SYMPOSIUM REPORT

Central and peripheral neuroimmune responses: hyporesponsiveness during pregnancy

Sarah J. Spencer, Abdeslam Mouihate, Michael A. Galic and Quentin J. Pittman

Hotchkiss Brain Institute and Institute of Infection, Immunity and Inflammation, Department of Physiology and Biophysics, Faculty of Medicine, University of Calgary, Calgary, Alberta, Canada

There are periods in the life of a healthy animal (including humans) when the febrile response to an immune challenge is suppressed. One such period is during late pregnancy, particularly around the time of parturition. In the 30 or so years since this 'febrile hyporesponsiveness' was first noted, much work has been done to investigate the mechanisms and adaptive significance of this phenomenon. In this review we present some insight into how and why the body deliberately re-programmes itself to develop smaller fevers in response to an immune challenge and therefore to be potentially less successful at fighting infection.

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Corresponding author Q. J. Pittman: Health Sciences Centre, 3330 Hospital Dr., N.W. Calgary, Alberta, Canada T2N 4N1. Email: pittman@ucalgary.ca

An overview of the innate immune system and fever

The innate immune system. An appropriate immune response is an essential component of the body's defence against the invading pathogens to which it is daily exposed. The two arms of the immune system are the generalized, innate response and the more specific, adaptive response, which are designed to recognize and attack invading pathogens.

While the adaptive immune response, which we will not discuss in detail here, is specifically targeted to particular antigens, the innate immune response is designed to recognize more generalized and conserved microbial patterns, known as pathogen-associated molecular patterns, and to mount a rapid non-specific immune response. Thus, a systemic immune challenge activates pattern recognition receptors, of which the toll-like receptors are an example. These receptors can be found on myeloid cells such as monocytes and macrophages, and their activation can lead to the release of pro-inflammatory cytokines. These act either on afferent nerves, directly on the brain at circumventricular organs, or on endothelial cells at the blood–brain barrier, stimulating the cyclo-oxygenase (COX)-mediated conversion of arachidonic acid into prostaglandins, such as pro-inflammatory prostaglandin E_2 (PGE_2), that will act centrally to further amplify the immune response and produce fever, at the same time stimulating negative feedback mechanisms to regulate the response (Conti *et al.* 2004; Turrin & Rivest, 2004; Danese *et al.* 2007).

This innate immune response comes in a temporally double-pronged attack. The initial response, i.e. elevation in body temperature, is too fast to be accommodated by the synthesis of cytokines in the periphery and subsequent transit in the circulation to the brain. Thus, it is argued that when administered intraperitoneally, pathogens initially produce fever by activation of the complement cascade in the liver, leading very rapidly to PGE_2 generation. This PGE_2 either activates vagal afferents, which then signal via the nucleus of the solitary tract to activate ascending noradrenergic fibres, or possibly is released into the circulation to access the brain (Romanovsky *et al.* 1999; Conti *et al.* 2004; Blatteis, 2006). There is also some evidence that an initial response involves the rapid stimulation of PGE_2 production via the activation of constitutively expressed COX-1, perhaps directly activated by toll-like receptors in the brain vasculature (Turrin & Rivest, 2004) or possibly via free radical generation (Riedel *et al.* 2003).

Whereas the mechanisms responsible for the initial rise in temperature are still not completely clear, those for later components of the response are better understood. The second, delayed, response comes via pro-inflammatory cytokine-induced PGE_2 synthesis catalysed by the inducible COX-2 enzyme, which is produced via nuclear factor (NF) κB-mediated transcriptional mechanisms (e.g. Turrin & Rivest, 2004). Prostaglandin E_2 then

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acts at its EP_3 receptor in the preoptic area to generate febrile responses and other behavioural adaptations. Nuclear factor κB activation also leads to the transcription of genes coding for many other factors such as cytokines, chemokines and inducible nitric oxide synthase (iNOS). Prostaglandin E_2 then further stimulates downstream immune adaptations. Importantly, PGE_2 also potentially acts through several different EP receptor subtypes in a number of brain areas to activate cells in the paraventricular nucleus (PVN) of the hypothalamus that release corticotrophin-releasing-hormone (CRH) (Lazarus *et al.* 2007). The net result of this pathway's activation is CRH secretion into the median eminence, triggering adreno-corticotropic hormone release into circulation, and ultimately stimulating glucocorticoid synthesis and release from the adrenal gland. Glucocorticoids then exert negative feedback control over further enhancement of the inflammatory response via inhibition of NFκB signalling pathway, limiting the effects of the inflammatory response (Conti *et al.* 2004; Turrin & Rivest, 2004; Danese *et al.* 2007).

