from the trigeminal ganglion that innervate cerebral arteries could affect the cerebral circulation via an axon reflexlike mechanism (27, 28). Putative mediators of this response include Substance P, calcitonin gene-related peptide, and Neurokinin A (27, 28). Recent evidence indicates that trigeminal innervation may be linked to migraine headaches and pain associated with intracranial hemorrhage (28).

Vasopressinergic Stimuli

Vasopressin is known to produce potent vasoconstriction in a variety of vascular regions (29), but the influence of vasopressin on cerebral hemodynamics is not clear. Immunocytochemical studies have provided evidence for vasopressin as a neurotransmitter or neuromodulator in the brain (30). Endogenous vasopressin could gain access to brain blood vessels through three different mechanisms: via the blood, the CSF, and from the nerves. The contribution of plasma vasopressin to the control of the cerebral circulation is thought to be minimal (31), but vasopressin is detectable in the CSF in concentrations that are in the vasoactive range (13, 32). The presence of vasopressin-immunoreactive nerve fibers has been demonstrated in guinea pig pial arteri-

oles and rat brain microvessels (33, 34). Recently, a preliminary communication has reported that vascular tissue obtained from the aorta, vena cava, renal artery, and the mesenteric artery of both Sprague-Dawley and hypophysectomized rats contains immunoreactive stores of vasopressin (35). These data suggest that vascular stores of vasopressin could be of a nonpituitary origin (35). The origin of the CSF vasopressin, therefore, could be locally derived from pial vessel stores for vasopressin or from nerves associated with those vessels.

Vasopression has been observed to have varied effects on the cerebral circulation. For example, vasopressin has been reported to produce contraction in isolated cerebral arteries from the cat, goat, human, and rat (36, 37), dilation in the cat and dog (38), or no effect in the rat (39). Infusion of vasopressin into the internal carotid artery of the rat is followed by an increase in cerebral blood flow (40), whereas decreases in cerebral blood flow are observed when vasopressin is infused into the internal maxillary artery of the goat (37). In contrast, intravenous infusion of vasopressin elicits large pial artery dilation without changing blood flow due to autoregulatory constriction of small cerebral vessels (41). Consistent with this observation is the fact that topical vasopressin elicits pial arteriolar constriction in the rat (20).

A partial explanation for the divergent cerebrovascular responses observed for vasopressin could be that responses to vasopressin are tone dependent. Previously, we have observed that topical vasopressin produced cerebral vasodilation during normotension and vasoconstriction when cerebrovascular tone was decreased by hemorrhagic hypotension in the piglet (13). Both the dilation and the constriction were produced by activation of the V_1 receptor (13). Vasopressin-induced cerebrovascular dilation is independent of the cyclooxygenase pathway of arachidonic acid metabolism, since responses were unchanged in the presence of indomethacin (13). In contrast, vasopressin-induced vasoconstriction is modulated by prostanoids; indomethacin potentiates vasopressin-induced pial arteriolar constriction during hypotension in the piglet (13). Additionally, vasopressin could elicit dilation through the release of an endothelium-derived relaxant factor, since responses in the canine basilar artery are dependent on the integrity of the endothelium (38).

