Current Insights and Future Perspectives on Neuro-Endocrine-Immune Circuity Challenging Pregnancy Maintenance and Fetal Health

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Psychological stress is a prevailing facet of daily life, usually triggered by a stimulus (stressor), which induces a reaction in the brain (stress perception). Subsequently, so-called supersystems are activated in the body, such as the immune, endocrine, and nervous system (stress response) [1]. Based on Walter Cannon's hypothesis, the stress response may be an evolutionarily adaptive psychophysiological survival mechanism [2]. This allows the individual to either "fight or flight" an acute stressor, e.g., a predator or – as a result of exposure to chronic stress – to save energy. However, stressors have changed and the present nuance of stress does not fulfill the "fight or flight" concept any more. Hence, pathophysiological changes associated with the stress response are misrouted towards a dysequilibrium of the supersystems (Fig. 1). This dysequilibrium serves as aggravating or triggering factor in the pathogenesis of many diseases, e.g., inflammatory, autoimmune or allergic diseases [3–6].

Systemic Response Patterns to Stress: Neuro-Endocrine-Immune Circuitry

Activation of neurohormones by psychological stress arise largely via the central stress response, activating the hypothalamus-pituitary-adrenal (HPA) axis. This results in the up-regulation of key stress hormones, such as corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH) or prolactin (PRL) [1, 7, 8]. Via these stress-related hormones, additional elements of stress response execution like glucocorticoids (GCs), catecholamines, and neurotrophins are activated [9, 10] (Fig. 2), which subsequently profoundly alter immune responses [7, 8, 11]. For example, GCs inhibit the production of interleukin-(IL)-12, interferon-(IFN-)-γ, and tumor necro-

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Figure 1. Principles of the stress response. The coordinated cross talk of the three supersystems (nervous, endocrine, and immune system) may be challenged by psychological stress and ultimately affects fertility, pregnancy maintenance, and fetal health.

Figure 2. Central stress response and elements of stress response execution. In response to the perception of psychological stress, the central stress response leads to the activation of the HPA axis, which causes the release of CRH, ACTH, and PRL and a down-regulation of GnRH and LH. Peripheral elements of stress response execution are subsequently activated, including the glucocorticoids, catecholamines, and neurotrophins. In mice, stress exposure has been shown to result in decrease of progesterone and possibly estradiol. CRH = corticotropin-releasing hormone; ACTH = adrenocorticotropic hormone; PRL = prolactin; GnRH = gonadotropin-releasing hormone; LH = luteinising hormone; HPA = hypothalamus-pituitary-adrenal.
sis factor (TNF) by antigen-presenting cells (APCs) and T helper (Th) 1 cells, but up-regulate the production of IL-4, IL-10, and IL-13 by Th2 cells [12]. This may induce the selective suppression of the Th1-mediated cellular immunity and trigger a shift towards Th2-mediated humoral immunity. It has been postulated that this Th2 shift may actually protect the organism from systemic "overshooting" with Th1/pro-inflammatory cytokines with tissue-damaging potential [13].

**Immunity’s Adaptation to Pregnancy**

To date, the understanding why a woman’s immune system does not reject her “histoincompatible” fetus is still very limited. At a functional level, the developing placenta must integrate maternal and fetal physiology, whereby spatial adjacencies at the interface of fetal cytотrophoblast cells and maternal tissues guarantee nourishment of the fetus [14]. However, such spatial adjacencies of fetal tissue, carrying paternal antigens, and maternal tissue does generally not provoke fetal rejection via maternal immune cells [14, 15]. Immune integration and tolerance at the feto-maternal interface appear to be prerequisites for successful pregnancy maintenance. Hence, plural tolerance mechanisms evolve to ensure the maintenance of the feto-placental “graft” (Fig. 3). Such mechanisms include (1) the predominance of anti-inflammatory Th2 cytokines over pro-inflammatory Th1 cytokines in the decidua [16, 17]; (2) the decidual expression of indoleamine 2, 3-dioxygenase (INDO), an enzyme which famishes immune rejection by depriving the T cells of tryptophan and/or by inhibiting lymphocyte proliferation [18, 19]; (3) the presence of CD4+CD25bright regulatory T (Treg) cells which suppress an aggressive allogeneic response directed against the fetus in humans [20] and mice [21]; and (4) the synthesis of asymmetric IgG antibodies (AAbs), which have been suggested to camouflage paternal antigens expressed by the placenta [22]. In addition, it has become apparent in the past few years that dendritic cells (DCs) seem to be an essential regulatory cell subset at the feto-maternal interface in mediating tolerance [23–25].