In addition to stimulating the hypothalamic-pituitary-adrenal (HPA) axis, prostaglandin production leads to a number of additional physical manifestations of the immune response. Collectively known as sickness behaviours, these include anorexia, anhedonia, hyperalgesia, social withdrawal and general reductions in activity, and are all thought to be short-term energy conservation adaptations to compensate for the high metabolic demands made by the immune system, and to discourage the animal from engaging in potentially dangerous social or food-seeking activities (Dantzer, 2001; Dantzer & Kelley, 2007).

One of the more important weapons in this, the body's arsenal against infection, is the febrile response. The pro-inflammatory cytokines, particularly interleukin (IL)-6 (Chai *et al.* 1996) within regions such as the vascular organ of the lamina terminalis (OVLT), mediate fever by promoting heat conservation (peripheral vasoconstriction, piloerection) and heat generation (shivering, heat-seeking behaviours, increased brown adipose tissue metabolic activity) mechanisms. In addition EP_3 activation in the median preoptic nucleus by prostaglandins disinhibits γ-aminobutyric acid (GABA) neurons that project to the dorsal medial hypothalamus and other downstream nuclei, resulting in activation of brown adipose tissue thermogenesis, and elevation of body temperature (Lazarus *et al.* 2007). In association with the activation of these thermogenic pathways, the bed nucleus of the stria terminalis (BNST) is, conversely, involved in a thermolytic action to cause antipyresis via an arginine vasopressin (AVP)-ergic input to the PVN or the ventral septal area (VSA) (Naylor *et al.* 1988; Pittman & Wilkinson, 1992; Hare *et al.* 1995). Other putative endogenous antipyretics include, for example, natriuretic peptide (Miyoshi *et al.* 2006), nitric oxide (Gerstberger, 1999; Begg *et al.* 2007), α melanocyte-stimulating hormone (Tatro, 2000), a variety of anti-inflammatory molecules derived from arachidonic acid (Kozak *et al.* 1998; Mouihate *et al.* 2004), and possibly a peripherally generated splenic factor (Feleder *et al.* 2003). Details of the pathways and mechanisms by which these work are still limited in most cases.

The importance of fever. Fever is thought to be essential for survival and, indeed, those animals that are prevented from developing a febrile response to infection display strong heat-seeking behaviours and have higher morbidity and mortality (Hart, 1988). Despite routine use of antipyretic agents to quell fever, it seems clear that the benefits of an intact febrile response, except perhaps in the case of very high fevers, outweigh the risks (Kluger *et al.* 1998; Greisman & Mackowiak, 2002). Fever induction has even been used successfully in humans to combat pathogens. For instance, in the early 1900s clinicians deliberately infected their patients with malaria, which produces high fevers, in order to combat the syphilis spirochete *Treponema pallidum*, a bacterium that is very sensitive to high temperatures (Hart, 1988; Raju, 2006). Fever is thought to work principally by reducing bacterial and viral load, either by enhancing host defence mechanisms, such as phagocytosis by neutrophils, or by providing suboptimal temperature conditions for pathogen proliferation (Hart, 1988; Jiang *et al.* 2000).

