

Regulation of Fetoplacental Vascular Bed by Hypoxia

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Summary

Important fetal and perinatal pathologies, especially intrauterine growth restriction (IUGR), are thought to stem from placental hypoxia-induced vasoconstriction of the fetoplacental vessels, leading to placental hypoperfusion and thus fetal undernutrition. However, the effects of hypoxia on the fetoplacental vessels have been surprisingly little studied. We review here available experimental data on acute hypoxic fetoplacental vasoconstriction (HFPV) and on chronic hypoxic elevation of fetoplacental vascular resistance. The mechanism of HFPV includes hypoxic inhibition of potassium channels in the plasma membrane of fetoplacental vascular smooth muscle and consequent membrane depolarization that activates voltage gated calcium channels. This in turn causes calcium influx and contractile apparatus activation. The mechanism of chronic hypoxic elevation of fetoplacental vascular resistance is virtually unknown except of signs of the involvement of morphological remodeling.

Key words

Placenta • Hypoxia • Intrauterine growth restriction • Vasoconstriction • Ion channels

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Introduction

The placenta is a crucial organ for the fetus, combining the function of several essential postnatal organ systems (lung, kidney, alimentary tract, endocrine

functions, ...). Consequently, defects of the placental function are important causes of fetal and neonatal morbidity and mortality. It is thus not surprising that the transport function of the maternal-fetal interface in the placenta has been extensively studied for decades (Štulc *et al.* 1990, Pavek *et al.* 2003, Staud *et al.* 2006). Likewise, another important factor in the utero-placental function, namely the maternal perfusion of the uterine vessels under various conditions, is also quite well understood (Moore 2003, Osol and Mandala 2009). On the other hand, another important aspect of placental function – fetal perfusion of the placenta and its regulation – has been receiving relatively little attention.

One of the quite common conditions that are challenging to the developing fetus is placental hypoxia. It could result from maternal hypoxemia (e.g. during exposure to high altitude or due to maternal cardiovascular or respiratory diseases) or from impaired uterine blood flow (e.g. maternal hypertension or diabetes and especially preeclampsia). Regardless of its cause, placental hypoxia is commonly assumed to be an important factor in the development of serious fetal and perinatal disorders, especially intrauterine growth restriction (IUGR). By reducing fetoplacental blood flow, hypoxia is thought to cause fetal undernutrition and thus impairs fetal growth. IUGR is one of the most serious problems of current neonatology. With incidence of 5-7 %, it is a frequent cause of neonatal morbidity and increases the risk of disorders such as hypertension or diabetes in adulthood (Brodsky and Christou 2004). Umbilical artery Doppler ultrasound flow-velocity measurements indicate increased fetoplacental vascular impedance in IUGR (Arbeille 1997, Zamudio 2003). Nevertheless, the effects of hypoxia on fetoplacental

vasculature are little studied.

This brief review therefore aims to summarize what is currently known about the regulation of already established fetoplacental vascular bed under the conditions of acute and chronic hypoxia. The review intentionally omits data about the effects of hypoxia on creation of placental vasculature and trophoblast invasion. These important topics are reviewed elsewhere (Straszewski-Chavez *et al.* 2005, James *et al.* 2006).

Acute hypoxia

Most vascular beds respond to acute hypoxia with more or less severe vasodilation. This is part of the autoregulatory response that brings more blood (and thus oxygen and nutrients) to tissues whose actual metabolic needs exceed current rate of perfusion. Postnatally, the only exception to this rule is the lung, where hypoxia acts as a potent vasoconstrictor stimulus. This hypoxic pulmonary vasoconstriction helps to divert blood flow from poorly ventilated towards better oxygenated lung areas and thus maintains ventilation/perfusion ratio and blood oxygenation.

The first author to suggest that a similar mechanism would make sense also in the placenta was R. Howard in 1987. He hypothesized that “fetoplacental vascular resistance is controlled locally by a reversible hypoxic fetoplacental vasoconstriction (HFPV) in response to reduced local maternoplacental oxygen delivery” (Howard 1987). This idea was partly based on a study showing that reductions in maternal perfusion of the uterus decrease fetal perfusion of the placenta (Stock *et al.* 1980) and on the finding that maternal and fetal flow correlate (Power *et al.* 1981). Howard’s group soon published an experimental study on perfused human cotyledon showing that, indeed, reduction of partial pressure of oxygen of the perfusate of the maternal lacunas resulted in reversible and reproducible vasoconstriction of the fetoplacental vascular bed (Howard *et al.* 1987). It is somewhat surprising that – even though they immediately recognized the potential of HFPV to “contribute to poor fetal prognosis in preeclampsia” and this view was later widely accepted (Myatt 1992, Poston *et al.* 1995, Brodsky and Christou 2004, Reynolds *et al.* 2006) – only exceptional studies mentioning HFPV were published during the ensuing decade (Byrne *et al.* 1997, Challis *et al.* 2000).

