SA1

Placental transport; regulation and interactions

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During pregnancy, the fetus is entirely dependent on its mother for nutrition. Most nutrients are transferred from the mother across the placenta. A series of transport mechanisms have evolved to carry out these tasks and there has been substantial effort in elucidating their regulation and modulation. Our initial work studied transfer of micronutrients such as copper and iron. We identified several steps in the transfer process, how they adapt to changing nutritional environment and how the transfer is regulated (for reviews see Andersen & McArdle, 2004; Gambling & McArdle, 2004). Recently, we have been examining how different nutrients interact during pregnancy.

Iron and copper have long been known to influence each other. In the liver, copper deficiency results in an increase in iron levels while iron deficiency increases copper, at least in the maternal liver. In the fetal liver, in contrast, maternal iron deficiency induces a decrease, not an increase, in copper levels(Gambling et al., 2004). Associated with these changes are alterations in the expression of genes regulating iron status while mRNA levels of genes of copper metabolism do not change. This fits with their regulation taking place through altered cellular location rather than changes in transcription.

The regulation of iron transfer across the placenta is complex. We demonstrated, using an iron deficiency model, a hierarchy of delivery. The fetal liver drives the regulation, with levels being maintained at the cost of the mother. Second in the hierarchy comes the maternal blood supply and maternal stores third. The data explain why, in humans, a mother will lose as much as 300 mg of iron from her stores with every pregnancy (Bothwell, 2000).

Changing nutrient status, however, has wider consequences than just for that nutrient. We have used the BeWo cell line as a model for placental function for many years. More recently we started using the b30 clone, which has several advantages over the ATCC clone we used originally. This clone has been shown by several groups to demonstrate differentiation and transport properties similar to placenta (Moe et al., 1994) and has been used to examine polarisation and transport across the cell layer (Liu et al., 1997). We have used these cells as part of an integrated approach to understanding modulation of transfer of nutrients.

Our initial experiments studied amino acid transporter systems, specifically those involved in System A, which transports amino acids such as alanine and glycine, Using the b30 cells, we were able to adopt an integrated approach, examining transcellular transfer, gene and protein expression in the same experiments. We grew the cells on filters and measured transcellular flux, then used immunohistochemistry, Northern and western blotting to determine protein and gene expression. We have used 14C-labelled Methyl amino isobutyric acid (Me-AIB) as a non-metabolisable substrate for System A. Changing amino acid levels in the apical medium results in an increase in amino acid transfer. This is associated with a change in localisation of SNAT2, one of the major System A proteins. Longer periods of deprivation result in increased synthesis of SNAT2, both at mRNA and protein levels (Jones et al., 2006).

Importantly, deprivation of other nutrients will also stimulate these responses. We have shown that both iron and copper deficiency induce increased transfer of amino acids, together with the changes described in the previous paragraph. The implication, which is potentially very significant, is that increased amino acid transfer across the placenta is a generic stress response, rather than a particular change in response to alterations in one nutrient (Jones et al., 2006).

Studying how nutrients interact in generating changes in placental function led us to develop a placental cDNA array, with which we could identify a wider number of genes altered by nutrient stress. We tested whether the same genes and gene pathways would be modulated by nutritional and endocrine effectors. In summary, we demonstrated that they were not. When we used amino acid restriction, we had genes both up- and down-regulated. Using cortisol as an endocrine inducer gave a very different response. In fact, only two genes were affected in common by the two stressors, and of these, one was regulated in the opposite manner.

In summary, it is clear that transplacental transfer of nutrients is a well regulated and efficient process. This has, of course, been accepted for many years. Now, however, we also have to take into account the cross talk between different substrates, and have to elucidate the mechanisms underpinning the interactions. This promises a whole new and exciting arena for placental transport studies.

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SA2

The placenta and fetal programming

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Human epidemiological observations and experimental animal studies have shown that size at birth is critical in determining life expectancy (1). The smaller the neonate the less likely it is to survive at birth and the more prone it is to adult-onset degenerative diseases like hypertension and Type 2 diabetes. These observations have led to the hypothesis that adult disease arises *in utero*, in part, as a result of tissue programming during suboptimal intrauterine conditions associated with impaired fetal growth (1). The main determinant of fetal growth is the placental nutrient supply to the fetus, which, in turn, depends on the size, morphology, blood supply and transporter adundance of the placenta and on the synthesis and metabolism of nutrients and hormones by the placenta itself (2). However, very few studies have examined placental programming *per se.*