Fever and the inflammatory response during pregnancy

Febrile hyporesponsiveness during pregnancy – an adaptive response? Despite fever being thought of as an essential component of the immune response, there are a number of instances in the life of a healthy animal when the febrile response to an immune challenge can be notably suppressed. For instance, during the later stage of pregnancy, animals of many species do not mount their usual fevers in the face of an immune challenge (Kasting *et al.* 1978; Martin *et al.* 1995). Even infections that usually cause very high febrile responses, such as *Plasmodium falciparum* malaria, can go unnoticed and therefore untreated during pregnancy because such fevers are not seen (Desai *et al.* 2007). It should be noted that this phenomenon is not ubiquitous, with rabbits and some sheep displaying normal fevers during pregnancy (Heap *et al.* 1981; Blatteis *et al.* 1986, 1988). It also has not been definitively demonstrated in humans and it can be seen that fever can be a problem in humans with maternal intrapartum fever (Kuczkowski & Reisner, 2003; Apantaku & Mulik, 2007). However, this febrile hyporesponsiveness

during late pregnancy has been seen frequently across many species, from sheep to guinea pigs and rats, and the mechanisms for it and its adaptive functions are still unclear.

There are a number of reasons why such an adaptation could be beneficial to the mother and the fetus. High or prolonged fever is associated with a number of potentially harmful effects that can include disregulated maternal water balance, cardiovascular alterations, and altered mental status. These could indirectly have an impact upon fetal health. Perhaps one of the more immediately apparent reasons for this adaptation is that hyperthermia can have direct and severe adverse effects on the offspring. Even the small increases in the mother's body temperature that occur during very warm ambient conditions have been associated with serious birth defects. For example, guinea pigs and humans subjected to high ambient temperatures *in utero* have been born with cranio-facial, neural tube or heart defects (Edwards, 2006). This would seem to be a primary and even sufficient reason for the mother to develop a suppressed febrile response to infection. However, such effects of hyperthermia are very much dependent upon the developmental stage at which they occur, and many of these crucial developmental time points are reached early in the pregnancy, before the maternal febrile response is altered. For instance, neural tube defects are only seen if high ambient temperatures are encountered at the time the neural tube begins to close, which occurs very early in the pregnancy (Edwards, 2006). Although it would seem desirable for the mother to therefore have developed mechanisms to suppress her febrile responses, and/or basal core temperatures, for the entire duration of her pregnancy, it is likely that the costs of such a process would outweigh the benefits. As discussed earlier, the inability to mount an appropriate febrile response can lead to a compromised ability to fight infection and a corresponding increased morbidity and mortality. In this light, we have shown increased *E. coli* pyrogen-induced mortality in mother rats at the time of parturition, coincident with the febrile hyporesponsive period (Martin *et al.* 1995). It is easy to see that it could be of no possible benefit to the fetus if the mother was to die from infection during early pregnancy.

There is a second major time point during pregnancy when hyperthermia is potentially very damaging to the offspring, and that is during parturition itself. Hyperthermia during parturition has been linked to cerebral palsy, hypoxic encephalopathy and to otherwise unexplained neonatal seizures (Grether & Nelson, 1997; Lieberman *et al.* 2000; Impey *et al.* 2001; Perlman, 2006). Unlike with early pregnancy, this period of fetal vulnerability does coincide with the maternal suppression of the febrile response. In rats febrile hyporesponsiveness is evident up to 48 h prior to parturition, approximately 10% of the pregnancy (Martin *et al.* 1995). In sheep it is seen anywhere from 10 to 15 days prior to parturition (approximately 10% of the pregnancy) (McClure *et al.* 2005) to only 4 days prior to parturition (Kasting *et al.* 1978). It is likely that it is a positive consequence of this phenomenon that potentially damaging hyperthermia during parturition is avoided in many cases. The adaptive value of this response as a mechanism for protection against hyperthermia-associated hypoxia becomes particularly evident when one considers that there are other, unrelated, mechanisms in place to guard against the same processes. For instance, in the rat there is a switch in the GABA reversal potential from excitatory to inhibitory that occurs during parturition in the fetal hippocampus, which prevents potential hypoxia-induced damage to this region (Tyzio *et al.* 2006). It is also possible that this febrile hyporesponsiveness has adaptive effects on the mother. It is interesting, in this light, that prolactin, which is a major player in the generation of maternal–offspring interactions, is also able to prevent stress-induced hyperthermia when administered centrally (Drago & Amir, 1984; Torner & Neumann, 2002).

