Central nervous system regulation of reflex responses to hypotension during fetal life

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Wood, Charles E., and Haiyan Tong. Central nervous system regulation of reflex responses to hypotension during fetal life. Am. J. Physiol. 277 (Regulatory Integrative Comp. Physiol. 46): R1541–R1552, 1999.—The ability of the fetus to survive, grow, and successfully complete the transition from fetal to neonatal life is critically dependent on the appropriate regulation of fetal blood pressure, blood volume, and fluid dynamics. This is a short review of the physiological mechanisms controlling the fetal cardiovascular system, focusing mainly on the neural and endocrine elements in the schema of cardiovascular function and control. The fetal cardiovascular system is arranged anatomically to provide for perfusion of the umbilical-placental circulation, the organ of gas exchange of the fetus, and to largely bypass the lungs. Fetal blood volume and pressure, maintained at levels that are appropriate for this function, are influenced by neural and endocrine control mechanisms, which are similar to, but quantitatively different from, the adult animal. Baroreceptors and chemoreceptors located in the carotid sinuses and aortic arch sense changes in blood pressure and blood gases and comprise the afferent limb of the major reflexes that maintain normal fetal blood pressure and volume. Fetal hypotension stimulates reflex decreases in fetal heart rate, which are apparently mediated by chemoreceptor input. Arginine vasopressin responses to hypotension are most likely mediated by baroreceptor input. Recent evidence suggests that the reflex responses to hypotension in the fetus are modulated by paracrine or endocrine factors. For example, baroreceptor or chemoreceptor reflex pathways are modulated by the endogenous production of prostanoids and by the preparturient changes in fetal plasma estrogen concentration.

heart rate; blood pressure; blood volume; development; birth; adrenocorticotropicin; vasopressin; renin

THE ABILITY OF THE FETUS to survive, grow, and successfully complete the transition from fetal to neonatal life is critically dependent on the appropriate regulation of fetal blood pressure, blood volume, and fluid dynamics. Disturbances in the development and regulation of fetal cardiovascular function can produce a variety of problems that increase both mortality and morbidity of the late-gestation fetus and newborn. This is a short review of the physiological mechanisms controlling the fetal cardiovascular system, focusing mainly on the neural and endocrine elements in the schema of cardiovascular function and control.

Perhaps the best framework on which to base this discussion is the general principles governing control of blood pressure and volume in the adult mammal. It is generally accepted that in the adult, minute-to-minute control of blood pressure is accomplished via neural afferent control mechanisms (i.e., baroreceptors and chemoreceptors), and long-term control of blood pressure is accomplished via changes in vascular volume, compliance, and other variables that are heavily influenced by endocrine factors (46). This view of cardiovascular regulation will not be reviewed here, although several points bear mention. First, control within the adult cardiovascular system is based on the general principle of negative feedback. Elevated blood pressure stimulates an increase in the firing rate of arterial baroreceptors, which activate a reflex response that ultimately reduces heart rate, cardiac contractility, sympathetic vasoconstrictor tone, and the rate of secretion of the hormones, which either effect vasoconstriction or water or electrolyte conservation. Second, the hormonal systems that influence blood pressure or volume are themselves influenced by neural receptors on both the high- and low-pressure segments of the cardiovascular system. Arginine vasopressin (AVP), for example, is tonically inhibited by both arterial baroreceptors and by atrial receptors. Nonhypotensive remo-
rhage increases the rate of secretion of AVP in the adult primarily by reducing the afferent firing of the atrial receptors, and hypotensive hemorrhage increases the rate of AVP secretion by reducing the firing of both atrial and arterial stretch receptors (29, 97). Third, the mechanisms controlling ventilation in the adult are integrated with the mechanisms controlling blood pressure. Severe and rapid hemorrhage, for example, might stimulate increases in heart rate by both baroreceptor and chemoreceptor stimulation. These and several other principles will form a basis of comparison of the fetal and adult control mechanisms. In some respects, the fetal cardiovascular control systems are similar to those of the adult. In many respects the control of the fetal cardiovascular system is different, but rather more appropriate for control of a cardiovascular system that is optimized for perfusion of the placenta as the organ of gas exchange.