Vasopression could interact with prostanoids during hemorrhagic hypotension and, therefore, could have a greater contribution to the regulation of cerebral hemodynamics during pathophysiologic conditions. Although the concentration of CSF vasopressin under resting conditions is in the vasoactive range in the piglet (32), a V_1 receptor antagonist has no effect on regional cerebral blood flow, cerebral vascular resistance, or cerebral metabolic rate (42). These data indicate that vasopressin does not normally influence the cerebral circulation to a great extent. Prostanoids are prominent in the cerebrovascular physiology of the neonate and appear to contribute to the maintenance of cerebral blood flow during hypotension (15). In the conscious newborn pig, indomethacin produces a decrease in blood flow to the brain (15) (see Paracrine-Autocrine Stimuli, above). The indomethacin-induced fall in cerebral blood flow resulted from an increased cerebral vascular resistance. Indomethacin-induced cerebral vasoconstriction could result from either the removal of dilator prostanoids or from the unopposed activation of some vasoconstrictor stimulus. Previous studies have been designed to address the hypothesis that unopposed activation of a vasoconstrictor system may participate in indomethacin-induced cerebral vasoconstriction during hypotension. We found that indomethacin-induced cerebral vasoconstriction in hypotensive piglets does not result from removal of inhibition of sympathetic nerve stimulation (43). In contrast, a V_1 receptor antagonist blocked indomethacin-induced cerebral vasoconstriction during hypotension (42). In the newborn pig, vasopressin is a cerebral vasodilator under normotensive conditions, but vasopressin is a cerebral vasoconstrictor under hemorrhagic hypotensive conditions (13). This constrictor potential is enhanced after indomethacin. Therefore, vasopressin could contribute to indomethacin-induced vasoconstriction during hemorrhagic hypotension. Accordingly, vasopressin could contribute to the regulation of the cerebral circulation to a greater extent during pathophysiologic conditions.

Opioid Stimuli

Opioids could contribute to the regulation of cerebral hemodynamics. Opioid receptor binding has been demonstrated on cerebral microvessels (44). Enkephalin and dynorphin immunoreactivity, indicative of innervation, have been shown in large cerebral arteries of the pig and guinea pig, respectively (45, 46). Furthermore, opioids have been detected in CSF (47) and CSF opioid concentrations are in the vasoactive range under control conditions in the newborn pig (12, 48).

Investigations into the ability of opioids to influence the cerebral circulation have resulted in conflicting data. For example, enkephalins have been observed to produce modest dilation in isolated feline middle cerebral arteries, but minimal dilation in feline pial arteries at very high doses (49, 50). Responses after activation of cerebrovascular opioid receptors have been less well defined in *in vivo* as compared with *in vitro* studies. Topical methionine enkephalin, for example, has been shown to decrease feline cortical blood flow (51) and systemically administered (D-Met^2, Pro^5)-enkephalinamide, a stable synthetic enkephalin analog, dilated feline pial vessels (52). Moreover, others have observed that anesthetic agents can influence the cerebrovascular activity of opioids. Depending on the presence or ab-

sence, as well as the level of anesthesia, opioids have been observed to increase, decrease, or have no effect on cerebral blood flow (53, 54); therefore, the baseline metabolic rate could influence the cerebrovascular activities of opioids.

In contrast to the somewhat inconsistent results from the above studies in adult animals, we have observed that topically applied opioids have prominent effects on newborn pig pial arterioles *in vivo*. Although synthetic analog possessing higher affinity for opioid receptor subtypes are available, these studies were designed to evaluate the cerebrovascular activity of naturally occurring opioids. These results indicate that μ (methionine enkephalin)- (55) and δ (leucine enkephalin)- (55) receptor activation elicit dilation, whereas ϵ (β-endorphin) (55) receptor activation produces cerebrovascular constriction (12, 48). κ (Dynorphin)- (55) receptor activation produces tone-dependent responses (dilation during resting tone; constriction when cerebrovascular tone is decreased) (12, 48). We have also observed tone-dependent responses for vasopressin (see above). Although the mechanisms for tone-dependent responses are not known, alterations in the physical state of cell membranes that occur during dilation and constriction may play a role in the tone-dependent nature of vascular responses. We speculate that such membrane changes could result in similar alterations (activation-deactivation of intracellular mechanisms) for the dynorphin and vasopressin receptor-effect coupling mechanisms.