**Epidemiology of Stress and Reproduction**

Provocatively spoken, becoming or being pregnant during a stressful period of life may be a serendipitous coincidence since the Th2 shift triggered by stress hormones may protect from “overshooting” of Th1/pro-inflammatory cytokines leading to fetal rejection. So one wonders why maternal stress perception has long been suspected as a possible cause of infertility, implantation failure, late pregnancy complications, and impaired fetal development, notions that exist since ancient times and across all cultures. Despite frequent limitations of studies related to these topics, e. g. due to conceptual and methodological problems such as a retrospective design, there is now growing epidemiological evidence that stress serves as an additional risk factor for infertility as well as pregnancy complications [26–31]. More recently, such insights from epidemiological studies have been further supported by experimental evidences linking high stress perception during mammalian pregnancy to a failure of neuro-endocrine-immune integration [6, 32, 33].

**Failure of Neuro-Endocrine-Immune Integration Challenging Fetal Tolerance**

Nothing in reproductive immunology seems to be as simple as it first appears, e. g. the alleged assumption that high stress perception and increased levels of GC may protect from “overshooting” of Th1/pro-inflammatory cytokines can be easily portrayed as rudimentary and
Further, neuro-endocrine responses to stress also include an activation of the sympathetic nervous system with the subsequent increase of catecholamines [9], an area that has received much less attention than the stress-triggered activation of the HPA axis. For half a century it is known that lymphoid organs are prominently innervated by noradrenergic nerves fibres [35] and evidence accumulated since then supports that the immune system is regulated via the sympathetic nervous system/catecholamines at regional, local, and systemic levels [1]. For example, lymphocytes express adrenergic receptors, and respond to catecholamine stimulation with the development of stress-induced lymphocytosis, and distinct changes in lymphocyte trafficking, circulation, proliferation, and production of pro-inflammatory Th1-like [9, 36, 37], all of which may subsequently challenge fetal tolerance.

Besides the classical stress-related neurohormones like the players of the HPA axis (CRH, ACTH, cortisol) or catecholamines, the neurotrophin nerve growth factor (NGF) is now recognised as an important regulator involved in stress responses [38]. Besides its function as a trophic factor for peptidergic and sympathetic neurons and their axon sprouting, NGF acts as a potent immunomodulator, promoting cross-talk between neuronal, glial, and immune cells and facilitating monocyte/macrophage migration through vascular endothelium [39, 40]. Recently, experimental evidence revealed that stress exposure up-regulates the frequency of abortion and the expression of uterine NGF in a murine model [41]. Further, adhesion molecules ICAM1 and selectin platelet (SelP, formerly P-Selectin) and their ligands Integrin alpha-L (ITGAL) and Selp ligand (Selpl), respectively, increase in murine deciduas in response to stress. Subsequently, decidual cytokines are biased towards a pro-inflammatory and abortogenic cytokine profile and render NGF to serve as a proximal mediator in the hierarchical network of immune rejection by mediating an abortogenic environment comprised of classical signs of neurogenic inflammation.

Apart from neurohormones and neurotrophins, it is well known that progesterone mediates effects which are beneficial for the onset, development, and maintenance of pregnancy [32, 42, 43]. Interestingly, stress interfering with the course of pregnancy has been linked to decreased levels of luteinising hormone (LH) and progesterone in mice and humans [44, unpublished observations] (Fig. 2). Previous studies in our laboratory have also demonstrated that stress-triggered abortion can be therapeutically approached by application of a progesterone derivative [32, 44].

