Prenatal Excess Glucocorticoid Exposure and Adult Affective Disorders: A Role for Serotonergic and Catecholamine Pathways

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Abstract

Fetal glucocorticoid exposure is a key mechanism proposed to underlie prenatal 'programming' of adult affective behaviours such as depression and anxiety. Indeed, the glucocorticoid metabolising enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), which is highly expressed in the placenta and the developing fetus, acts as a protective barrier from the high maternal glucocorticoids which may alter developmental trajectories. The programmed changes resulting from maternal stress or bypass or from the inhibition of 11β-HSD2 are frequently associated with alterations in the hypothalamic-pituitary-adrenal (HPA) axis. Hence, circulating glucocorticoid levels are increased either basally or in response to stress accompanied by CNS region-specific modulations in the expression of both corticosteroid receptors (mineralocorticoid and glucocorticoid receptors). Furthermore, early-life glucocorticoid exposure also affects serotonergic and catecholamine pathways within the brain, with changes in both associated neurotransmitters and receptors. Indeed, global removal of 11β-HSD2, an enzyme that inactivates glucocorticoids, increases anxiety- and depressive-like behaviour in mice; however, in this case the phenotype is not accompanied by overt perturbation in the HPA axis but, intriguingly, alterations in serotonergic and catecholamine pathways are maintained in this programming model. This review addresses one of the potential adverse effects of glucocorticoid overexposure in utero, i.e. increased incidence of affective behaviours, and the mechanisms underlying these behaviours including alteration of the HPA axis and serotonergic and catecholamine pathways.

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Developmental Programming

Low birth weight and other indicators of reduced fetal growth are associated with adult cardio-metabolic and psychiatric diseases. This association is the result of 'developmental programming', whereby a stimulus during a sensitive period of early development exerts permanent effects on structure, physiology or metabolism [1]. The environmental mechanisms of developmental programming identified so far can be simplified into two major groups: fetal stress exposure and maternal nutrition, although changes in glucocorticoids appear to underpin

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the programming effects of both [2–4]. In many mammals, including mice and humans, there is an increased exposure of the developing fetus to glucocorticoids late in pregnancy, as they have a crucial role in the structural development and functional maturation of fetal organs. However, glucocorticoid overexposure of the fetus can be detrimental as glucocorticoids cause a shift from cell proliferation to differentiation. Therefore, exposure to excess glucocorticoids in utero alters fetal organ growth and maturation patterns, which can result in adverse consequences in later life. In humans, the actions of glucocorticoids are exploited for preterm births to advance fetal lung maturation [5], although this may set the stage for adverse effects in later life [6–16]. This review addresses one of the potential adverse effects of glucocorticoid overexposure in utero, i.e. increased incidence of affective behaviours, and the mechanisms underlying these behaviours including alteration of the hypothalamic-pituitary-adrenal (HPA) axis and serotonergic and catecholamine pathways.

The Feto-Placental Glucocorticoid Barrier: 11β-Hydroxysteroid Dehydrogenase Type 2

As glucocorticoids are highly lipophilic, they readily diffuse across biological membranes and, therefore, control of intracellular levels of bioactive glucocorticoids is critical. This control arises from the enzyme 11β-hydroxysteroid dehydrogenase (11β-HSD) which interconverts the active glucocorticoids cortisol and corticosterone with their biologically inactive forms, cortisone and 11-dehydrocorticosterone, respectively. There are two distinct forms of 11β-HSD: 11β-HSD1 is a low-affinity, NADP(H)-dependent bidirectional enzyme, although in vivo it appears to act predominantly as an 11β-oxoreductase to enhance glucocorticoid activity. 11β-HSD2 is a high-affinity NAD-dependent enzyme which exhibits exclusive 11β-dehydrogenase activity (conversion of corticosterone to 11-dehydrocorticosterone) to reduce glucocorticoid potency. 11β-HSD2 is highly expressed in aldosterone-selective target tissues such as the distal nephron [17], colon [18], salivary glands [19] and skin [20], thus serving to confer aldosterone specificity on the mineralocorticoid receptor (MR) to which both corticosterone and aldosterone can bind. Importantly, 11β-HSD2 does not always colocalise with MR, such as within placental and fetal tissues, and so its function has expanded beyond its involvement in the electrolyte transport to include regulation of corticosteroid action.

