Abstract

Pregnancy and postpartum changes affect more than a half of women in the world. Neuroactive steroids play a vital role in mental health, behavior, mood development, neuron-protection and memory. This review sums up what is well-known regarding the two types of neuroactive steroids viz. allopregnanolone (ALP) and tetrahydrodeoxycorticosterone (THDOC). There is a strong correlation between body progesterone concentration and ALP production. The stage of estrus cycles determines the levels of ALP in body, however, THDOC is a stress induced neuroactive steroid and its level is changeable with the type and severity of stress. The physiological response of stress is affected by THDOC and influences paraventricular nucleus in hypothalamus which in turn controls hypothalamic-pituitary-adrenal and gonadal axis. Both neuroactive steroids are potent endogenous modulators of γ-aminobutyric acid type A (GABA_A) receptors and their production gets higher during pregnancy. Now a question arises “do both classes of neuroactive steroids have a potent correlation in their action?” This manuscript will bring you up to date on the interaction and function of these two during pregnancy and postpartum depression.

Keywords: Tetrahydrodeoxycorticosterone; Allopregnanolone; Pregnancy; Postpartum period; Neuroactive steroid; Depression

Introduction

Neurosteroids like tetrahydrodeoxycorticosterone (THDOC) and allopregnanolone (ALP) are metabolites of steroids and formed by the action of 5α-reductase type-1 and 3α-hydroxysteroid dehydrogenase enzymes [1,2]. THDOC and ALP has anticonvulsant, anxiolytic, sedative effects [3,4] and induces behavioural/health changes during pregnancy and menstruation while, anxiety and depression in epilepsy [5-9]. Neuroactive steroids are manufactured in the neurons, astrocytes and glial cells and can be produced from the same tissue [10]. The γ-aminobutyric acid (GABA) system is one of the many inhibitory systems and present in about 25% of the brain receptors [11]. There are three types of GAB_A receptors viz. GAB_A, GAB_A and GAB_A. Both of these neuroactive hormones are GAB_A receptor agonist which is pentameric and has an ion channel in its center [12]. Barbiturates are also GABAA agonist, and these anesthetics inhibit ovulation in rats [13]. There is also a known correlation of ALP and THDOC with GnRH, LH and FSH [14]. Since, there are few studies on the function and working of ALP and THDOC, however, the correlation of neurosteroid influencing the pregnancy and postpartum period is not yet well known. It is likely that GABAergic progesterone metabolites work singularly or coordinally to induce physiological/pathologic effects.

What is allopregnanolone?

ALP is a 3α-hydroxy-A ring-reduced steroid. It is synthesized de novo either in brain [15], in the adrenal gland cortex [10,16], and in corpus luteum during the ovulatory menstrual period [17]. The alteration in physiological rhythms of progesterone depends upon stress, stage of menstrual cycle, menopause, and pregnancy. When there is sudden decrease in body progesterone before premenstrual bleeding is the cause of premenstrual syndrome with similar symptoms in the postmenopausal women [18,19]. ALP levels get higher during early and postmenopausal women receiving dehydroepiandrosterone and the values get as much higher as are pragmatic in pregnancy [20]. This steroid metabolite exerts neuromodulatory possessions in CNS and is a GABA_A receptor agonist that affects mood, modulating anxiety, and memory [21,22]. There is a positive correlation between body ALP levels and the level of progesterone [23,24]. In estrus cycle, the body ALP level diverges with the change in phases of estrus. During luteal phase the level of ALP is about four times higher than the follicular phase [25] and gets at its peak with the advancement in pregnancy [24]. Animal studies show that the ALP levels remain elevated in the brain than blood circulation [16]. After the exposure to stress there is an increase of circulating ALP [25] than the normal calm and quite state, however, in adrenalectomized rats [10] the concentration of ALP remained undetectable in the plasma.

What is THDOC?

An increased activity of hypothalamic-pituitary-adrenal (HPA)-axis is due to more production of corticotropin releasing hormone (CRH), which is a key arbitrator of CNS stress [26]. After acute stress the hypothalamus production of CRH increases that prompts the discharge of ACTH from the anterior pituitary gland, which ultimately excites cortex of the adrenal for the production of glucocorticoids and neuroactive steroid precursors [27]. There are two types of glucocorticoids present eg. cortisol (human & non-human primates) and corticosterones (rodents); these give negative feedback upon