**Dendritic Cells: Switchboard Between Fetal Rejection and Tolerance?**

ICAM1/ITGAL interaction has pleiotropic effects, it is involved in T cell recruitment and promotes cross-talk between antigen-presenting cells (APC) and T cells [45]. APC constitute a complex system of cells, which, under different microenvironmental conditions and dependent on their maturation status, can induce such contrasting states as immunity or tolerance. Immature dendritic cells (DCs) as the main population with APC potential have been described to reside in early pregnancy decidua in humans [23, 24] and mice [25] and possibly serve as sentinel cells of the tissue environment for potential danger signals. Numerous factors induce and/or regulate DCs maturation via Toll-like receptors (tlr), including the balance between Th1 and Th2 signals in the local microenvironment, such maturation provides the ability of DCs to become mature APC and initiate adaptive immune responses [6, 45]. During gestation in mice, approximately a quarter of all DCs are mature, and – strikingly – when implantation occurs (Gd 5.5–8.5), this percentage is markedly down-regulated in low abortion pregnancies [25]. However, in pregnancies with high abortion rates, e. g. as induced by stress challenge or adoptive transfer of ITGAL cells, an increase of mature DCs, as identified by their CD80, CD80, MHC II, and ICAM1 positivity, can be observed [6]. The crucial factor required to induce T cell activation is the interaction between such co-stimulatory molecules and maturation markers, e. g. CD80 and ICAM1 expressed by APC, and their ligands, e. g. CD28 and ITGAL expressed by T cells [6, 46, 47].

Independent studies in mice have revealed that the ICAM1/ITGAL interaction appears to be important for polarising cells towards Th1 predominance, most prominent in this respect is IL-12 derived from mature DCs [45, 48, 49], which is increased e. g. in response to stress in abortion prone matings, but not in low abortion matings.

In response to steroids, e. g. glucocorticoids and possibly progesterone, a considerable plasticity of DCs can be observed, which may affect maturation phenotype and cytokine bias of the adaptive immune response [50]. Emerging research is likely to provide detailed insights on the impact of hormones on DC phenotype, e. g. at the feto-maternal interface, in the near future.

**Stressed Mothers: Calamity for the Offspring?**

Pre-term births and low birth weight are among the most recognised effects of maternal stress during pregnancy on the offspring, as established by almost two decades of animal and human research. Pre-term babies are susceptible to a range of complications in later life, including chronic lung disease, developmental delays, learning disorders and infant mortality. Compelling evidence from epidemiological studies and animal research further indicates that offsprings who experience stress in utero are more likely to develop chronic health problems as adults, such as heart disease, high blood pressure, diabetes, and atopic diseases [51–53]. Further, maternal stress perception during pregnancy may have consequences for the neurobehavioural development, behaviour, and intelligence quotient.

It has been hypothesised that the effects of maternal psychosocial stress and stress-related maternal HPA dysregulation affects fetal developmental and health outcomes via placental CRH-dependent pathways. Placental CRH is identical to hypothalamic CRH in structure, immunoreactivity, and bioactivity [54]. During human pregnancy, the CRH and respective receptor genes are richly expressed in the placenta, and subsequently lead
to the production of CRH in the placenta and its release into maternal and fetal compartments [55]. Further studies are necessary to address if and how maternal stress perception affects fetal health via CRH-dependent pathways.

Lastly, anecdotal reports describe suppressive effects of stress on lactation, which is often perceived as a key moment of motherhood. Stressful events during this period of life may cause a down-regulation of prolactin and therefore interfere with the lactation process [56] and subsequently contribute to the onset of atopic diseases.

Conclusions

In view of the vast complexity of regulatory nervous, endocrine, and immune mechanisms involved in pregnancy maintenance, it is evident that pregnancy failure is likely not due to a single entity condition, but may be the result of a complex dysregulation as it can be triggered by stress perception. However, one should be cautious and refrain from dogmatic suggestions that stress perception is the single entity condition responsible for infertility, pregnancy failure, and impaired health of the offspring. While there are still many more questions than answers, the neuro-endocrine-immune circuitry of pregnancy during the response to psychological stress is becoming increasingly defined, e.g. due to the development of particularly instructive rodent models.

However, translation of the results from basic science to men is a long-term and laborious process. Clinical studies have their own difficulties, since the patient population is generally rather heterogeneous, stress “quantification” is problematic and complex. Tissue collection can often only be performed retrospectively, leaving much room for cause versus effect discussions.

One goal to pursue research in this complex endeavour is clearly to prompt clinicians to become far more attentive to the effect of psychological stress on pregnancy complications. Together with basic science research elucidating hierarchical, temporal, and spatial interactions of key parameters during central and peripheral responses to psychological stress, a list of candidate targets for clinically useful therapeutic intervention can then be created.

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