During much of normal pregnancy, circulating levels of glucocorticoids in the fetus are substantially lower than in the mother. This difference arises in part from the high expression of 11β-HSD2 in both the placenta and fetus, and this 11β-HSD2 expression serves as a 'glucocorticoid barrier', thus enabling a tight regulation of the materno-fetal glucocorticoid transfer. Within the placenta, 11β-HSD2 is highly expressed at the interface between maternal and fetal circulations, in the syncytiotrophoblast in humans [16] and the labyrinthine zone in rodents [21]. In the rodent, 11β-HSD2 expression within the labyrinth zone of the placenta falls during late gestation, which may facilitate glucocorticoid passage to the fetus and thus lung maturation [22, 23].

Within fetal tissues, 11β-HSD2 is broadly expressed, particularly within the brain [23]. 11β-HSD2 is abundant in the neuroepithelium throughout mid-gestation and then strikingly and rapidly declines, coinciding with the terminal stage of neurogenesis [23, 24]. Similar patterns of expression occur in the human fetal brain, with 11β-HSD2 silenced between gestational weeks 19 and 26 [25]. Thus, this abundance and expression pattern of 11β-HSD2 suggests that 11β-HSD2 acts to protect immature mitotically active brain cells from premature exposure to the maturational effects of glucocorticoids. After birth, high levels of 11β-HSD2 are localised in mice to only the proliferating external granular layer of the cerebellum and in several nuclei of the thalamus [26, 27]. Therefore, in the early postnatal period the cerebellum is sensitive to glucocorticoid-induced remodelling caused either by exogenous administration or in response to the stress induced by maternal separation [28–30].

The high expression of 11β-HSD2 in placenta and fetal tissues and the growth retarding and maturational effects of glucocorticoids on the fetus [31] have led to the proposal that variations in feto-placental 11β-HSD2 may underlie developmental programming. Thus, placental 11β-HSD2 activity correlates with birth parameters in rodents and, less consistently, in humans [7, 32, 33], suggesting that normal variation in fetal exposure to maternal glucocorticoids may impact on fetal growth. Numerous studies have shown that inhibition, deficiency or bypass (poor substrate steroids such as dexamethasone or betamethasone) of 11β-HSD2 in gestation in rodents and humans associates with alterations in pregnancy duration, birth weight and programmed outcomes in the offspring [7, 15, 34–45]. Furthermore, maternal stress of rodents during pregnancy has been associated with a decreased expression of placental 11β-HSD2 [46–48]. Interestingly, in programming models involving mater-

nal low-protein diet, there is an increase in maternal and fetal glucocorticoid levels [49, 50] in addition to a decrease in placental 11β-HSD2 activity and/or expression [50–52]. Moreover, dexamethasone administration during pregnancy decreases food intake [53]. Consequently, there seems to be considerable overlap in mechanisms by which maternal undernutrition and fetal glucocorticoid overexposure elicit developmental programming.

Developmental Programming of Affective Disorders

The developing brain, as other fetal tissues, is extremely sensitive to glucocorticoids, which are crucial for normal cellular and biochemical maturation [54, 55]. Thus, glucocorticoids initiate terminal maturation, remodel axons and dendrites and determine programmed cell death [31]. In sheep, prenatal glucocorticoid administration retards brain weight at birth [56], delaying maturation of neurons, myelination, glia and vasculature [57]. The perinatal hippocampus is especially sensitive to glucocorticoids, with consequences for subsequent memory and behaviour [58–60]. Thus, antenatal treatment of rhesus monkeys with dexamethasone causes a dose-associated degeneration of hippocampal neurones and reduced hippocampal volume which persists at 20 months of age [61]. Prenatal stress (induced by repeated restraint of the pregnant female in the last week of pregnancy) reduces actively proliferating hippocampal cells and feminises sexually dimorphic parameters of the adult hippocampus [62].

A critical outcome of excess glucocorticoid exposure in early life is the programming of affective function. In the rat, central programming by glucocorticoids, be it from maternal administration of dexamethasone or prenatal stress, produces offspring that appear more anxious as adults. Thus, late-gestational dexamethasone exposure in rats impairs the offspring's 'coping' behaviours in aversive situations later in life, as exemplified by reduced exploration in the open field test and elevated plus maze [42]. Such increase in anxiety-like behaviour is evident as early as postnatal week 10 in rats prenatally exposed to dexamethasone [63]. In rodents, prenatal stress increases depressive-like symptoms with an increased immobility time in the forced swim test and tail suspension test and anhedonia [64], although not always [65]. Furthermore, offspring of prenatally stressed rats are anxious, with less time spent in the anxiogenic open arms of the elevated plus maze [66–68] and altered behaviour in the open field test [69–71].