*Corresponding author: Mansur A Sandhu, Department of Veterinary Biomedical Sciences, Faculty of Veterinary and Animal Sciences, PMAS, Arid Agriculture University, Rawalpindi, Pakistan. Tel: +92-321-7830305; E-mail: mansoonsandhu@uaar.edu.pk
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the pituitary gland and hypothalamus. To counteract the increase of ACTH or corticosterone in stressed rats 3α, 5α-THDOC come and play its role to decline hypothalamic CRH mRNA levels and vasopressin [28] ultimately ACTH discharge and corticosterone levels of rats. Out of adrenal cortex, the 3α, 5α-THDOC development calls for the accessibility of deoxycorticosterone, and its synthesis is under ACTH control [29]. This decrease of CRH level may have a positive effect to save animal from stressful conditions, returning the body back towards homeostasis and is critical for mental health in premenstrual dysphoric disorders. However, after adrenalcotomy the production of THDOC fades away from the brain along with disappearance of 2α-hydroxylase. THDOC synthesis in brain needs deoxycorticosterone production by adrenal cortex. Interestingly THDOC release is more after stress stimuli. During the time of stress there is about 7-8 folds increase in the formation of THDOC from rat adrenal cortex and in plasma [25,30], it takes about 10-30 minutes to get its peak after stress [4] stimuli. Together with adrenal cortex, THDOC is also renewed from its forerunner in the brain neurons [6]. Enzymatic cleavage of deoxycorticosterone is with 5α-reductase and 3α-hydroxysteroid oxidoreductase (Figure 1) to form 5α-DHDOC and 3α, 5α-THDOC increase during depression.

Interaction of THDOC and ALP with other hormones

To exert the effects in brain, cortisol also uses mineralocorticoid receptor and its affinity is 10-folds higher than glucocorticoid receptors. In brain mineralocorticoid receptor is primarily articulated in the hippocampus. Both glucocorticoid and mineralocorticoid receptors are blamed for the production of anxiety and cognitive conditions [31]. Different studies on laboratory animals have confirmed that after stress there is an increase in mineralocorticoid receptor of hippocampus [32,33] and anxiolytic if we block mineralocorticoid receptors [34,35]. On the other hand, Otte et al. [36] demonstrated the inter-relationship of human mineralocorticoid receptor blockage with anxiolytic effects and shown similar results. In human, there is an increased production of plasma cortisol concentration with the use of mineralocorticoid receptor blocking agents as described by Arvat et al. [37] and Welhöner et al. [38].

The ALP along with THDOC (Figure 2) is potent endogenous modulators of GABA receptors having the role of anxiolytic, anticonvulsant, and sedative actions [39]. Evidences show that THDOC has a predisposition to protect neurons of developing brain in opposition to unfavorable emotional conditions. It is important to note down that, GABAergic agonists have the tendency to persuade behavioral modifications for the period of perinatal life [40]. However the mechanism through which THDOC induces gene transcription of corticoids receptor and neuropeptides remain difficult to understand. Thus the hypothesis was put forward that different neuron-hormones can modulate glucocorticoid receptors and CRH gene transcription [41]. There are strong evidences that neuroactive steroids also interact with steroid receptors, after oxidation THDOC and THP have the tendency to bind with progesterone receptor [42]. With occurrence of catamenial epilepsy seizure there is a sudden decline in progesterone secretion during the premenstrual period [43] and the treatment with progestin is helpful [44]. There may be relationship of seizures attenuation by augmentation of GABA-mediated inhibition of neural excitability after progesterin treatment. Since, progesterone metabolites are potent allosteric modulators of GABA receptors [5]. Recent studies have revealed that serum FSH and LH reduces after I/V injection of ALP during the follicular phase and a negative relationship was flanked by ALP and FSH. In an animal model the increased concentration of ALP or it’s injection to boost the circulating levels has an opposing effects on the circulating levels of GnRH, LH, FSH and this will ultimately suppress the formation of follicle and release of ova [14,45]. Similar results of delayed follicular phase with THDOC enhancement are present in rats [13] but no effect in primates [46]. These results can be correlated with human where elevated levels of ALP may induce premature ovarian failure [47].

Relationship of THDOC and ALP with pregnancy and postpartum depression

Pregnancy is among the most common physiological condition with lofty levels of steroids in a woman at child bearing age that makes her more prone to depression [48,49]. This postpartum depression (PPD) is a transitory type during pregnancy and after childbirth. Two forms of PPD: either “baby blues” or “late onset”. The baby blues type exists as many as 80% of women subsequent to delivery and generally resolves in few weeks devoid of treatment. The later onset form of PPD is more ruthless and is diagnosed after few weeks of delivery and its existence is in about 10-16% of childbearing women. The indications of PPD consist of anxiety, problematic sleep, sadness, memory impairment, mood changes, and tearfulness [50]. An average of 20% women with blues will expand long-term depression. There are evidences that infant-mother bond gets disturbed with PPD [51] and later problems in child’s socio-emotional development [52,53]. In adrenal and CNS, neuroactive steroids (THDOC and ALP) are created de novo from cholesterol (Figure 2) [54] and the change in levels of steroid hormone ultimately changes the levels of neuroactive steroids [54]. A variety of physiological (pregnancy) and pathological (stress) alterations in the body lead to modify the levels of neuroactive steroids in the CNS. Exogenous administration of steroid hormones results in depression merely among all the women those have the history of postpartum depression [55]. This shows that some women must be predisposed to postpartum depression. Every individual either human or animal are at all times under the challenges of stress. Though, all