The fetal cardiovascular system is anatomically arranged in such a way as to allow blood to bypass the lungs and to provide perfusion of the placenta (Fig. 1). This is accomplished by the establishment of several shunts within the fetal cardiovascular system that establish both the lung and the placenta as parallel circuits within a circulation in which both ventricles pump in parallel. The majority of the blood pumped into the pulmonary artery from the right ventricle passes through the ductus arteriosus rather than through the lungs. Indeed, only ~8% of the combined ventricular output perfuses the lungs in the late-gestation fetus. Conversely, a portion of the blood entering the right atrium passes through the foramen ovale into the left atrium. The placenta is perfused in parallel to the other systemic vascular beds. The placenta does not exhibit much inherent autoregulation of blood flow; therefore, its flow is affected by the prevailing arterial blood pressure (but sensitively modified by vasoconstrictors such as ANG II; Refs. 54, 120, 121). For this reason, regulation of fetal arterial blood pressure is important for maintenance of efficient gas exchange within the umbilical-placental circulation.

Not coincidentally, the fetal blood volume (expressed as a proportion of fetal body weight) is higher, fetal blood pressure is lower, and fetal heart rate is higher than in the adult. The need for perfusion of the low-resistance circuit of the umbilical-placental circulation, combined with the need for fetal sequestration of fluid, which is essential for fetal growth, dictates a prevailing blood pressure that is ~50–60% that of the adult. The low blood pressure impairs the ability of the fetus to defend blood flow to critical organs during periods of transient hypotension; however, the perfusion of the placenta and the vasculature of the fetal membranes allows ready access to large stores of water and electrolyte (in the maternal circulation and in the amniotic and allantoic fluid), which can be called upon during fetal hemorrhage (10, 12). In part because of the relatively low blood pressure, the neural control of the fetal circulation is far more dependent on chemoreceptor control than is the adult circulation (113). As will be discussed later in this review, this adaptation is a particular advantage for the fetus, because the major function of the fetal cardiovascular system is the transport of oxygen and carbon dioxide from and to the placenta and because changes in gas exchange can only be effected via changes in placental perfusion. In other words, the fetus changes its rate of gas exchange by altering fetal arterial blood pressure and the circulating concentrations of constrictor hormones, and these changes are heavily dependent on chemoreceptor input, as is the control of ventilation in the postnatal animal (27, 115).

**REFLEX RESPONSES TO HYPOTENSION: FETUS VERSUS ADULT**

The reflex responses to hypotension in adult animals and human beings are classical examples of negative feedback control mechanisms within cardiovascular physiology. Decreased blood pressure, caused by hemorrhage, orthostasis, etc., decreases the rate of firing of the arterial baroreceptors (located in the carotid si-
nuses and aortic arch; Ref. 9). The decreased afferent traffic within the carotid sinus nerves and aortic depressor nerves is transduced into reflex increases and decreases in sympathetic and parasympathetic efferent activities, respectively. The resultant increase in heart rate, cardiac contractility, and vasoconstriction increase cardiac output and peripheral resistance, returning blood pressure to higher levels (106). Severe hypotension can reduce arterial blood pressure to a level that is not sufficient to maintain oxygen delivery to the arterial chemoreceptors. At these low levels of arterial blood pressure, the chemoreceptors increase their firing rate (responding to their own, flow-limited hypoxia), and the resultant reflex response augments the increase in sympathetic autonomic tone. Extreme hypotension compromises blood flow to the central nervous system (CNS), triggering the so-called CNS ischemic pressor response (47). The precise mechanism of the CNS ischemic pressor response is not known but generally assumed to be the direct result of tissue hypoxia within the brain. In the adult, rapid hemorrhage (79) can produce a paradoxical decrease in heart rate. This reduction in heart rate is caused by the activation of ventricular C fiber afferents, and is thought to be important for the defense of cardiac output. During such periods of dramatically reduced venous return, a reduced heart rate allows increased diastolic filling time. Although this classical physiological control system is learned by all beginning students of cardiovascular physiology, the function of the same system in the fetus is remarkably different.