In animal models of antenatal glucocorticoid administration, prenatal stress and maternal dietary restriction, these programmed changes in behaviour are frequently accompanied by alterations in the HPA axis. Thus, maternal dexamethasone treatment increases corticosterone and adrenocorticotrophic hormone (ACTH) levels in the adult offspring, although, interestingly, mostly in males [13, 39, 42, 72]. These effects seem to reflect a change in the feedback of the HPA axis at the level of the hypothalamus, as corticotrophin-releasing hormone (CRH) mRNA increases in the paraventricular nucleus, whereas the hippocampal MR and glucocorticoid receptor (GR) both decrease [41, 73]. Furthermore, the HPA axis period of hyporesponsiveness in early postnatal life is abolished in adult rats exposed to prenatal stress [74], whilst normal age-related HPA axis dysfunction is accelerated by prenatal stress [75]. In sheep, a single injection of betamethasone on gestational day 104 alters the HPA axis function in offspring at 1 year of age, with elevated basal and stimulated plasma cortisol concentrations [76]. In contrast, repeated maternal betamethasone injections elevated the offspring's ACTH responses to a CRH/arginine vasopressin challenge in addition to increased basal ACTH levels but decreased basal and stimulated cortisol levels [76, 77]. In primates, offspring of mothers treated with dexamethasone during late pregnancy have elevated basal and stress-stimulated cortisol levels [78, 79].

Moreover, prenatal stress and alterations in the offspring's HPA axis function have also been associated in humans. Thus, children of mothers present at or near to the World Trade Center atrocity on 9/11, who themselves developed symptoms of post-traumatic stress disorder (PTSD), had lower cortisol levels [80]. Importantly, these changes were most apparent in babies born to mothers who were in the last 3 months of their pregnancies when the trauma occurred, suggesting these observations can be attributed to developmental programming phenomena rather than to a genetic susceptibility or the presence of PTSD per se [80]. Such effects may transmit into subsequent generations, since healthy adult children of Holocaust survivors with PTSD (and therefore lower plasma cortisol levels) themselves have lower cortisol levels though no PTSD [81]. This appears to be confined to the children of Holocaust-exposed mothers with PTSD [81]. In contrast to PTSD, maternal anxiety and depression seem to elevate cortisol in the child [82, 83]. Therefore, the mechanisms of prenatal stress programming HPA axis function in humans seem complex, with possibly different pathways involved. Intriguingly, in Finland, women who voluntarily ingest liquorice-containing

foodstuffs (that potently inhibit placental 11β-HSD2 [84]) in pregnancy have somewhat shorter gestations and their 8-year-old offspring show altered cognitive function, affective disturbances (notably markedly increased rates of attention-deficit/hyperactivity disorder), HPA axis hyperactivity and sleep disturbances [85, 86]. However, while it is tempting to conclude that an altered HPA axis response is the underlying mechanism to anxiety-related behaviour, it is important to note that these behavioural changes can occur in the absence of HPA axis alteration [70, 87].

Gaining Functional Insight: Genetic Modifications of 11β-HSD2

As 11β-HSD2 appears to be a hub for eliciting programming effects, genetically modified mouse models have provided useful insight into underlying mechanisms. An initial mouse model of targeted 11β-HSD2 disruption on an outbred MF1 background revealed mice with an apparently normal phenotype at birth; however, within 48 h, 50% exhibit motor deficiencies, perhaps due to hypokalaemia, and die [88]. Survivors are fertile, but exhibit severe hypertension, hypokalaemia and polyuria [88], all typical characteristics of apparent mineralocorticoid excess and, thus, apparent mineralocorticoid actions of corticosterone were revealed by 11β-HSD2 deficiency. Interestingly, these mice did not exhibit reduced fetal weight, although this was clearly apparent in later studies on a 11β-HSD2 knockout model congenic on a C57BL/6J background [35]. In assessing the relevance of 11β-HSD2 in developmental programming, two separate breeding approaches have been taken. In homozygous breeding experiments, male and female mice null or wild-type for 11β-HSD2 are mated, although this experimental model is complicated by the potential effects that life-long loss of 11β-HSD2 has on maternal care of offspring. To eliminate these effects, a heterozygous mating approach has also been taken and has been the main method for assessing the importance of 11β-HSD2 in developmental programming.