Potential mechanisms for pregnancy-related febrile hyporesponsiveness. *Suppression of pro-inflammatory processes.* There are any number of changes occurring during pregnancy that may provide a mechanism for the relative suppression of the immune system. It now seems fairly clear that the suppressed febrile response to immune challenge in late-pregnant animals is linked to a reduction in PGE_2 production (Imai-Matsumura *et al.* 2002). We have seen a suppression of COX-2 in the hypothalamus of parturient rats given the non-replicating gram negative bacterial mimetic lipopolysaccharide (LPS) (Mouihate *et al.* 2002). The production of downstream PGE-synthesizing enzymes is also reduced (Aguilar-Valles *et al.* 2007), as are concentrations of PGE_2 itself in relevant brain areas such as the OVLT, in response to immune challenge (Fewell *et al.* 2002). We have also seen effective fever suppression in pregnant *versus* virgin rats to PGE_2 administered intracerebroventricularly (Chen *et al.* 1999), indicating that PGE_2 may also be acting less effectively at its receptors. Although we did not see differences in expression levels of the EP_3 protein (Mouihate *et al.* 2002), this does not discount the involvement of other prostaglandin receptors. For example, EP_4 receptors may be involved in antipyresis (Oka *et al.* 2003, 2004; Lazarus, 2006) and it is possible that these may be up-regulated during pregnancy.

It is still unclear however, what is responsible for the altered COX-2 in late pregnancy. It has been suggested that late pregnancy is also associated with changes in cytokine production and some studies have shown immune challenge-induced pro-inflammatory cytokine elevations are attenuated in pregnancy. For instance,

intramuscular turpentine oil-induced plasma IL-6 levels have been reported as lower in pregnant animals than in non-pregnant (Aguilar-Valles *et al.* 2007). Some research has also shown LPS-induced plasma IL-6 and IL-1β levels to be attenuated in late pregnancy (Fofie *et al.* 2005). However, very similar experiments have been conducted in our laboratory and we have not observed any alterations in circulating pro-inflammatory cytokines that might account for fever suppression (Mouihate *et al.* 2005). It is unclear why there are such discrepancies between groups. This issue has not been addressed carefully and standardization of cytokine assays between laboratories may be warranted.

Augmentation of anti-inflammatory processes. In addition to potential suppression of pro-inflammatory activities in the brain, there is also the possibility that compensatory anti-inflammatory responses are up-regulated, or at least are not suppressed and may therefore have greater influence. Some studies have reported elevated levels of anti-inflammatory cytokines to an immune challenge during pregnancy. Luheshi and colleagues showed that plasma levels of IL-1ra, an important anti-inflammatory cytokine, were significantly greater after LPS injection in late pregnant rats than in cycling females or males (Ashdown *et al.* 2007). Tumour necrosis factor (TNF)α, although typically considered to be pro-inflammatory, also has antipyretic properties. Tumour necrosis factor α may trigger the hypothermic response, and its neutralization with antiserum results in enhanced LPS-induced fevers (Long *et al.* 1990; Derijk & Berkenbosch, 1994). Tumour necrosis factor α and IL-1ra have been shown to be up-regulated to the same degree in pregnancy as in non-pregnant animals after immune challenge despite the relative attenuation of the pro-inflammatory cytokine response (Fofie *et al.* 2005). Nitric oxide is another potentially important antipyretic molecule in pregnancy. The expression of NOS is up-regulated by oestrogen and progesterone during pregnancy and the resulting nitric oxide contributes to vascular remodelling to support the increases in blood volume required (Carbillon *et al.* 2000; Kelly *et al.* 2004). Nitric oxide production is also increased in the hypothalamus during pregnancy and is thought to be involved in thermoregulation. Thus, an antipyretic role for nitric oxide during pregnancy has been recently suggested in a study which showed that central administration of an iNOS inhibitor leads to the restoration of virgin-like LPS-induced fevers in pregnant rats (Begg *et al.* 2007).