Fetal blood pressure is regulated at a level that is low (~40 mmHg in mid-to-late gestation) compared with the neonate (~60 mmHg) or adult (~90 mmHg). Fetal heart rate is high (~180 beats/min in mid-to-late gestation) when compared with the neonate (~100 beats/min) or adult (~60 beats/min; Ref. 108). Acute hypotension in the fetus stimulates a reflex response, which often includes both bradycardia and vasoconstriction (11, 106, 115). The vasoconstriction is dependent on increases in both sympathetic autonomic activity and the rate of secretion of several vasoactive hormones, including arginine vasopressin and the renin-angiotensin system. The increase in peripheral resistance redistributes the combined ventricular output of the fetus away from the metabolizing tissues of the fetal body and preserves the flow within the umbilical-placental circulation. Interestingly, the bradycardia appears to mimic the (ventricular C fiber) response to rapid hemorrhage in the adult (79). It is possible that, because fetal heart rate is relatively high in the resting state, reductions in venous return are best compensated for by decreases in fetal heart rate (to maximize diastolic filling). Despite the similarities, however, the mechanism of the hypotension-stimulated bradycardia of the fetus is different from that of the adult. The fetal bradycardia is most likely caused by activation of the peripheral chemoreceptors, not ventricular afferent nerves (112). It is important, however, to point out that the fetal sheep does respond to mild hypotension with small increases in heart rate. For example, progressive hemorrhage can increase fetal heart rate (60, 115). However, the degree of hypotension needed to produce bradycardia appears to be much lower in the fetus than in the adult.

**Fetal Arterial Chemoreceptors**

Peripheral chemoreceptors are found within the fetal circulation in the carotid sinuses and aortic arch (9). The afferent nerves from the carotid sinus chemoreceptors travel within the carotid sinus nerves to the glossopharyngeal nerves (cranial nerves IX), then on to synapse at the nucleus of the solitary tract (NTS). The carotid sinus chemoreceptors are active as demonstrated by direct nerve recordings (8, 9). The arterial chemoreceptors of the fetal sheep produce a reflex bradycardia when exposed to cyanide (59) or hypoxia (55, 56, 90, 117). The evidence is clear that transient bradycardia in fetuses in utero, especially during labor and delivery, is related to the activity of the arterial chemoreceptors (55).

The late-gestation fetal sheep appears to be quite susceptible to hypotension as a stimulus to bradycardia. This reflex bradycardia has been demonstrated in response to hemorrhage (69, 70), vena caval obstruction (112, 118), and vasodilator infusion (111). Although this response has been proposed to be the result of cardiac receptor activation, experimental evidence suggests that the response is mediated by the arterial chemoreceptors (112). Vena caval obstruction, a method that can be used to produce controlled decreases in venous return and therefore combined ventricular output, stimulates decreases in fetal heart rate, which are proportional to the induced decrease in fetal arterial blood pressure (Fig. 2). However, prior carotid sinus denervation prevents the heart rate response (112). In other experiments, bilateral carotid occlusion stimulated transient reductions in fetal heart rate in intact fetal sheep (114). These studies suggest that the decrease in fetal arterial blood pressure stimulates the arterial chemoreceptors by reducing the blood flow through them. It is important to recognize that interpre-

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Fig. 2. Relationship between changes in heart rate and changes in mean arterial pressure (MAP) in intact (INT; ○ and solid regression line) and sinoaortic-denervated (SAD; ● and dashed regression line) fetuses during a 10-min period of hypotension produced by vena caval obstruction. Significant relationship between these variables during vena caval obstruction was abolished by SAD. [Borrowed with permission (112)].
tation of many denervation and physiological stimulation experiments is complicated by the fact that carotid sinus and aortic arch denervation procedures eliminate afferent fibers from both baroreceptors and chemoreceptors and that reductions in blood pressure can both reduce baroreceptor activity and increase chemoreceptor activity. Because there is no "clean" method of eliminating one set of receptors without altering the function of the other, the interpretation of the relative roles of chemoreceptors and baroreceptors in the control of fetal cardiovascular function must be based on multiple approaches and information obtained from multiple experiments.