We became interested in the idea of HFPV at the turn of the millennium. We hypothesized that the lack of

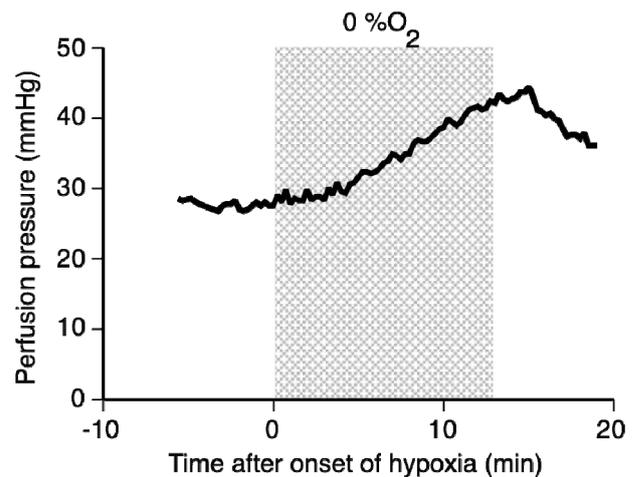


Fig. 1. Acute hypoxic fetoplacental vasoconstriction. Example recording of perfusion pressure in isolated cotyledon of a human placenta during constant flow rate perfusion illustrates vasoconstrictor response to acute hypoxia (shaded area).

interest in HFPV until then was due to the small magnitude of the response in the study of Howard *et al.* (at constant flow perfusion, pressure rose by ~10%). The small magnitude, in turn, according to our reasoning, might have been due to suboptimal experimental conditions, too different from in vivo situation. By optimizing experimental conditions, we were able to show that HFPV can be considerably larger – perfusion pressure increased by at least 20% (Hampl *et al.* 2002) (Fig. 1). Thus, HFPV has a potential to be physiologically and pathologically relevant. This was subsequently confirmed in a study that also showed that the magnitude of the vasoconstrictor response is proportional to the degree of hypoxia (Ramasubramanian *et al.* 2006). The response appears to be localized predominantly in small resistance vessels, since large ones (isolated in organ baths) either do not respond to hypoxia at all (Hampl *et al.* 2002) or even dilate (Figueroa *et al.* 1993). Whether predominantly arteries or veins are involved has not been directly studied, even though there is a study showing that hypoxia potentiates vasoconstrictor responses to a thromboxane analog, U46619, in isolated small chorionic plate arteries but not veins (Wareing *et al.* 2006b). When hypoxia is extended to 6 hours, narrowing of the lumina of vessels in terminal villi can be observed morphologically (Bachmaier *et al.* 2007).

In the lungs, there is solid evidence that the mechanism of hypoxic vasoconstriction involves hypoxic inhibition of potassium channels (especially the voltage-gated family) in the vascular smooth muscle cell membrane which causes depolarization and that in turn is

a stimulus for activation of voltage-gated calcium channels. Their opening increases intracellular calcium concentration (this is most likely amplified by calcium-induced calcium release from the sarcoplasmic reticulum) and thus activation of the contractile apparatus (Hampl and Herget 1991, Archer and Michelakis 2002).

As a working hypothesis, we assumed that a similar chain of events might be responsible for HFPV. In isolated human placental vessels we and later others demonstrated that fetoplacental vessels express several types of potassium channels of both the voltage-gated and other families (e.g. calcium-activated potassium channels) (Hampl *et al.* 2002, Wareing *et al.* 2006a). In smooth muscle cells freshly isolated from peripheral fetoplacental vessels hypoxia inhibited potassium channels-dependent current (Hampl *et al.* 2002). And in perfused human cotyledon, inhibitor of voltage-gated group of potassium channels, 4-aminopyridine, mimicked hypoxia by causing vasoconstriction on the fetal side (of a similar magnitude as did hypoxia) and blocked further rise in perfusion pressure in response to a superimposed hypoxic challenge (Hampl *et al.* 2002). Iberiotoxin, a selective inhibitor of calcium-activated potassium channels, was without effect. Thus, as in the pulmonary vessels, the hypoxic vasoconstrictor response in the fetoplacental vessels involves hypoxic inhibition of potassium channels, specifically those of the voltage-gated family. Calcium-dependent potassium channels are not affected by hypoxia. Whether other types of potassium channels also play a role in this mechanism remains to be studied.