Environmental factors, such as nutrition, temperature and glucocorticoid concentrations, are known to alter the placental capacity for nutrient transfer in several species. In sheep and rats, both under- and over-nutrition affect placental size, morphology and abundance of glucose transporters (GLUT1 & 3), although the specific effects depend on the severity, duration and gestational age at the onset of the perturbation. When nutrient deprivation occurs throughout pregnancy, placental efficiency measured as the fetal to placental weight ratio increases even though both fetal and placental weight is reduced. Similar increases in placental efficiency are seen when placental and fetal growth are restricted by maternal glucocorticoid treatment during late gestation. In some small placentae, this increased efficiency is coupled with enhanced transfer of glucose and/or amino acids per unit placental weight, which may reflect elevated transporter abundance or a relative increase in the surface area for nutrient exchange (2,3). In addition, in sheep, undernutrition and glucocorticoid overexposure alter placental glucose consumption and reduce the absolute amount and proportion of uterine glucose uptake delivered to the fetus (4). These insults also change the placental handling of lactate and specific amino acids. Furthermore, ovine placental production and metabolism of the eicosanoids and sex steroids are affected by uteroplacental nutrient availability and by fetal glucocorticoid concentrations during late gestation (5). Similarly, in rats and sheep, undernutrition and glucocorticoid treatment down-regulate the placental activity of 11β-hydroxysteroid dehydrogenase, the enzyme that inactivates glucocorticoids and limits feto-placental exposure to the higher maternal glucocorticoid concentrations (2). This increases glucocorticoid exposure and further compromises feto-placental development.

The molecular mechanisms by which environmental signals alter placental nutrient transfer capacity remain unknown but many involve *Igf2* and other imprinted genes (6). The *Igf2* gene controls placental growth and its placental expression is down regulated in rodents by undernutrition and glucocorticoid treatment (3, 6). Disruption or deletion of the *Igf2* gene either from all feto-placental tissues (complete null) or specifically from the labyrinthine trophoblast (*Igf2*P0 null) causes placental growth retardation and alters placental morphology with the result that the diffusion capacity and surface area for nutrient exchange are reduced (3, 7). Despite these changes, placental efficiency is increased in the *Igf2*P0 mutant compared to its wild type littermate (3). Measurements of unidirectional materno-fetal nutrient transfer have shown that the small *Igf2*P0 placenta transports more glucose and methly-aminoisobutyric acid (MeAIB) per gram than the wild type placenta in late gestation. These changes are accompanied by up-regulation of the *Slc2a3* and *Slc38a4* genes, which encode GLUT3 and an isoform of the System A family of amino acid transporters (7). None of these adaptations are observed in the small placenta of the complete *Igf2* null (6). Indeed, the complete *Igf2* null placenta is less efficient and transfers less MeAIB per gram than their wild type counterparts (7). The nutrient transfers capacity of the murine placenta is, therefore, responsive to the nutrient demands of fetal tissues still expressing *Igf2* and regulated by the interplay between placental and fetal *Igf2*.

In summary, the nutrient transfer capacity of the placenta is responsive to a range of environmental stimuli and to the genetic drive for fetal growth. Both nutritional and endocrine signals alter placental development and the ensuing phenotype although the molecular mechanisms involved have yet to be identified. Environmentally induced changes in the placental capacity for nutrient transfer have an important role in regulating fetal development and may either ameliorate or acerbate the programming effects of the insult on the fetus.

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SA3

Control of uterine activity

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How can activity be regulated in a spontaneously active tissue? This simple question underlies efforts to enable us to control uterine contractions, so that we can better help women suffering threatened pre-term labour or labouring dysfunctionally (inadequately) at term. The fact that the uterus is a myogenic smooth muscle, requiring neither nerves nor hormones to produce its rhythmic contractions, tells us that there is a powerful intrinsic mechanism that has to be understood, if we are going to be successful in regulating its activity.

Activity in myometrial smooth muscle cells begins with a pacemaking depolarization and action potential firing. The mechanism of that pacemaker activity remains obscure. We recently reported the occurrence of interstitial cells of Cajal-like cells (ICCs) in rat uterus, but although capable of producing outward current, inward currents were not apparent, making them unlikely pacemakers (1). It may be more likely that a subset of myocytes, perhaps expressing a modified set of ion channels, and scattered throughout the uterus, act as pacemakers. We have for example found that around 30% of rat uterine myocytes express Ca-activated Cl channels and produce inward current (2). Spontaneous firing of action potentials and elevations of Ca can be observed in freshly isolated uterine myocytes. Selective targeting of these cells may become a future therapeutic goal. As Ca entry through L-type Ca channels is crucially important for uterine contractility, changes of channel activity will modify uterine activity. However because of their wide distribution in other tissues, there use is limited, although nifedipine remains a first choice tocolytic.