**Fetal Arterial Baroreceptors**

The arterial baroreceptors are active in late-gestation fetal sheep. The stimulus-response characteristics of these receptors suggest that they are more responsive to increases than to decreases in fetal arterial blood pressure (8, 9). Indeed, the reflex heart rate response to acute hypertension is blocked by prior denervation of the carotid sinus and aortic arch baroreceptors (57, 58).

In adult animals, sinoaortic denervation acutely increases arterial blood pressure but chronically produces a near-normal arterial blood pressure with a large increase in the minute-to-minute variability in blood pressure (32). The role of the arterial baroreflex in the adult is therefore to defend blood pressure against short-term challenges but not to control blood pressure in the longer term. Despite the fact that fetal arterial blood pressure is regulated at levels that are lower than in the adult, this concept holds true in the late-gestation fetal sheep. Chronic sinoaortic denervation does not produce substantial changes in fetal arterial blood pressure (27, 57, 112, 119) but does increase the variability in fetal arterial blood pressure (57, 119).

**Atrial Receptors**

In adult mammals, cardiovascular and endocrine reflex response variables are influenced by the activity of the receptors located in the atria and at the atrio-caval junctions (31, 82). Atrial receptors, specifically, have well-documented inhibitory effects on the rate of secretion of renin, AVP, and ACTH (3, 5, 6, 44, 97, 98). Responses to nonhypotensive hemorrhage in the adult are heavily influenced by cardiac receptors (3, 19). The relative importance of the atrial receptors is quite different in the fetus. It appears that the atrial receptors are not physiologically important with regards to control of endocrine variables in the late-gestation fetal sheep. In contrast to the adult, in which bilateral vagotomy blocks or inhibits the AVP, ACTH, and adrenal corticosteroid response to hemorrhage (43, 97), bilateral vagotomy has no effect on the magnitude of the endocrine response to hemorrhage in late-gestation fetal sheep (115). Indeed, blockade of all cardiac receptors with a subpericardial injection of procaine has little effect on circulating hormone concentrations and has no effect on the magnitude of the endocrine response to hemorrhage (25, 26).

It is not known when or how the atrial receptors become functionally important. There are no published studies that report the response characteristics of the atrial receptors in fetal or newborn sheep and there are no studies that demonstrate the CNS effects of controlled stimulation of the atrial receptors. It is possible that the atrial receptors gain physiological importance after birth as a consequence of neuronal maturation, either in the peripheral receptors themselves or within the fetal brain stem. However, it is also possible that the atrial receptors become active as a consequence of the rearrangement of the circulation at birth. In the transition from intrauterine to extrauterine life, the circulation loses its fetal characteristics with the closure of the foramen ovale, the ductus arteriosus, and the ductus venosus (93). The decrease in pulmonary vascular resistance and the closure of the ductus arteriosus combine to increase left atrial pressure relative to the right. The increase in left atrial pressure closes the foramen ovale, effectively separating the right and left atria. It is possible that, before birth, the neuroanatomical pathways, which include atrial receptors and their central connections, might be intact and that they might be effectively activated by the increase in atrial volume that accompanies the closure of the ductus venosus. Resolving this issue will require new experiments but will be important in terms of understanding the responsiveness to hemorrhage in the peripartal period.

**Ventricular Receptors**

One of the most robust and dramatic physiological reflexes is the Bezold-Jarisch reflex, the bradycardia that is stimulated by the intravenous injection of veratrum alkaloids (123). The intravenous injection of veratrum alkaloids stimulates the activity of the ventricular C fiber afferents from the cardiac ventricles, which, in turn, stimulates a reflex increase in the vagal efferent activity, which slows heart rate (123). Although few details concerning ventricular receptor function in fetal animals are known, available evidence suggests that this reflex is slow to develop in the fetus (78). It is likely that the overall control of the fetal cardiovascular system does not rely on the activity of the ventricular receptors. Nevertheless, input from these receptors might be more important during the process of parturition, a time in which they are likely to be more mature and a time during which there are likely to be physiologically important changes in venous return and cardiac end-systolic volume.

**Hormonal Response Variables**

Endocrine responses to cardiovascular perturbation in the fetus are homeostatic. That is, proper control of fetal arterial blood pressure and distribution of combined ventricular output requires the responses of several endocrine systems acting in concert with the autonomic nervous system. Perhaps best studied in
In this regard are the renin-angiotensin-aldosterone system (RAAS) and arginine vasopressin (AVP).

