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Review

Neuroactive steroids and stress axis regulation: Pregnancy and beyond

Paula J. Brunton*

Division of Neurobiology, The Roslin Institute & R(D)SVS, University of Edinburgh, Easter Bush Campus, Midlothian EH25 9RG, Scotland, UK

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ABSTRACT

The hypothalamo–pituitary–adrenal (HPA) axis plays a critical role in regulating responses to stress and long term dysregulation of the HPA axis is associated with higher rates of mood disorders. There are circumstances where the HPA axis is more or less responsive to stress. For example, during late pregnancy ACTH and corticosterone responses to stress are markedly suppressed, whereas in offspring born to mothers that experienced repeated stress during pregnancy, the HPA axis is hyper-responsive to stress.

Neuroactive steroids such as allopregnanolone, tetrahydrodeoxycorticosterone (THDOC) and androstanediol can modulate HPA axis activity and concentrations of some neuroactive steroids in the brain are altered during pregnancy and following stress. Thus, here altered neurosteroidogenesis is proposed as a mechanism that could underpin the dynamic changes in HPA axis regulation typically observed in late pregnant and in prenatally stressed individuals. In support of this hypothesis, evidence in rats demonstrates that elevated levels of allopregnanolone in pregnancy induce a central inhibitory opioid mechanism that serves to minimize stress-induced HPA axis activity. Conversely, in prenatally stressed rodents, where HPA axis stress responses are enhanced, evidence indicates the capacity of the brain for neurosteroidogenesis is reduced.

Understanding the mechanisms involved in adaptations in HPA axis regulation may provide insights for manipulating stress sensitivity and for developing therapies for stress-related disorders in humans.

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1. Introduction

The hypothalamo–pituitary–adrenal (HPA) axis is the key neuroendocrine system that responds to stress (Fig. 1). The final

* Fax: +44 131 651 9105.
E-mail address: p.j.brunton@ed.ac.uk (P.J. Brunton).

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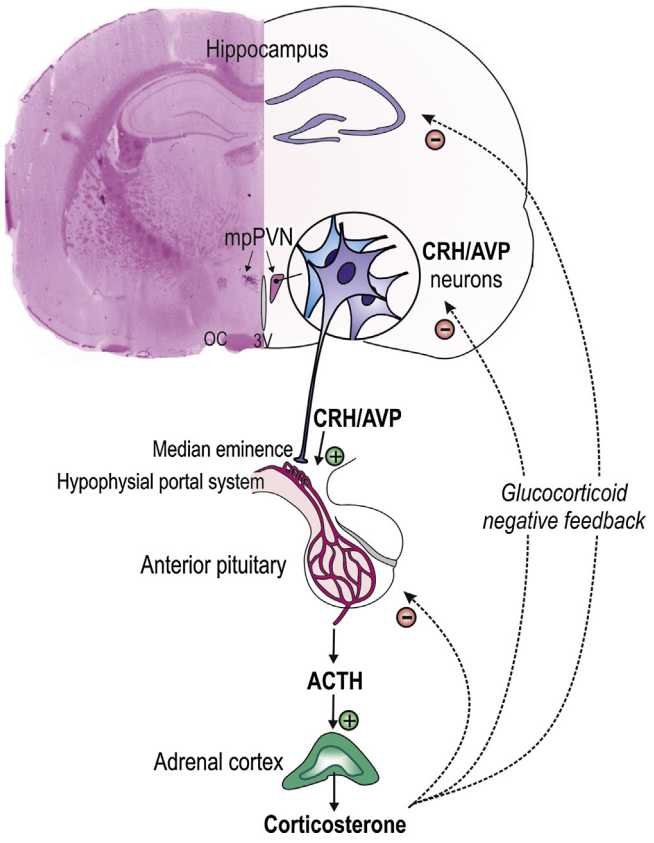

Fig. 1. The hypothalamo–pituitary–adrenal (HPA) axis.
Stress activates corticotropin releasing hormone (CRH) and/or arginine vasopressin (AVP) containing neurons in the medial parvocellular paraventricular nucleus (mpPVN) of the hypothalamus. These neurons secrete CRH and AVP from their nerve terminals at the median eminence into the hypothalamo-hypophysial portal blood. CRH and AVP act *via* their receptors on anterior pituitary corticotroph cells to stimulate the release of ACTH into the general circulation, which in turn stimulates the secretion of glucocorticoids (*e.g.* corticosterone in rodents, cortisol in humans) from the adrenal cortex. Glucocorticoids act *via* glucocorticoid receptors in the anterior pituitary, PVN and hippocampus and mineralocorticoid receptors in the hippocampus to exert negative feedback control over HPA axis activity. 3V, third ventricle; OC, optic chiasm.

output of HPA axis activation is glucocorticoid secretion from the adrenal cortex which facilitates appropriate metabolic, behavioural, cardiovascular and immunological responses to stress and also act *via* a negative feedback loop to terminate the stress response.