To elucidate the role of voltage-gated calcium (L-type, Ca_v1 family) channels in HFPV, hypoxic responses were compared in isolated perfused human cotyledon before and after addition to the perfusate of a selective L-type channels inhibitor nifedipine (or its solvent DMSO in a control group). Even a very low dose of nifedipine (1 nM) completely wiped-out hypoxic reactivity (Jakoubek *et al.* 2006). Thus, the L-type channels activation, presumably by depolarization caused by hypoxic inhibition of potassium channels, is essential for HFPV. This does not exclude the possibility that calcium release from the sarcoplasmic reticulum induced by calcium influx *via* L-type channels partly mediates this effect. Our results do seem, however, to exclude the role of capacitive calcium influx, because that current is carried by TRP channels and they, although present in the placental vessels (Wareing *et al.* 2006a), are not sensitive to nifedipine.

Vasomotor reactivity in all vascular beds is variably modulated by endothelial diffusible factors, such as nitric oxide or prostanoids, especially prostacyclin. From the limited data we have so far it seems that HFPV is not normally modulated by prostaglandins, inasmuch administration of meclofenamate, a cyclooxygenase inhibitor, affects neither basal fetoplacental vascular tone nor the magnitude of HFPV (Hampl *et al.* 2002). As for nitric oxide, the available data are somewhat controversial. There is a consensus that nitric oxide helps to keep resting vascular tone in the placenta low, as evidenced by a vasoconstriction elicited by administration of nitric oxide synthase inhibitor, L-NAME (Byrne *et al.* 1997, Hampl *et al.* 2002). However, the response to hypoxia was found unchanged by L-NAME in one study (Hampl *et al.* 2002) and abolished in another (Byrne *et al.* 1997). Consequently, the two studies differ markedly in their conclusions about the role of nitric oxide in HFPV – one excludes it, the other considers it important. The reason for the discrepancy is currently unknown. We suspect that the reason could be the highly hyperoxic baseline conditions and a high dose of L-NAME (known to have numerous side-effects in addition to nitric oxide synthase inhibition) in the study of Byrne *et al.* (1997).

Chronic hypoxia

The effects of chronic hypoxia on fetoplacental vasculature are even less studied than acute HFPV, despite the likelihood that chronic rather than acute hypoxia might be the culprit in important fetal and neonatal pathologies such as IUGR. In the lungs, chronic hypoxia causes pulmonary hypertension that is not a simple prolongation of acute hypoxic vasoconstriction. While vascular wall tension may or may not be elevated, the increased pressure is maintained also by structural remodeling of the vessels and thus is not readily reversible upon reoxygenation (Herget and Hampl 1995).

We hypothesized that in the fetoplacental vessels chronic hypoxia also causes a chronic elevation in vascular resistance (although in contrast to lungs, it would not have to be expressed as hypertension *in vivo*, since the consequence of the increased resistance in the fetoplacental vessels could be redirection of blood flow away from the placenta, with little increase in fetoplacental blood pressure). In fact, a similar hypothesis was envisaged by Howard in 1987: „... it is proposed that

chronic local maternoplacental ischemia ... can induce an irreversible fetoplacental vasoconstriction by a mechanism different from HFPV in order to permanently shut down fetal blood flow to the area(s) affected“ (Howard 1987). Using isolated dually perfused rat placenta we showed that, indeed, vascular resistance (measured as pressure-flow relationship) was increased by about 20 % when measured at the end of hypoxic exposure lasting for the last third of gestation (Jakoubek *et al.* 2008) (Fig. 2). As the measurements were not performed under hypoxic conditions, it is evident that this increase in resistance is refractory to acute reoxygenation.

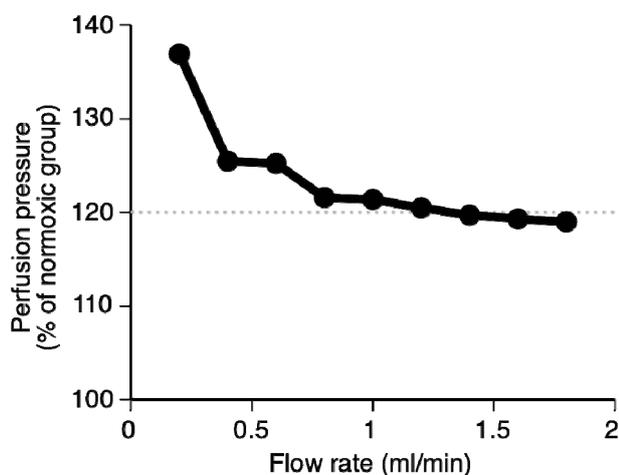


Fig. 2. Chronic hypoxia increases fetoplacental vascular resistance in isolated perfused rat placenta. The graph shows perfusion pressures in the chronically hypoxic group at given levels of perfusion flow rate expressed as % of the respective values in the normoxic control group.