RAAS responses to hypotension and hypoxia are mediated at least in part by arterial baroreceptors and chemoreceptors. Plasma renin activity (PRA) responses to hypotension produced by a 10-min period of vena caval obstruction are proportional to the degree of hypotension (Fig. 3; Refs. 112, 118). The mechanism of this response is presumably similar to the PRA response to infusion of vasodilator (111) or hemorrhage (115). The response to vena caval obstruction is partially blocked by prior sinoaortic denervation, demonstrating the role of baroreceptors and/or chemoreceptors in this response (112). However, the PRA response to hypotension is not entirely reflex in nature. It is likely that the intrarenal baroreceptor plays an important role in the response to changes in arterial blood pressure.

The RAAS is also responsive to changes in blood gases (Fig. 4). Hypoxia, hypercapnia, and asphyxia stimulate renin secretion in the fetal sheep (91, 117). The renin response to hypoxia is relatively weak (91). Nevertheless, the relatively small renin response to hypoxia and/or hypercapnia is attenuated (but not eliminated) by sinoaortic denervation (117). Although

the RAAS response to hypoxia, hypercapnia, and transient asphyxia is small, it is possible that asphyxia or hypotension severe enough to produce ischemia of the arterial chemoreceptors might be sufficient to stimulate substantial RAAS responses.

AVP responses to hypotension are partially mediated by the arterial baroreceptors. Analogous to the RAAS response to arterial baroreceptor input, the AVP responses to vena caval obstruction are attenuated by sinoaortic denervation (112). AVP responses to hypotension are vigorous, often increasing plasma concentrations from 2–5 pg/ml to concentrations near 1,000 pg/ml (104). In contrast, the AVP responses to hypoxia are relatively small, increasing concentrations to 30–50 pg/ml (89, 90). It is somewhat counterintuitive that AVP responses to hypoxia are not attenuated by sinoaortic denervation (89). Rather, the AVP response to hypoxia appears to be mediated by the generation of adenosine, because blockade of adenosine receptors inhibits the AVP response (64).

Hemorrhage, hypotension, hypoxia, hypercapnia, and asphyxia in the fetus are probably best thought of as integrative stimuli, because they cannot in reality be separated from each other. Hemorrhage, for example, produces some degree of disturbance in fetal blood gases because of an impairment of umbilical-placental blood flow (11, 54, 106, 115). Hypercapnia produces systemic vasodilation, which reduces blood pressure, which, in turn, decreases arterial baroreceptor activity (28). Conversely, hypoxia stimulates reflex increases in blood pressure that would be expected to increase arterial baroreceptor activity (8, 59). Thus each type of stimulus, whether primarily hemodynamic or respiratory in nature, would be expected to produce a mixed blood pressure/blood gas stimulus. The responses to
these mixed inputs to the fetal reflexes are not always predictable. A good example of this is the stimulus of acute hypoxia: one might ask whether the increased blood pressure that occurs as a result of the reflex response to hypoxia modulates the reflex AVP and RAAS responses to the stimulus. Interestingly, the answer to this question is that the RAAS response to hypoxia is not modulated significantly by the concomitant period of hypertension (90). AVP responses, on the other hand, were significantly attenuated by the increased blood pressure in fetuses between 115 and 127 days gestation (Fig. 5) but not in older fetuses, between 129 and 136 days gestation. This is in contrast to the situation in the adult animal (49). This observation suggests that the input to the fetal brain from baroreceptors can be effectively “ignored” during some physiological circumstances. This is analogous to the lack of effect of arterial baroreceptor input during exercise in the adult (18, 85) or to the adaptation of the CNS to the chronic lack of baroreceptor and chemoreceptor afferent traffic after sinoaortic denervation (32, 57).

CNS INTEGRATION OF REFLEX AFFERENT AND Efferent ACTIVITY

There is a vast literature concerning CNS pathways controlling cardiovascular function in adult animals, but there is relatively little information published on the fetus. Specifically, the integrity and development of these pathways and neuronal interconnections in response to cardiovascular modifications are unknown in the fetus. This short review cannot serve as a comprehensive review of this subject. Nevertheless, it is perhaps useful to introduce the subject as a brief overview and to identify the areas in which some progress has been made in the fetus or neonate.