The mechanism for opioid-induced vascular activity has been of considerable interest. Opioid-induced vascular effects could be caused directly by opioids acting on vascular receptors, or indirectly as a consequence of an alteration in metabolism. Recently, we observed that opioid-induced vascular effects do not result from secondary changes in cerebral metabolic utilization of glucose (56). On the other hand, methionine enkephalin, leucine enkephalin, and dynorphin-induced pial arteriolar dilation and β-endorphin-induced pial arteriolar constriction are associated with increased periarachnoid cortical CSF prostanoid levels (12). Indomethacin blocks methionine enkephalin, leucine enkephalin, and dynorphin-induced dilation, but potentiates β-endorphin-induced constriction and dynorphin-induced constriction during hypotension (12). Therefore, prostanoids appear to mediate methionine enkephalin, leucine enkephalin, and dynorphin-induced dilation, but attenuate β-endorphin-induced constriction and the constriction caused by dynorphin in hypotensive piglets, acting, in all these cases, as dilator influences.

Alternatively, opioids could contribute to the regulation of cerebral hemodynamics through interactions with other vasoactive systems. For example, opioids have been observed to be localized with vasopressin in the posterior pituitary and could, therefore, influence vasopressin secretion (57). Previously, it has been shown that opioids can both stimulate and inhibit plasma vasopressin release (58, 59). Additionally, it has been shown that dynorphin increases plasma vasopressin concentration and that a V_1 receptor antagonist blocked the pressor response to dynorphin in the fetal lamb (60). Recently, it has been observed that vasopressin modulates opioid cerebrovascular responses in the newborn pig (32, 61). For example, dynorphin-induced dilation, β-endorphin-induced constriction, and dynorphin-induced constriction during hypotension were all associated with increased periarachnoid cortical CSF vasopressin concentration (61). Furthermore, a V_1 receptor antagonist potentiated dynorphin-induced dilation, but attenuated β-endorphin-induced constriction and the constriction produced by dynorphin during hypotension (32). In contrast, responses to methionine enkephalin and leucine enkephalin were not associated with a change in CSF vasopressin concentration and the dilator responses were unchanged by a V_1 receptor antagonist (32, 61). Therefore, vasopressin appears to attenuate dynorphin-induced dilation, but to contribute to β-endorphin-induced constriction and constriction to dynorphin during hypotension through the activation of V_1 receptors. The origin of the vasopressin could not be determined from these studies. Possible sources of the vasopressin include vasopressinergic nerves associated with pial vessels (33) and pial vessel stores for vasopressin (see Vasopressinergic Stimuli, above). Once released, this vasopressin could also affect the cerebral circulation, since similar vasopressin concentrations have been observed to produce dilation during normotension and constriction during hypotension (13).

Similar to vasopressin, opioids could also have a greater contribution to the regulation of cerebral hemodynamics during pathophysiologic conditions. Although the concentration of CSF opioids under resting conditions is in the vasoactive range (48), naloxone has no effect on regional cerebral blood flow, cerebral vascular resistance, cerebral metabolic rate, or pial arteriolar diameter (12, 62). However, CSF opioid concentrations increase during hemorrhagic hypotension and opioids could contribute to pial arteriolar dilation in response to hypotension (48). Since naloxone attenuates the increase in CSF vasopressin concentration in response to hemorrhagic hypotension (61), opioids could contribute to this pathophysiologic stimulus for vasopressin release. Furthermore, opioids could interact with prostanoids in the control of the cerebral circulation during hemorrhagic hypotension. For example, indomethacin potentiates dynorphin- and β-endorphin-induced constriction (12), indicating that dilator prostanoids inhibit constriction to these two opioids. Additionally, naloxone blocks indomethacin-induced

vasoconstriction during hemorrhagic hypotension (62). Moreover, indomethacin potentiates vasopressin-induced constriction (13) and a vasopressin receptor antagonist blocked indomethacin-induced constriction during hypotension (42). Therefore, several vasoactive systems could contribute to indomethacin-induced cerebral vasoconstriction during hemorrhagic hypotension.