![Figure 1: Structural alteration of Deoxycorticosterone (DOC) to 5α-dihydrodeoxy corticosterone (DHDOC) and then Tetrahydrodeoxy corticosterone (THDOC) through enzymes 5α-reductase and 3α-hydroxysteroid oxidoreductase.](image-url)
environments pose its unique set of stresses and the body must be
talented for proper response to maintain homeostasis [56]. The stress
in pregnancy also activates HPA-axis resulting in overproduction of
corticosteroids and high levels in both circulating and brain THDOC
(from 1-5 nM to 15-30 nM) as given by Reddy and Rogawski, [3];
Maguire and Mody, [57] and ALP (about 8-folds) as described by
Purdy et al. [10]. Another factor of increased ALP during pregnancy
is high levels of progesterone (about 200-folds) [58] and exogenous
steroids especially in the treatment of preterm labor may result in
an increases of neuroactive steroids ALP and THDOC [59]. So, we
can state that both THDOC and ALP are important in pregnancy
and have a direct role in PPD production. Neuroactive steroids such
as 3α, 5α-tetrahydroprogesterone (THP) and THDOC work mutually
as positive modulators of GABA receptors [60]. With the use of
antidepressant medicines the production of THP and THDOC in rat’s
brain increase with no change in blood levels [61]. In a human study
imbalance in these neurostroids was observed with the use of fluoxetine
and fluvoxamine and control group got higher levels of neurostroids
then clinically depressed patients [62]. During first trimester of
gestation noticeable dizziness is pragmatic, which is later decreased in
next trimesters of the gestation. This can be correlated with the levels
of neuroactive steroids, even in later pregnancy progesterone and ALP
gets higher those effects on sedation. In non-pregnant women sedation
takes place with lower concentrations of ALP [63]. This may be due to
GABA_A tolerance to ALP at some stage in pregnancy. Perhaps, the
change in mood and neurological disorders during PPD is due to down
regulation of GABA_A receptors during pregnancy, as there is abrupt fall
of progesterone and their metabolites. The results of an animal study
reveals that, at 18 days of rat pregnancy a decline in the appearance
of GABA_A receptor δ subunit in hippocampus was observed, which
bounces back to virgin levels within 48 hours postpartum [64]. The
eminent high levels of THDOC not only affect GABA_A but also alter
neuronal excitability. The psychological health changes of the ‘third
day blues’ and PPD [65,66] are hormone-related indications similarly
as premenstrual dysphoric disorder [67]. It is also stated that GABA_A
receptors down-regulated is one among all causes of adverse behavior
change. However, Sanna et al. [68] stated more complex regulation of
GABA_A receptors throughout pregnancy or there may be species
differences in steroid hormone-mediated GABA_A receptors regulation.
They proposed if there is deficiency of GABA_A receptor regulation in
pregnancy and postpartum period, this may influence mood disarray
during postpartum such as PPD. The association of mood disorders with
postpartum period is particularly related to changing levels of steroid
hormone or the site of steroid hormone action namely the GABA
receptor δ subunit. When the mice are deficient in GABA_A receptor δ
subunit (Gabrd^-/- mice), they show signs of depression within 48 hours
postpartum with forced swimming stress. These mice also fail to
make nest and keep their pups away from dam those die due to neglecting
behavior or cannibalism [63,64]. Based on the presented data we
can put forward a hypothesis (Figure 3) that different psychological
changes, mood disorders, intolerance, and problematic sleep may be
due to the change in neurosteroid (ALP and THDOC) concentration,
sensitivity or down/up regulation of the hormone/GABA_A receptors.

**Concluding Remarks**

The authors have tried to summarize the evidences pertaining
THDOC and ALP with pregnancy and postpartum depression (PPD). Though discussion is very brief, still we can state that a strong
correlation exists between THDOC and ALP. Both of these neuroactive
steroids have anxiolytic, anticonvulsant and other protective
properties. Almost all neuroactive steroids share similar receptors for
steroid hormones, have an important role in the up-regulation and
down-regulations of GABA_A receptors. Further studies are strongly
needed before ascertaining any conclusion from the interactions of
neuroactive steroids with other endocrine hormones, responses in
stress, pregnancy and generation of postpartum depression.

**References**

neurosteroids regulate GABAA receptors through two discrete transmembrane

Characterization of brain neurons that express enzymes mediating

neurosteroids modulate GABA(A) receptor function and seizure susceptibility.


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