Baroreceptor afferent fibers project toward the brain in the glossopharyngeal and vagus nerves (cranial nerves IX and X, respectively) and synapse at the NTS in the medulla (37). The neurons of the NTS project to various sites; however, the baroreflex control of sympathetic tone is probably subserved by projections to the cells of the so-called caudal ventrolateral medulla (CVLM). Within the CVLM, these fibers synapse with GABAergic neurons, which, themselves, project to the rostral ventrolateral medulla (RVLM). The neurons of the RVLM that are inhibited by the release of GABA send projections in both ascending and descending directions. Vasomotor tone is influenced by descending projections to the intermediolateral column of the spinal cord (IML), where they synapse with sympathetic preganglionic cells. Vagal efferent tone is influenced by ascending projections to the dorsal motor nucleus of the vagus and to the nucleus ambiguus. Secretion of ACTH and AVP are influenced by projections from the RVLM to the hypothalamus, especially direct projections to the paraventricular nucleus (PVN) and supraoptic nucleus (SON) (50). The secretion of AVP can also be affected by a polysynaptic pathway from the NTS to the locus ceruleus, then on to the perinuclear region of the PVN and SON, then to an inhibitory (GABAergic) interneuron, which synapses with the PVN and SON (61). Throughout this basic pathway, the NTS and RVLM are essential for baroreflex control of sympathetic efferent tone and vasoactive hormone secretion (20, 37, 92, 100). However, the activity of this reflex is influenced by input from other regions. For example, inputs have been demonstrated from the periaqueductal gray, the limbic system, the cerebellum, and the cerebral cortex. There are also projections from the area postrema, a circumventricular organ adjacent to the NTS, which allows influence by circulating hormones such as ANG II (40, 41). Although this general description of the baroreflex pathway is a gross simplification of a complex integrated circuit, the activity and characteristics of the neurons within the NTS, RVLM, CVLM, IML, and PVN can yield important information concerning the basic function and modulation of function in fetal animals. Overlaid on the basic neuronal circuitry are the actions of various paracrine or autocrine modulators of neuronal function. As previously mentioned, for example, adenosine modifies AVP secretion, largely accounting for the AVP response to hypoxia in utero. We have been interested in the potential modulatory effects of prostanoids, given their synthesis in the fetus and the clinical usefulness of prostaglandin synthase [cyclooxygenase (COX)] inhibitors. We will argue below that prostanoids are important modulators of the fetal CNS cardiovascular and endocrine control mechanisms and that blockade of prostanoid biosynthesis might alter the probabili-
ity of fetal survival after stress in utero. Prostanoids have actions both within the brain to directly alter neuronal function and indirectly via changes in cerebral blood flow (CBF). Complicating this issue are the converse observations that 1) prostanoids alter cerebral vascular tone and 2) the biosynthesis of prostanoids within the cerebral circulation is altered by changes in CBF. It is possible that the prostanoids generated within the cerebral vasculature and/or within the brain interstitial fluid modulate or even mediate some of the cardiovascular and endocrine responses to fetal hypotension or fetal cerebral ischemia.

**PROSTANOID MODULATION OF FETAL CARDIOVASCULAR FUNCTION: EFFECTS ON CEREBRAL PERFUSION**

Prostanoids are a class of compounds that we proposed could modulate hormonal reflex responses to hypotension in the fetus. One site of production of prostanoids is in the local cerebral vasculature during cerebral hypoperfusion (22). In addition to being made by and released into the vasculature, prostanoids are synthesized within neurons in the brain of fetal sheep (63, 81). Physiologically, this endogenous production of prostanoids can be demonstrated by central administration of indomethacin to late-gestation fetal sheep at doses that preferentially block prostaglandin synthesis in the CNS relative to that in the peripheral circulation (62). CNS production of prostanoids has also been demonstrated in response to the central injection of cytokines (30).