Adrenergic Stimuli

The sympathetic nervous system could contribute to the regulation of the cerebral circulation. Cerebral vessels receive sympathetic innervation primarily from the superior cervical ganglia (2, 63). Postganglionic fibers form a well-developed plexus around cerebral arteries (63). The density of innervation, however, is considerably less in veins (63). Interestingly, the α-adrenoceptors in the cerebral circulation exhibit a lower sensitivity to norepinephrine than other regional circulations (64). Transmural electrical stimulation of cerebral arteries activates sympathetic nerves and produces constriction in pial and basilar arteries of rabbits, sheep, and dogs (65, 66). In contrast, in large cerebral arteries of the pig, transmural electrical stimulation results primarily in vasodilation (67, 68). The latter dilation can be blocked by 6-hydroxydopamine and guanethidine (67). A partial explanation for these observations could be that there is a nonadrenergic dilator transmitter released from adrenergic-like nerve terminals (69). For example, nitric oxide has recently been suggested to be co-stored with norepinephrine in adrenergic nerve terminals and to mediate the dilation observed with electrical stimulation of isolated cerebral arteries (18) (see Paracrine-Autocrine Stimuli, above).

Similarly, exogenously and endogenously released norepinephrine have been observed to have variable effects on the intact cerebral circulation. Kuschinsky and Wahl (70) showed that sympathetic nerve stimulation and exogenous norepinephrine constrict pial arteries (40–240 μm in diameter) in the adult cat. In contrast, Wei *et al.* (71) observed that cat pial arteries greater than 100 μm constricted to both neurogenic and exogenous norepinephrine, but smaller arteries were unresponsive to these stimuli. Similarly, sympathetic nerve stimulation constricts large arteries in the adult rabbit with no associated change in cerebral blood flow, presumably due to dilation of small vessels (72). Additionally, cerebral arteries have been observed to escape from sympathetic stimulation (73). However, Busija *et al.* (74) observed that the degree of responsiveness of pial arteries to sympathetic nerve stimulation and exogenous norepinephrine was unrelated to initial vessel diameter in the newborn pig.

Recently, it has been suggested that the contribution of adrenergic mechanisms to cerebrovascular regulation may be more important in the fetus and newborn than in the adult (75). Electrical activation of sympathetic nerves maintains pial arteriolar constriction and reduced cerebral blood flow in piglets and lambs for as long as the stimulation period lasts (74–76). Moreover, *in vitro* studies of baboon cerebral arteries (77) and *in vivo* studies in sheep (75) provide evidence for an age-dependent decrease in cerebral arteriolar responsiveness to norepinephrine. Furthermore, while exogenous and endogenous norepinephrine constrict cerebral resistance vessels in piglets (74), these interventions fail to do so in adult pigs (67). The reasons for these observed developmental changes are presently unclear. These findings do, however, support the concept that sympathetic nerves could be more important in the regulation of cerebral blood flow in the perinatal period.

The mechanism for norepinephrine-induced cerebral vasoconstriction has been an area of considerable interest. In some species, the cerebral adrenoceptor is primarily α_1 (sheep, rabbit) (75, 78), whereas in others, it is α_2 (pig, dog) (79, 80). In the piglet, norepinephrine-induced cerebral vasoconstriction is associated with increased periarachnoid cortical CSF prostanoid concentrations which attenuate that vasoconstriction (10). Finally, responses to norepinephrine are pH sensitive and are inhibited by alkalosis (81).

Although sympathetic nerves appear to have little effect on the cerebral circulation under normal conditions or during hypotension (43), there is considerable evidence that sympathetic nerves protect cerebral vessels during sudden increases in arterial blood pressure. For example, sympathetic stimulation attenuates the increased cerebral blood flow and disruption of the blood-brain barrier during severe arterial hypertension (82). Similarly, sympathetic nerves attenuate increases in cerebral blood flow in response to seizures and asphyxia (75, 83). Therefore, sympathetic nerves could play a greater role in the control of cerebral hemodynamics in pathophysiologic conditions.