We have investigated the role played by the internal Ca store, the sarcoplasmic reticulum (SR) in the uterus. The studies in animal and women's uteri have led us to suggest that the SR does not play a major role in augmenting Ca for contraction, even during hormonal stimulation (3). Although in other smooth muscles a role for the SR in controlling excitability has been shown, via a Ca spark – BK (Ca-activated K channels, producing small outward current events, STOCs) (4), this remains unclear in the uterus. This is because Ca sparks are not produced (5) and although BK channels are expressed, their pharmacological inhibition e.g. with iberiotoxin or 1 mM tetraethyl ammonium, has little effect on uterine contractility. It may be that small conductance Ca-activated K channels (SK) have a role to play, but this is still being investigated .

An additional mechanism for affecting signalling pathways in the uterus has recently been proposed – lipid microdomains known as rafts or caveolae (6). We have found that manipulation of rafts, through altering membrane cholesterol (a key component of rafts), has a profound affect on Ca signalling and contractility, with increasing cholesterol being deleterious. (6). As elevated cholesterol is often associated with obesity, we have hypothesised that disturbance of lipid raft signalling mechanisms in obese women, may account for the increased number of caesarean sections for dysfunctional labour, found in this group (7). As oxytocin receptors have been found to also be affected by their lipid environment and working best in caveolae, and as caveolae numbers may be under oestrogenic control, new insights into how hormonal influence affects uterine activity may be gained.

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SA4

Placental corticotropin-releasing hormone (CRH); role in human pregnancy and labour

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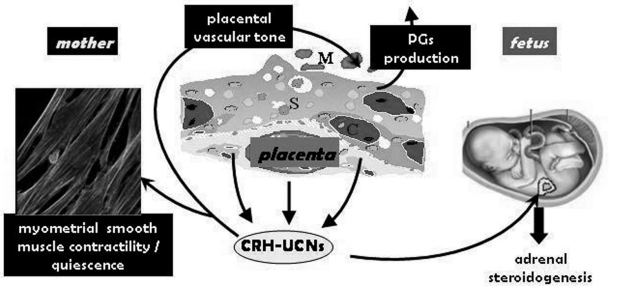
CRH, the 41-aminoacid hypothalamic peptide, plays a fundamental role in mammalian survival and response to events that require "either a flight or fight" response. CRH's role is to initiate and coordinate a series of adaptation mechanisms, involving activation of the HPA axis. It belongs to a family of mammalian peptides that includes the urocortins (UCNs-UCNI, UCNII and UCNIII. CRH expression was identified in human placenta, almost 20 years ago; however, its role during pregnancy and labour still remains a scientific enigma. Plasma levels of CRH might be an important predictor of the duration of human gestation. Furthermore, there are substantially increased concentrations of maternal circulating CRH in abnormal pregnancy states, for example in pre-eclampsia and intrauterine growth retardation. In some women with idiopathic preterm labour, concentrations of CRH increase up to 10 weeks before the development of any symptoms.

During human pregnancy CRH appears to target multiple feto-maternal tissues, including the myometrium, placenta and fetal adrenals, implicating CRH in the mechanisms regulating uterine transition from relaxation to active contractions (1). In addition, CRH/urocortin, may generate prostaglandins from the fetal membranes and decidua, play a role in placental vasodilatation (2)and participate in fetal adrenal function and organ maturation. The actions of CRH are mediated via a wide network of specific G-protein coupled membrane-bound receptors (3). These receptors have various distinct and possibly opposing functional properties, depending on the receptor subtype, the ability of agonists to activate specific signalling cascades and the stage of pregnancy. In addition, their function is dependant upon other intracellular signals via communication between signalling cascades, suggesting potential multiple roles of CRH and other CRH-like peptides during pregnancy and labour. Established and emerging hypotheses about the role of CRH and CRH-R during pregnancy and labour will be discussed.