To assess the involvement of elevated vascular tone in the increased resistance, we measured the effect of a strong vasodilator, sodium nitroprusside. As found previously (Hampl *et al.* 2002), it had no effect in the control placentas (normal placental vessels have minimal vascular tone, possibly at least in part due to the lack of sympathetic innervation). Somewhat surprisingly, also in the chronically hypoxic placentas sodium nitroprusside did not alleviate the elevated resistance. This implies that the observed elevation in vascular resistance in chronic hypoxia is not caused by increased vascular tone, at least not in a situation when the tissue has been exposed to normoxia for several tens of minutes. This does not exclude the possibility – and indeed likelihood – that *in vivo*, under persisting hypoxic conditions, the elevation in vascular resistance is even higher due to superimposed hypoxic

vasoconstriction. In fact, we found that HFPV is potentiated by chronic hypoxic exposure (Jakoubek *et al.* 2008).

The elevated vascular resistance refractory to vasodilator treatment implies that morphological remodeling of the vessels is a likely mechanism. While the effects of chronic hypoxia on uteroplacental vessels are relatively well studied (Moore 2003), little is known about fetoplacental vasculature (after it has developed – the effects of hypoxia on trophoblast invasion are studied extensively). There are data that chronic hypoxia (of high altitude) stimulates vascularization of villi and increases the villous capillary diameter (Scheffen *et al.* 1990, Khalid *et al.* 1997, Espinoza *et al.* 2001, Zamudio 2003, Tissot van Patot *et al.* 2004). These changes would be expected to reduce, rather than increase, vascular resistance. However, in principal, morphological changes at the capillary level are less important from the point of view of the overall resistance of the whole vascular bed as compared to changes at the arteriolar level. For example, in a comparable situation of the chronic hypoxic pulmonary hypertension, the total lumen of the resistance lung arterioles is reduced despite increased capillary density (Farber and Loscalzo 2004, McLaughlin and McGoon 2006). There are preliminary results indicating that hypoxia during the last 2 weeks of a 3-week gestation in rats reduces the number of chorionic plate arteries and internal diameter of both chorionic plate and intraplacental arteries (Hampl *et al.* 2007). In addition, the vascular wall was found to have irregularly distributed thin and thick sections, and the thick ones were significantly thicker in chronically hypoxic as compared to normoxic placentas. These findings may help to explain the elevated fetoplacental vascular resistance in chronic hypoxia.

The mechanisms responsible for the elevated fetoplacental vascular resistance in chronic hypoxia are completely unknown at present. We can only assume that some of the mechanisms known in chronic hypoxic pulmonary hypertension, such as oxidative vascular wall injury from oxygen radicals (Lachmanová *et al.* 2005) and nitric oxide and its derivatives (Archer *et al.* 1994, Hampl and Herget 2000, Hampl *et al.* 2006) leading to collagenous repair (Zaidi *et al.* 2002, Herget *et al.* 2003) by activated mast cells (Vajner *et al.* 2006, Baňasová *et al.* 2008), serotonin metabolism alterations (Bělohávková *et al.* 2001, Dempsey and MacLean 2008) and/or Rho kinase pathway activation (Fagan *et al.* 2004, Parker *et al.* 2006), are likely to play significant roles in the placenta as well.

Conclusions and perspectives

The long suspected chain of events, in which uteroplacental hypoxia (due to maternal hypoxia or illness) increases fetoplacental vascular resistance and consequently hypoperfusion of the placenta, fetal undernutrition and growth restriction, now has its major steps experimentally proven, described and methodologically accessible for further study. For acute hypoxia, there are even important insights into the mechanisms involved, including hypoxic inhibition of potassium channels in fetoplacental vascular smooth muscle cells, leading to membrane depolarization, voltage-dependent calcium channels activation, calcium influx and thus contractile apparatus activation. For chronic hypoxia, the mechanisms are currently mostly unknown, but do seem to include morphological remodeling of fetoplacental vessels. In addition to the

mechanisms, other issues that need further study include the physiological role and effectiveness of HFPV (redirection of blood flow to better oxygenated areas, coordination with the rest of the fetal cardiovascular system) and possible therapeutic intervention in chronic hypoxia.

Conflict of Interest

There is no conflict of interest.

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