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Allopregnanolone in the brain: Protecting pregnancy and birth outcomes

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ABSTRACT

A successful pregnancy requires multiple adaptations in the mother's brain that serve to optimise foetal growth and development, protect the foetus from adverse prenatal programming and prevent premature delivery of the young. Pregnancy hormones induce, organise and maintain many of these adaptations. Steroid hormones play a critical role and of particular importance is the progesterone metabolite and neurosteroid, allopregnanolone. Allopregnanolone is produced in increasing amounts during pregnancy both in the periphery and in the maternal and foetal brain. This review critically examines a role for allopregnanolone in both the maternal and foetal brain during pregnancy and development in protecting pregnancy and birth outcomes, with particular emphasis on its role in relation to stress exposure at this time. Late pregnancy is associated with suppressed stress responses. Thus, we begin by considering what is known about the central mechanisms in the maternal brain, induced by allopregnanolone, that protect the foetus(es) from exposure to harmful levels of maternal glucocorticoids as a result of stress during pregnancy. Next we discuss the central mechanisms that prevent premature secretion of oxytocin and consider a role for allopregnanolone in minimising the risk of preterm birth. Allopregnanolone also plays a key role in the foetal brain, where it promotes development and is neuroprotective. Hence we review the evidence about disruption to neurosteroid production in pregnancy, through prenatal stress or other insults, and the immediate and long-term adverse consequences for the offspring. Finally we address whether progesterone or allopregnanolone treatment can rescue some of these deficits in the offspring.
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Abbreviations: 3αHSD, 3α-hydroxysteroid dehydrogenase; ACTH, adrenocorticotropic hormone; AgRP, agouti-related peptide; AVP, arginine vasopressin; CCK, cholecystokinin; CB1, cannabinoid receptor type 1; CeA, central nucleus of the amygdala; cGMP, cyclic guanosine monophosphate; CRH, corticotropin releasing hormone; CRH-R1, corticotropin releasing hormone receptor type 1; CRH-R2, corticotropin releasing hormone receptor type 2; DA, dopamine; DAP, depolarising after-potential; DHP, dihydroprogesterone; eCB, endocannabinoids; ER, estrogen receptor; GABA, gamma-aminobutyric acid; GR, glucocorticoid receptor; HPA, hypothalamo-pituitary-adrenal; i.c.v., intracerebroventricular; IL-1β, interleukin-1β; IUGR, intrauterine growth restriction; MAP-2, microtubular associated protein-2; MBP, myelin basic protein; MC-2, melanocortin-2; MCNs, magnocellular neurones; MPOA, medial preoptic area; MR, mineralocorticoid receptor; nNOS, neuronal nitric oxide synthase; NO, nitric oxide; NPY, neuropeptide Y; NTS, nucleus tractus solitarii; ORL1, opioid receptor-like receptor; OTR, oxytocin receptor; pENK-A, proenkephalin-A; PNS, prenatally stressed; POMC, pro-opiomelanocortin; PR, progesterone receptor; PRP, prolactin releasing peptide; PVN, paraventricular nucleus; pPVN, parvocellular subdivision of the paraventricular nucleus; V1b, vasopressin receptor type 1b.

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1. Introduction

It is well established that sex steroids, such as oestrogens and progestogens play critical roles in the brain both during development and throughout adult life. They shape and organise the central nervous system (CNS) during development and have activating effects which influence brain function and a variety of behaviours.

Progestogens are a group of steroid hormones that include progesterone and are named as such due to their vital function in maintaining pregnancy i.e. pro-gestational, though they also function in the non-pregnant animal. In females, they are synthesised primarily by the ovaries (corpus luteum), but can also be produced in the adrenals and liver and during pregnancy by the placenta and serve as precursors for the biosynthesis of other steroids, including estrogens, androgens, glucocorticoids and mineralocorticoids. Progestogens are also produced within the central nervous system where they are commonly referred to as neurosteroids.

Progesterone is present in high levels during gestation and its actions in the uterus that serve to establish and maintain pregnancy, e.g. facilitating blastocyst implantation and maintaining uterine quiescence by reducing myometrial contractility, are well known (Graham and Clarke, 1997). Progesterone also acts in the brain during pregnancy and contributes to the preparation of the neural circuitry involved in the expression of maternal

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