In fetal and newborn animals, CBF is maintained during changes in arterial blood pressure (23, 83, 107). In the fetal sheep, CBF is held relatively constant during changes in arterial blood pressure between 45 and 80 mm Hg (83, 88, 107). Therefore, decreases in arterial blood pressure below the normally regulated level result in a decreased CBF. Substantial physiological data in vivo point to a significant role for dilator prostanoids in the regulation of cerebral vascular tone and CBF in newborns (65, 67). Decreases in CBF can liberate arachidonic acid (80, 109) and decrease cerebrovascular concentrations of dilator prostanoids (86) and increase constrictor prostanoids (22). PGE2 and PG\(_I\)_2 are potent vasodilators, whereas thromboxane A\(_2\) (TxA\(_2\)) and PGF\(_2\) are vasoconstrictors (24, 73–75, 110).

Inhibition of COX, an enzymatic step in arachidonic acid metabolism, has an improvement effect on the outcome during cerebral ischemia. Indomethacin, a COX inhibitor, has been used for pharmacologic closure of the patent ductus arteriosus (42, 45, 51), and it has a potential ability to prevent or attenuate the development of intraventricular hemorrhage (2, 48, 71, 72). Free indomethacin crosses the blood-brain barrier (4). It can be found in the brain within 30 min of systemic administration (4). It is generally assumed that the duration of action of indomethacin is long, but the plasma half-life is relatively short and the cerebrospinal fluid concentration is closely related to that of plasma (4). In piglets, indomethacin decreases CBF at rest (66). These decreases in CBF occur concomitantly with decreases in cerebrospinal fluid levels of dilator PGs.

**PROSTANOID MODULATION OF FETAL CARDIOVASCULAR FUNCTION: EFFECTS ON NEURONAL PROCESSING AND HORMONE SECRETION**

Prostanoids might alter cardiovascular function by affecting neuronal processing within the CNS. For example, Breuhaus and coworkers (13–15) and Cudd and Wood (33) have demonstrated that infusions of PGE\(_2\) into the carotid arteries of conscious adult sheep increase heart rate and blood pressure. This effect is not mediated by an action of PGE\(_2\) on arterial baroreceptor or chemoreceptor afferent activity (13) and is therefore a direct effect on the brain. PGE\(_2\) also has a direct effect on the fetal brain to alter blood pressure and heart rate, presumably by altering autonomic efferent tone (34). Analogously, thromboxane also stimulates increases in arterial blood pressure and heart rate by an action in regions perfused by carotid artery (116). The concept of a neuronal action of prostaglandins within the fetal CNS is likely not a new one. There is a rich history of experiments demonstrating that PGE\(_2\) inhibits fetal breathing movements (84, 99) during late gestation. Indomethacin, which blocks prostanoid biosynthesis, increases the frequency of fetal breathing movements (1). Indeed, it had been proposed that the source of PGE\(_2\), which tonically inhibits breathing movements in utero, was the placenta (103), although more recent experiments suggest that the site of PGE\(_2\) that affects fetal breathing movements is the fetal CNS itself (77).

An important component of the effect of prostanoids on the cardiovascular system is their effect on the hormones that, in turn, influence blood pressure or fluid balance. It has been demonstrated that PGE\(_2\) has a direct effect on the fetal sheep pituitary gland by enhancing AVP-stimulated, but not CRH-stimulated, ACTH secretion from dispersed fetal anterior pituitary cells in culture (17). Young and Thorburn (122) found that PGE\(_2\) has potent stimulatory actions on the late-gestation fetal sheep pituitary to increase both the absolute concentration and the biologically active fraction of ACTH-containing peptides in the fetal circulation. It also directly stimulates glucocorticoid secretion from the fetal adrenal gland. It has also been shown that PGE\(_2\) increases AVP secretion (53). Intracerebroventricular infusion of PGE\(_2\) can stimulate ACTH and cortisol secretion in fetal sheep (16), and treatment with indomethacin decreases ACTH release (102). TxA\(_2\) is also a potential mediator of corticotropin-releasing factor (CRF) release. In vitro treatment of adult rat hypothalami with U-46619 (a TxA\(_2\) mimic) causes secretion of CRF (7). We have found that TxA\(_2\) is a powerful and specific stimulator of ACTH secretion in both adult and fetal sheep (35, 36, 116). In the adult sheep, endogenously generated TxA\(_2\) stimulates ACTH secretion (36) and, in the fetal sheep, infusions of U-46619 into the carotid arterial blood supplying the fetal brain stimulates increases in fetal ACTH secretion (116). The ACTH response to a stimulus that
causes TxA2 generation is blocked through the inhibition of COX or through blockade of TxA2-PGH receptor (35, 36).