With regard to neurodevelopment, cerebellar size is reduced in homozygously bred 11β-HSD2$^{-/-}$ mice in early postnatal life due to a decrease in the molecular and internal granular layers [89]. This associates with a delay in the attainment of neurodevelopmental landmarks such as negative geotaxis and eye opening [89]. Thus, the timing of exposure of the developing brain to glucocorticoids seems to be tightly regulated by the presence of local 11β-HSD2 and the cell-specific patterns of its downregulation during maturation.

As adults, 11β-HSD2$^{-/-}$ offspring generated from either a homozygous or heterozygous mating approach exhibit increased anxiety. Thus, exploration of the anxiogenic open arm of the elevated plus maze is reduced in 11β-HSD2$^{-/-}$ offspring in comparison to wild types [35]. Additionally, open field exploration is altered in the homozygously bred 11β-HSD2$^{-/-}$ offspring, with them being more reluctant to explore the anxiogenic central field [35]. Interestingly, open field exploration is unaltered in heterozygously bred 11β-HSD2$^{-/-}$ offspring, which implies that aspects of adult behaviour are influenced by maternal factors in this model [35]. The behavioural phenotype of heterozygously bred 11β-HSD2$^{-/-}$ offspring has been subsequently extended with the observation that 11β-HSD2$^{-/-}$ offspring exhibit depressive-like behaviour. Indeed, 11β-HSD2$^{-/-}$ offspring spent a greater percentage of total time immobile during the tail suspension test (11β-HSD2$^{+/+}$: 52.73 ± 3.5% vs. 11β-HSD2$^{-/-}$: 70.92 ± 3.7%; p < 0.05, unpaired t test; unpubl. data) and the forced swim test (11β-HSD2$^{+/+}$: 54.98 ± 2.4% vs. 11β-HSD2$^{-/-}$: 68.88 ± 4.8%; p < 0.05, unpaired t test; unpubl. data), both indicating increased depressive-like behaviour. However, it is unknown if similar behaviour is exhibited by homozygously bred 11β-HSD2$^{-/-}$ offspring. Support of the notion that altered 11β-HSD2 activity contributes to affective behaviour has also been found clinically. Thus, measurements of urinary glucocorticoids and their metabolites in depressed patients reveal changes in the intracellular regulation of glucocorticoid activity, in particular 11β-HSD2, in comparison to healthy controls [90, 91]. It is unclear, however, if this alteration in steroid metabolism is a consequence or cause of depression.

Interestingly, despite increased anxiety, the HPA axis activity of 11β-HSD2$^{-/-}$ offspring appears unaffected, perhaps a reflection of the additional effects of attenuated HPA axis reactivity due to the reduced glucocorticoid clearance in the absence of renal 11β-HSD2 [35]. However, as predicted, adrenal size is reduced and hence resetting of the HPA axis may have occurred during development. This, together with a decreased degradation of corticosterone, means that less corticosterone needs to be produced. Consistent with this, 11β-HSD2$^{-/-}$ mice exhibit no differences in the limbic expression of GR, MR or CRH during adulthood, but there are some transient changes within the postnatal period. In homozygous matings of 11β-HSD2$^{-/-}$ mice, transient elevations in the GR transcript were observed in situ in all hippocampal

subfields of 11β-HSD2$^{-/-}$ offspring at postnatal day 14 [92]. Similar transient changes were observed with MR, Sgk1, Fkbp5 and BDNF [92]. It should be noted though that while no overt changes in adult HPA axis function are apparent, as 11β-HSD2 is widely expressed in the CNS during development, it still remains to be determined if the observed behavioural effects are mediated by local fine-tuning of glucocorticoids.