Alterations in steroid hormones. There are many alterations to the mother's physiology during the course of pregnancy that may cause these differences in the inflammatory cascade. Two such candidates are oestrogen and progesterone. During pregnancy the levels of circulating oestrogen and progesterone rise. Progesterone then declines rapidly immediately before birth, disinhibiting oestrogen-mediated myometrial contractility and triggering parturition (Mesiano & Welsh, 2007). Oestrogen remains high at this time. We have seen that hormonal treatment in rats mimicking the high levels of oestrogen and progesterone seen in late pregnancy is able to reproduce the suppression of febrile responses associated with pregnancy (Mouihate & Pittman, 2003). Thus, when we gave ovariectomized rats high oestrogen and progesterone replacement, we saw a reduction in febrile responses to LPS and corresponding reductions in hypothalamic COX-2 compared with oestrogen replacement alone. Interestingly, although we have not seen alterations in circulating cytokines after LPS in rats that were actually pregnant (Mouihate *et al.* 2005; Harre *et al.* 2006), in our steroid-hormone-treated rats we saw reduced IL-1β responses (Mouihate & Pittman, 2003). Interleukin-6 responses were not affected in either pregnant or oestrogen-treated rats (Mouihate & Pittman, 2003; Harre *et al.* 2006). Both oestrogen and progesterone have, however, also been shown to have central anti-inflammatory effects, reducing LPS-induced TNFα in neonatal mouse midbrain astrocytes (Kipp *et al.* 2007). In addition to altering pro-inflammatory cytokine production, oestrogen and progesterone possibly also act during pregnancy to reduce fevers by up-regulating nitric oxide production as discussed above (Begg *et al.* 2007). Although these data are interesting and certainly imply an important role for these steroid hormones in temperature regulation after an immune challenge, it remains to be seen what their role is during the peri-partum period. Although part of our experiment involved rats with high oestrogen and no progesterone replacement, we did not see an attenuation of febrile or associated responses in this group (Mouihate & Pittman, 2003), which we may have expected if progesterone withdrawal was primarily responsible for suppressed febrile responses at parturition. Clearly there are other key players involved.

Another major candidate for mediating this pregnancy-associated fever suppression to immune challenge is corticosterone (cortisol in humans). As discussed briefly, glucocorticoids are important in providing negative feedback to dampen the inflammatory response. During pregnancy, basal glucocorticoid concentrations are elevated (Smith *et al.* 1997; Douglas *et al.* 2003) and immune challenge fails to significantly influence them further (Brunton *et al.* 2005). It is possible that this reflects a chronically heightened negative feedback mechanism. However, glucocorticoids exert direct negative feedback on the inflammatory response by their action on NFκB-stimulated transcription, and in our investigations we have seen no alterations of either NFκB or the extracellular signal-regulated kinase signalling pathways in the hypothalamus (Mouihate *et al.* 2005). Perhaps glucocorticoids are acting at more remote regions that project into the PVN. For example, glucocorticoid receptor

mRNA is increased in the dentate gyrus during pregnancy (Johnstone *et al.* 2000), indicating a possible role for this region.

Oxytocin. Oxytocin is another hormone that is closely involved in parturition and may have a role in modulating febrile responses to immune challenge. Indeed, this laboratory has shown that pre-treatment with oxytocin can attenuate febrile responses to intracerebroventricular IL-1α. It is likely this occurs via an interaction with the antipyretic AVP in the VSA or BNST (Poulin & Pittman, 1993). Central release of oxytocin is known to increase towards the end of pregnancy (Landgraf *et al.* 1991) and this release may be further augmented by local interleukin (Landgraf *et al.* 1995).

The inflammatory response in cerebral ischaemia. In addition to protecting the body from invading pathogens, it is becoming clear that inflammation is a facet of many neurological disease states. For instance, Parkinson's disease, Alzheimer's disease, multiple sclerosis, and stroke all have inflammatory components (Esiri, 2007). It is unclear in many instances, however, whether this neuroinflammation represents a degenerative role, itself contributing to further destruction, or a protective mechanism for the brain, to prevent further neurodegeneration. In reality, it probably participates in both. Whatever its role, there is ample evidence that some of these degenerative processes are altered during pregnancy. For example, multiple sclerosis symptoms are greatly attenuated during pregnancy (Schwendimann & Alekseeva, 2007) and susceptibility to stroke may be enhanced (Jaigobin & Silver, 2000; James *et al.* 2005; Bashiri *et al.* 2007). We have thus investigated the contribution of inflammation to the severity of brain ischaemia-induced damage in order to examine possible alterations during pregnancy.