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SA5

Suppression of neuroimmune responses at term: investigations of possible mechanisms

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It is well known that there is a general reduction in the stress response throughout pregnancy and lactation. However, in several mammals, including rats, the response to the neuroimmune stressor, lipopolysaccharide (LPS) is particularly attenuated at near term. This is manifested as a marked reduction in the febrile response in the day or so around parturition, but which recovers in the post partum period. We have carried out a series of physiological and neurochemical investigations to attempt to identify the mechanisms underlying the reduced neuroimmune response. As a number of pro-inflammatory cytokine are know to mediate LPS fever, we measured circulating cytokines using ELISAs to test the hypothesis that there was an alteration in peripheral cytokines at term. However, levels of pro-inflammatory cytokines (IL-1β, IL-6, IFNγ, and TNFα) in the plasma taken 2h after LPS were similar at gestational day (G) 15, G22 or lactation day (L) 5. In addition to pro-inflammatory cytokines, LPS also causes synthesis and release of a variety of anti-inflammatory molecules, but neither IL-1ra and IL-10, nor the immunosuppressive hormone, corticosterone, were different at the 3 stages of reproduction. Peripheral pyrogens, including cytokines are known to cause fever by initiating the synthesis of prostaglandin E (PGE) that acts on neurons in the anterior hypothalamus /preoptic area to activate thermogenesis and reduce heat loss. To test the hypothesis that PGE synthesis or action was altered at term, we used semi-quantitative Western blots to measure levels of inducible COX-2, the rate limiting enzyme for the synthesis of PGE that is found in endothelial cells of the brain vasculature. We found that COX-2 levels are reduced at G22 compared to G15 or at L5. Pro-inflammatory cytokines activate COX-2 through a number of signaling pathways, so we explored if these were similarly altered. However, the reduced COX-2 expression was not associated with alterations in activation of transcriptional factors NFκB, STAT 3 and STAT5 or of ERK1/2. While lipocalin-prostaglandin D2 synthase, an enzyme that could potentially produce anti-inflammatory cytokines, was generally reduced at late gestation, its further reduction at L5 dissociated the activity of this enzyme from the reduced neuroimmune response at term. Thus we concluded that the reduced fevers at term were most likely associated with a reduction in PGE synthesis in the brain, but the mechanisms responsible for the reduced COX-2 induction remain elusive.

There also appear to be changes within the brain itself that will affect febrile responses. For example, febrile responses to intraventricular application of PGE are reduced specifically at near term. This does not appear to be associated with alterations in hypothalamic levels of the prostaglandin receptor EP-3, but does appear to reflect a generalized suppression of sympathetic output at this time; activation of brown adipose tissue (which in rats is a major contributor to the elevation in body temperature), heart rate and blood pressure were all attenuated to a similar extent at term. The brain contains neurotransmitters such as arginine vasopressin (AVP) that act as antipyretics; as their levels are increased in brain during pregnancy we asked if the suppressed sympathetic output was associated with either altered receptors numbers or action of AVP However, neither mRNA nor protein levels of the V1 AVP receptor were altered at term and central application of an AVP antagonist failed to reverse the attenuated PEG responses.
We conclude that the reduction in neuroimmune responses seen at term in the pregnant rat can be explained by a reduction in the synthesis of prostaglandins due to reduced COX-2 induction as well as a reduced effectiveness of the thermogenic outputs activated by the hypothalamic PGE. Further studies are required to identify the mechanism for these altered responses.

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SA6

Suppressed maternal hypothalamo-pituitary-adrenal (HPA) axis responses to cytokines in late pregnancy

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Glucocorticoids have powerful actions on metabolism and the immune system, especially when secretion is increased by stressors. In pregnancy glucocorticoid is important in fetal maturation, and in determining the onset of parturition via actions on the placenta. Protection of these fetal processes, and the mother's metabolic and immune systems, from stress levels of maternal glucocorticoid may be advantageous for a successful pregnancy. One protective mechanism is placental 11β-hydroxysteroid dehydrogenase 2, which inactivates cortisol (human; corticosterone in rats); another is attenuation of maternal HPA axis responses to stress. Failure of these mechanisms in late pregnancy, as revealed by giving the synthetic glucocorticoid dexamethasone (which crosses the placenta), results in adverse fetal programming. Attenuated HPA axis stress responses in the last week of rat pregnancy (gestation is ca. 22 days) are seen with a mild emotional/physical stressor (e.g. forced swimming; [1]). Measurement by in situ hybridisation (ISH) of rapid gene expression changes in the hypothalamic parvocellular paraventricular nucleus (pPVN), reflecting activation of the corticotropin releasing factor (CRF)/ vasopressin (VP) neurones, shows they are less excited by stressors in late pregnancy. Since CRF and VP cause corticotropin (ACTH) release from the anterior pituitary, and

individuals or women at risk for premature pregnancy termination.
In vitro data suggest a correlation between the rate of progesterone receptor expression as well as PIBF production and the success or failure of pregnancy, but provide no direct evidence for their role in maintaining gestation. To test the biological significance of our findings, we used animal systems. In vivo studies revealed that: a) The anti-abortive effect of the PIBF in vivo is manifested via inducing a Th2 dominant cytokine pattern and keeping the NK activity at a low level: b) A proper stimulation of the maternal immune system is required for the operation of the progesterone-dependent immunomodulatory pathway: c) Neutralization of endogenous PIBF results in pregnancy termination. These data allow the conclusion that the operation of progesterone-dependent immunomodulation contributes to maintaining normal gestation.