Placental 11β-HSD2 Is More than Just a Glucocorticoid Barrier

As described above, placental 11β-HSD2 may underpin aspects of developmental programming by allowing excess glucocorticoid passage from the 'high' glucocorticoid maternal circulation to the 'low' glucocorticoid fetal environment [93] and, thus, impair fetal growth by direct effects of glucocorticoids on the fetus. Fetal growth is, however, dependent on an array of maternal, placental and fetal endocrine signals, and glucocorticoid-mediated fetal growth retardation must also be related, at least in part, to disturbances in placental growth and function. Indeed, maternal treatment with dexamethasone impairs normal vascular growth in the rat placenta and has marked effects on the amino acid and glucose transport [94]. Furthermore, an elegant recent study has revealed that the placenta is a source of serotonin for the fetal forebrain [95], which, while yet to be investigated in the 11β-HSD2$^{-/-}$ model, could also potentially impact on the development of adult affective behaviours. Nonetheless, the current data provide a convincing argument that while maternal glucocorticoids could play a direct role in programming the fetus, notably its brain, placental development and function additionally play a key role. It must be noted, however, that until tissue-specific knockouts of 11β-HSD2 in placenta and fetal tissues are developed, the differential significance of feto-placental 11β-HSD2 for development cannot be elucidated.

A Role for Altered Neuronal Serotonergic and Catecholamine Pathways?

In addition to altered HPA axis function, early-life glucocorticoid exposure can also affect serotonergic and catecholamine pathways. Indeed, in a mouse model of prenatal stress, a depression-like phenotype was accompanied by increased serotonin (5-HT) output and decreased reuptake, as indicated by reduced 5-HT transporter levels in the hippocampus and a trend for decreased tryptophan hydroxylase-2 expression in the dorsal raphe [96]. In contrast, another model of strong prenatal restraint stress increased both serotonin and tryptophan hydroxylase expression within the dorsal raphe nuclei [97], whilst others have shown prenatal stress to decrease hippocampal 5-HT$_{1A}$ receptor binding in young male offspring [98]. Neonatal handling, a model of early-life stress, increases hippocampal 5-HT levels and turnover [99, 100]. Maternal separation also has dramatic effects on the adult offspring, with an increase in the inhibitory effect of the 5-HT reuptake inhibitor citalopram on serotonergic neuron firing frequency in the dorsal raphe [101], a reduced sensitivity of 5-HT$_{1A}$ receptors in the dorsal raphe [102] and layer II/III cortical pyramidal neurons [103]. Furthermore, perinatal glucocorticoid exposure increases the size and alters the distribution of adult dopaminergic populations within the substantia nigra pars compacta and the ventral tegmental area [104], while maternal dexamethasone treatment reduces serotonin turnover in the offspring [72]. Maternal protein restriction also alters serotonergic and dopaminergic systems, with the normal rise in dopamine following restraint stress of adult offspring being dampened and serotonin release enhanced [105]. Interestingly, there is evidence for serotonergic involvement in programming of the HPA axis. Thus, serotonin, via 5-HT$_7$ receptors, is involved in mediating the permanent upregulation of GR following neonatal handling [106, 107]. Furthermore, in the rat, allelic variations in the serotonin transporter alter the changes in hippocampal GR mRNA and corticosteroid stress response that occur during postnatal stress [108].

Preliminary data suggest that altered 5-HT and catecholamine pathways in 11β-HSD2$^{-/-}$ adult brains may be responsible, at least in part, for anxiety-related behaviour [C.S.W., M.C.H., unpubl. obs.]. Thus, levels of 5-HT and its metabolite 5-hydroxyindole acetic acid were measured using high-performance liquid chromatography, as was dopamine and its metabolites dihydroxyphenylacetic acid, homovanillic acid and noradrenaline in homogenates of the cortex, hippocampus, hindbrain and diencephalon of 8-month-old male mice from 11β-HSD2 heterozygous matings. Significant changes were found within the diencephalon region only, with levels of 5-HT increased by 1.6-fold in 11β-HSD2$^{-/-}$ offspring in comparison to 11β-HSD2$^{+/+}$ littermates (p < 0.05), with no change in metabolites, suggesting increased 5-HT synthesis and/or impairment of 5-HT breakdown (fig. 1). Furthermore, in the same region increases in the dopamine metabolites dihydroxyphenylacetic acid (1.5 fold; p <