During the lifespan there are periods when the 'set-point' of the HPA axis is reset and as a result the HPA axis is more or less sensitive to stressors. For example, in rats HPA axis responses to stress are suppressed during early post-natal life (referred to as the stress hyporesponsive period) and during late pregnancy and lactation [1,2]. Accumulating evidence indicates that comparable phenomena also occur in humans [3–5]. It has been proposed that these adaptations may serve to protect the rapidly developing brain from the impact of elevated glucocorticoids. Conversely, during ageing or in certain disease states (*e.g.* depression), the HPA axis may exhibit heightened basal activity and/or enhanced responses to stress [6–8]. Moreover, a growing body of evidence demonstrates that animals (including rodents, pigs, monkeys) and humans exposed to stress in early life (pre- or post-natal) typically display hyperactive HPA axis activity [9–14].

This article will focus on two extremes: HPA axis hyporesponsivity to stress in late pregnancy and the hyperactive HPA axis responses to stress in offspring whose mothers were exposed to stress during pregnancy. Neuroactive steroids play an important role in modulating HPA axis function [15] and evidence suggests that altered neurosteroidogenesis contributes to HPA axis regulation in both pregnancy [16] and in prenatally stressed offspring [17,18]. Thus, first the role of neuroactive steroids in regulating HPA axis activity will be discussed, before considering the role of increased neurosteroid production in the brain during pregnancy in dampening HPA axis responses to stress. Next the focus shifts to the impact of maternal exposure to repeated stress during pregnancy on programming offspring HPA axis reactivity and the consequences for neurosteroidogenesis in the offspring. Finally the evidence that neuroactive steroids can normalise hyperactive HPA axis responses in prenatally stressed offspring will be reviewed. The majority of evidence presented is from studies in rodents; however some relevant data from humans is included where available.

2. Neuroactive steroids

Neuroactive steroids (also referred to as neurosteroids) are endogenous steroids that exert rapid non-genomic effects on neuronal excitability *via* actions on membrane-bound receptors [19]. The term neurosteroid refers to steroids synthesized in the brain *de novo* or by metabolizing peripherally-derived steroid precursors, whereas neuroactive steroids are synthesized in the periphery (*e.g.* in gonads, adrenal gland) and enter the brain from the circulation [19].[1]

Neurosteroidogenesis in the brain relies upon the expression of the relevant biosynthetic enzymes, which are differentially expressed throughout the central nervous system [20]. One of the most well studied neurosteroids is allopregnanolone (3α-hydroxy-5α-pregnan-20-one). Allopregnanolone is synthesized from progesterone by the actions of two enzymes, 5α-reductase and 3α-hydroxysteroid dehydrogenase (3αHSD) [21] (Fig. 2). Both of these enzymes are expressed in the human and rodent brain by glial cells, with 5α-reductase activity also detected in neurons [21–26]. 5α-reductase and 3αHSD are also responsible for catalyzing the conversion of testosterone and deoxycorticosterone (DOC) into the neuroactive steroids, 3α-androstanediol (5α-androstane-3α,17β-diol; hereafter 3α-diol) and 5α,3α-tetrahydrodeoxycorticosterone (THDOC), respectively [27–29] (Fig. 2).

2.1. Neuromodulation by neuroactive steroids

The 3α-hydroxy ring A-reduced steroid metabolites of progesterone, DOC and testosterone: allopregnanolone, THDOC and 3α-diol, respectively (Fig. 2), do not act *via* classical intracellular steroid receptors. Instead they exert their action by binding with high affinity to membrane-bound $GABA_A$ receptors where they act as potent positive allosteric modulators, significantly augmenting GABA-activated chloride ion currents [30–32], and thus enhancing GABA-mediated inhibitory neurotransmission. Thus, in situations where neuroactive steroid levels are notably altered (*e.g.* during pregnancy or following stress), one would expect to observe alterations in neuronal activity (and potentially brain function) as a result of the neuromodulatory influence of neuroactive steroids.

2.2. Neuroactive steroids and the HPA axis

Acute stress triggers a rapid and robust increase in circulating and brain levels of allopregnanolone and THDOC [15] and up-regulates both mRNA and protein levels of 5α-reductase in the frontal cortex of rats [33]. The major source of increased THDOC in the brain following stress is the adrenal gland, however a significant portion of

[1] In this article the term neuroactive steroids is used regardless of whether the steroids are synthesized in the brain or in the periphery.

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