We recently reported that inhibition of prostanoid biosynthesis significantly and dramatically alters the fetal responsiveness to hypotension. Indomethacin pretreatment significantly reduces the magnitude of the ACTH and AVP responses to hypotension (104). It is interesting that the effect of indomethacin on these responses to hypotension requires intact baro- and chemoreceptive pathways. Prior sinoaortic denervation itself somewhat reduces the magnitude of the endocrine responses to hypotension. However, indomethacin does not impose any further reductions in endocrine responsiveness (Fig. 6). This suggests to us that prostanoid generation within the CNS augments the activity of this pathway.

The potential for prostanoids acting as neuromodulators within the fetal brain is supported by the observation that both the constitutive and inducible forms of prostaglandin endoperoxide synthase (PGHS-1 and PGHS-2, alternatively COX-1 and COX-2) are found within fetal neurons in regions important for cardiovascular and endocrine responses to hypotension, hypoxia, and other cardiovascular “stresses” (38, 39, 77, 94). We have also recently reported the presence of thromboxane synthase in neuronal and glial cells in these regions (52). It is also now known that various receptor subtypes for prostanoids are also found within these regions of the brain (101). Interestingly, it is also now recognized that both PGE2 and TxA2 can, in high concentrations, inhibit the activity of the GABA_A receptor (96). It is conceivable that prostanoids might be generated within GABAergic neurons or in GABA-receptive neurons themselves, thereby altering reflex responsiveness to cardiovascular stimuli. Supporting this general proposition is the observation that cerebral hypoperfusion stimulates increases in the concentration of PGE2 in the interstitial fluid of late-gestation fetal sheep (105).

OTHER MODULATORS OF FETAL CNS CONTROL

There are several other potentially important modulators of fetal CNS function that could significantly impact the control of the fetal cardiovascular system. An obvious candidate is estrogen, an important part of the steroid milieu that participates in the timing of parturition in most, if not all, mammalian species. We have reported that physiological increases in fetal plasma estradiol concentration stimulate fetal ACTH secretion, both during basal conditions and in response to hypotension (Figs. 7). This is interesting in light of the rising concentrations of estrogen in the fetal circulation at the end of gestation (21, 76). This increase in estrogen concentration results from an induction of cytochrome P-450c17 in the placenta of sheep or an...
increase in the rate of secretion of dehydroepiandrosterone from the fetal adrenal of primates and accounts for an important part of the “trigger” for parturition (68). It is likely that this rising tide of estrogen in the fetus progressively augments fetal ACTH secretion and progressively augments fetal CNS responsiveness to stress. Interestingly, the source of estrogen that is available for action within the fetal CNS is not limited to the unconjugated steroids. The ovine fetal brain is richly endowed with steroid sulfatase, the enzyme that deconjugates estrogen sulfates and makes the steroid available for action at the estrogen receptor (87).

CONCLUSIONS

Gaining a better understanding of the reflex and nonreflex mechanisms controlling the fetal cardiovascular system is important because of the interplay of blood pressure, umbilical-placental perfusion, maternal-fetal gas exchange, and delivery of oxygen and substrate to metabolizing tissue. Maintenance of fetal blood pressure is therefore essential for fetal growth, development, and ultimate outcome. The basic neurocircuitry within the fetal brain that mediates cardiovascular control is likely to be similar to that in the (better studied) adult. However, an interesting and important aspect of this system, which might be unique to the fetus, is the influence of various autocrine, paracrine, and endocrine substances that modify the basic reflex responsiveness and therefore alter the response to match the demands of the developmental stage. Gaining a better understanding of these interactions might therefore tell us much, not only about the fetal cardiovascular system, but also perhaps about fetal growth and development, survival of stress, and perhaps even about the control of parturition.

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