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SA8

Cytokines and myometrial intracellular signalling

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During human pregnancy the smooth muscle of the uterus, the myometrium, is relatively quiescent until the onset of contractile activity associated with labour. The cascade of events precipitating human labour remains unclear, but it is proposed that the myometrium becomes primed to contract at term by the activation of a complex array of genes encoding for proteins which include cyclo-oxygenase-II (COX-2), the oxytocin receptor and calcium regulatory proteins (TRPC isoforms and sarcoplasmic reticulum calcium ATPases). Several concordant stimuli ('physiological' inflammation, maternal and foetal endocrine signals and uterine stretch) have been implicated in this process and are proposed to drive the integration of uterine contractile activity and labour. In support of a central role for inflammatory cytokines, IL-1β, IL-8 and IL-6 have been found in myometrial tissue taken in late pregnancy, and raised concentrations are reported in amniotic fluid during human term and preterm labour. Experimental models of preterm labour have also demonstrated that introduction of bacterial products or cytokines into the amniotic cavity of pregnant animals leads to cytokine synthesis, up-regulation of Toll-like receptors and premature uterine contraction.
This presentation will discuss how the inflammatory mediator IL-1β modulates uterine excitability. It is well known that that IL-1β can stimulate myometrial prostaglandin synthesis, but our studies demonstrate for the first time that IL-1β can also enhance calcium signalling events. IL-1β treatment of human myometrial cells induces spontaneous calcium oscillations and increases resting calcium concentrations in parallel with an augmentation of store-dependent calcium entry and a substantial increase in TRPC3 protein expression. Interestingly, IL-1β treatment does not alter expression patterns of any other TrpC isoforms suggesting that TRPC3 is differentially regulated. IL-1β-treated smooth muscle cells also exhibit augmented calcium responses to a diacylglycerol analogue (OAG), a prominent activator of TrpC3 channels. These data implicate TRPC3 channels as key mediators of the IL-1β enhancement of myometrial smooth muscle calcium signalling, and provide a plausible mechanism by which uterine excitability may be augmented in term and preterm labour. This cell model may also prove useful as an endogenous 'overexpression' system with which to explore the function, regulation and role of TrpC3 proteins.

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SA9

Prolactin and the neuroendocrine adpatations of the maternal brain

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Levels of lactogenic hormones, prolactin from the maternal anterior pituitary and/or the closely related placental lactogen, are elevated during pregnancy and lactation. While these hormones are well established to have an critical role in mammary development and lactogenesis, they also exert important actions in the brain. Prolactin receptors are expressed in the choroid plexus and in several hypothalamic nuclei, and we have shown that levels of expression increase during pregnancy and lactation. Prolactin is known to influence a variety of hypothalamic functions, including regulation tuberoinfundibular dopamine (TIDA) neurons, stress responses, appetite and food intake, and fertility (1). Many of these prolactin-sensitive functions appear to change during pregnancy in a manner consistent with the influence of prolactin. Two specific examples have been examined to evaluate the role of prolactin in mediating neuroendocrine adaptation in the maternal brain: a) Decreased sensitivity of TIDA neurons to prolactin, leading to decreased secretion of dopamine and subsequent hyperprolactinaemia. b) Increased food intake and the development of leptin-resistance during pregnancy. Both changes are important maternal adaptations to pregnancy, providing high prolactin for mammary development and maternal behaviou, and increased energy storage to meet the metabolic demands of lactation, respectively.
Prolactin acts directly on prolactin receptors on TIDA neurons inducing phosphorylation of STAT5b and activation of tyrosine hydroxylase (TH, the rate limiting enzyme responsible for dopamine synthesis) and an increase in TH mRNA expression. We have measured mRNA for the long form of the prolactin receptor on TIDA neurons by in situ hybridisation and this does not change during pregnancy or lactation (2), although there is an increase in expression of met-enkephalin in prolactin-responsive TIDA neurons. Prolactin-induced phosphorylation of STAT5b in TIDA neurons is suppressed during lactation, associated with a prolactin- or suckling-dependent increase in mRNA for several endogenous inhibitors of STAT pathways (CIS, SOCS1