Fig. 1. Levels of serotonin (5-HT; **a**), dihydroxyphenylacetic acid (DOPAC; **b**), homovanillic acid (HVA; **c**) and noradrenaline (NA; **d**) in the diencephalon of 11β-HSD2$^{+/+}$, $^{+/-}$, and $^{-/-}$ adult male mice. Data are expressed as means ± SEM and analysed by one-way ANOVA followed by post hoc Tukey's test; n = 7–10 per group; * p < 0.05.
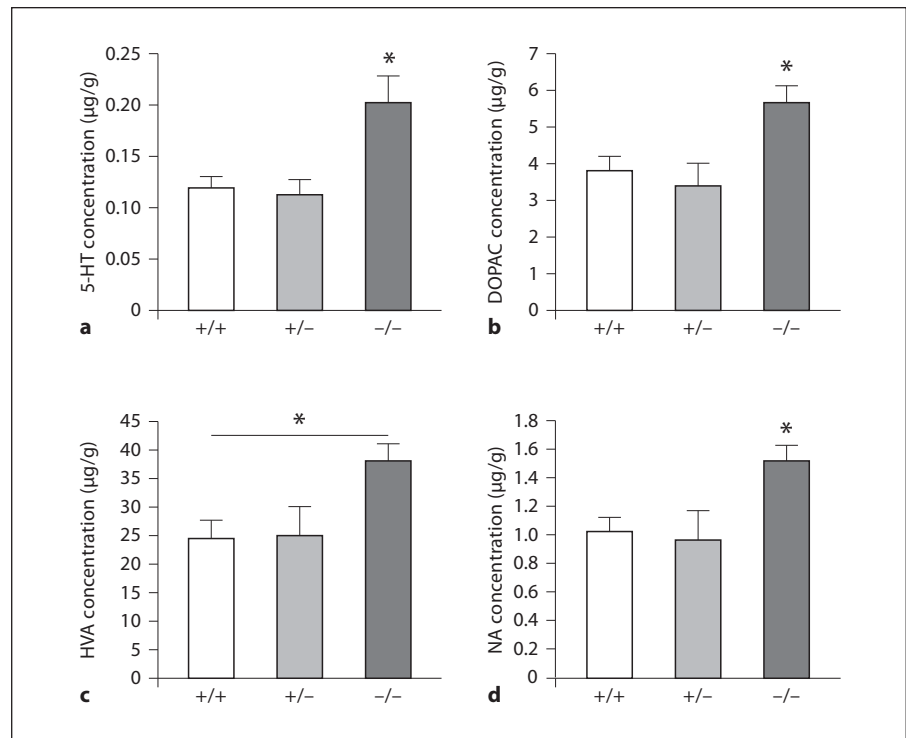
0.05), homovanillic acid (1.6 fold; p < 0.05) and noradrenaline (1.4 fold; p < 0.05), yet no alteration in dopamine, were found in 11β-HSD2$^{-/-}$ offspring, indicative of increased dopamine release and/or breakdown (fig. 1). The significance of these results, particularly given that the changes were observed in the diencephalon, is currently uncertain but is suggestive of increased 5-HT synthesis and/or impaired 5-HT breakdown in addition to increased dopamine release and/or dopamine breakdown. However, these results need to be followed up with further studies to place these current findings in context, in particular, characterising dopamine and serotonin transporters, receptors and enzymes. Furthermore, while the observed monoaminergic changes in 11β-HSD2$^{-/-}$ offspring are unaccompanied by alteration in the HPA axis function, this does not discount a direct role for glucocorticoids in altering monoamines, as local, intracellular glucocorticoid regulation has yet to be investigated in this model.

tributed to underlying these altered behaviours, changes also occur within the serotonergic and catecholamine pathways. Furthermore, the development of mice in the absence of 11β-HSD2 has proven instrumental in ascertaining the significance of 11β-HSD2 for the development of affective disorders. It is interesting that a common pathway altered in the developmental programming of affective disorders, the HPA axis, is in fact marginally affected in the 11β-HSD2$^{-/-}$ mouse. However, preliminary data suggest that changes in serotonergic and catecholamine pathways may, at least in part, underlie the altered behaviour of 11β-HSD2$^{-/-}$ mice. It should be noted though that these findings are potentially not just a consequence of feto-placental 11β-HSD2 loss but also of life-long renal 11β-HSD2 loss. Therefore, the development of tissue-specific knockouts of 11β-HSD2 will aid in eliminating this confounder.

Conclusions

In summary, prenatal exposure to glucocorticoids exerts long-term effects on the offspring, altering affective behaviours. While changes in the HPA axis are often at-

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