Using the two-vessel occlusion (2VO) with hypotension model of cardiac arrest in the rat that produces global cerebral ischaemia, we and others have seen increased hippocampal microglial activation, elevated postoperative temperatures, and sickness behaviour-like responses, clearly indicating the presence of an inflammatory process (Pforte *et al.* 2005; Spencer *et al.* 2006, 2007*a*,*b*). Inflammation is also an accepted signature in more focal models of stroke (Lucas *et al.* 2006). We have also demonstrated in the rat that an immune challenge can exacerbate ischaemic damage. Thus, we gave LPS immediately after a 2VO and observed approximately 50% fewer surviving cells in the hippocampus than similarly treated rats that had not received LPS. This was also associated with behavioural alterations (Spencer *et al.* 2007*b*). Other groups have demonstrated that prevention of inflammation leads to a reduction in infarct size. Thus, IL-1ra reduces ischaemic damage (Lucas *et al.* 2006), as does administration of iNOS inhibitors (Iadecola *et al.* 1995). As mentioned, one of the major dangers associated with parturition in the mother is hypoxia to the fetus, and the suppressed inflammatory response that we see at parturition may have an adaptive advantage in reducing the risk of hypoxia–ischaemia sequelae at this time. It must be noted that fetal temperatures are slightly elevated above maternal temperature *in utero* and tend to parallel the rise in maternal temperature during a fever (Harris *et al.* 1977; McClure *et al.* 2005); thus lower maternal fevers would lead to a lower fetal temperature increase.

In addition to the potential for suppressed inflammatory responses, such as that seen in late pregnancy, to be protective against ischaemic damage, there are other pregnancy-associated hormonal alterations that should be protective. There is some evidence to suggest that oestrogen is neuroprotective during ischaemia. Thus, ovariectomy exacerbates cerebral ischaemia-induced damage (Alkayed *et al.* 1998; Macrae & Carswell, 2006), and oestrogen administration, in male as well as female rodents, can rescue dying neurons after cerebral ischaemia (Hurn & Macrae, 2000; Macrae & Carswell, 2006; Gibson *et al.* 2006). It has been shown that the damage is greater in females when cerebral ischaemic insult occurs during met-oestrous, when endogenous oestrogen levels are low, than during pro-oestrous, when oestrogen levels are high (Carswell *et al.* 2000). In light of this information, we hypothesized that the damage associated with cerebral ischaemia in the late-pregnant rat would be less than that seen in a non-pregnant control. Interestingly, this did not prove to be the case. In our experiment we gave late-pregnant rats (gestational day 17) and non-pregnant controls a 2VO and tested them upon recovery for learning and memory in a fear-conditioning test, as well as conducting histological analysis of the brains for cell death. Our experiment demonstrated that pregnant rats had significant memory deficits following the 2VO as well as significant CA1 hippocampal cell loss. The same deficits were not seen in non-pregnant rats given the same 2VO (Spencer *et al.* 2007*a*).

These findings are interesting in that they reflect the complexity of the pregnant state. They also highlight the vast gap in our knowledge of the changes that occur during pregnancy, and the impact this has on the physiology and function of the pregnant individual and the role of the febrile hyporesponsive state.

Summary and perspectives

In many animal species, late pregnancy has been associated with suppressed febrile response to immune challenges. The raison d'être of such hyporesponsiveness is not completely understood. Given the beneficial value of fever, its suppression comes with a high cost. Efforts have been made by this and other laboratories to shed light on

the mechanisms underlying the reduced neuroimmune responses during the late phase of pregnancy. Despite some controversies over the importance of different inflammatory cytokines, it appears that the maternal innate immune response is reduced during this period of pregnancy. A reduced innate immune response is probably behind the dampening of brain machinery involved in fever generation, but does not seem to provide any brain protection from an insult such as global ischaemia. This simplistic explanation hides the tremendous complexity of the interaction of many systems such as the HPA axis, gonadal axis and different neuropeptides. More integrative studies of the interaction between these different systems are required to enhance our understanding of the hypo-responsiveness to immune challenges observed at late pregnancy.

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