A relatively recent observation has been the detection of neuropeptide Y (NPY) colocalized with norepinephrine in sympathetic nerve endings in the cerebral circulation (84, 85). Co-release of NPY is involved in the control of neurotransmitter release and the modulation of constriction through both pre- and postsynpatic activities. For example, NPY has direct constrictor effects on cerebral vessels and decreases cerebral blood flow (85, 86). NPY also potentiated the effects of exogenous norepinephrine and electrical stimulation on cerebral blood vessels (78).

Cholinergic Stimuli

Cerebral arteries appear to be innervated extensively by cholinergic nerves. The presence of the acetylcholine-synthesizing enzyme choline acetyl-transferase in the adventitia of cerebral blood vessels has been

documented (87, 88). The evoked release of acetylcholine from cerebral arteries and the presence of a high affinity uptake system have been described (87, 88). Moreover, muscarinic receptors have been identified on the endothelium of cerebral arteries (89, 90). The origins of this innervation include the sphenopalatine ganglion and the otic ganglion through the superficial petrosal nerve (91, 92).

Historically, cholinergic responses have been divided into two classes: nicotinic and muscarinic (93). More recently, the existence of at least two subtypes of muscarinic receptors has been proposed (94). Nicotine has been observed to produce modest, nonsignificant pial arteriolar dilation in the piglet (95).

Acetylcholine has been observed to produce both potent dilation and constriction in the cerebral circulation. Vasodilation appears to result from activation of muscarinic receptors and the subsequent release of an endothelium-derived relaxing factor in the cat and mouse (96, 97) that is not a cyclooxygenase product in many species (98) (see Paracrine-Autocrine Stimuli, above). Alternatively, vasoconstriction appears to result from direct activation of vascular smooth muscle muscarinic receptors (99). For example, the predominant response to acetylcholine is constriction in the pig and dog (95, 100). In the piglet, this constriction results from activation of M_1 receptors, is associated with a dramatic rise in periarachnoid cortical CSF prostanoid levels, and is blocked by indomethacin pretreatment and blockade of endoperoxide-thromboxane receptors (14, 95). Since the presence of the prostanoids PGH_2 and TXA_2 (even at subthreshold concentrations) appears to be sufficient to allow this constriction to occur, prostanoids appear to serve a permissive role in mediating acetylcholine-induced cerebrovascular constriction (14). Presently, it is unclear how the prostanoids exact their permissive influence. We speculate that, once activated, the prostanoid receptor may indirectly alter the M_1 receptor effector coupling mechanism through the release of second messengers, such as phosphoinoisitides (14).

Although cerebral blood vessels are innervated by cholinergic nerves, it has been difficult to demonstrate effects of cholinergic nerves on cerebral blood flow. For example, electrical stimulation of the greater superficial petrosal nerve has been observed to dilate pial arteries and increase cerebral blood flow (101, 102). In contrast, it has also been reported that stimulation of the greater superficial petrosal nerve or facial nerve has no effect on cerebral blood flow (103, 104). It is possible that activation of cholinergic nerves primarily decreases resistance of large arteries without changing blood flow due to autoregulatory constriction of small vessels (105).

Vasoactive intestinal polypeptide appears to share a similar anatomical pathway with acetylcholine (106), and this polypeptide has been observed to be released from cerebral blood vessels (107). Vasoactive intestinal polypeptide produces arteriolar dilation and increases cerebral blood flow (108, 109) via a prostanoid-dependent mechanism (109). The physiological significance of vasoactive intestinal polypeptide in the control of the cerebral circulation is undocumented.

Concluding Remarks

Cerebral vessels are innervated by sympathetic, parasympathetic, vasopressinergic, and opioid fibers and, consequently, are exposed to many neurotransmitters from these, as well as other, sources (neurons, glia). These four neurohumoral systems can act by themselves, interact with each other, or interact with other vasoactive systems to control the cerebral circulation. Prostanoids modulate these neurohumoral mechanisms at several levels of interaction. Endothelium-derived relaxant and contractile factors also contribute to the regulation of the cerebral circulation. In many of these areas, the physiological significance of the potential regulators of cerebral vascular tone is understood incompletely.

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