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Review Article

Dithymoquinone Prevents Preeclampsia and Conserves Foetal Health: A Perspective Study

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Abstract: Dithymoquinone is a poorly studied carbonyl polymer of thymoquinone component of black cumin seeds. It suppresses release of histamines and improves clearance of cortisol in the liver and maintains the strength of placental aryl hydrocarbon receptors. Furthermore, we hypothesized that the low percentage of it in black seeds and its slow reduction make it safe for both the mother and her foetus. As many studies suggest, high levels of both histamine and cortisol are associated with preeclampsia, miscarriage, still birth and preterm delivery. We hypothesized that administration of dithymoquinone during pregnancy will prevent pregnancy complications, certainly preeclampsia and maintain the foetus's life. Experimental research is required to know more about the role of dithymoquinone in maternal and foetal health.

Keywords: Dithymoquinone, Preeclampsia, Foetal health, Histamine, Cortisol, Aryl hydrocarbon receptor.

INTRODUCTION

Dithymoquinone was first recognized by Lalleniand in 18.57 and named by him xythymoile [1]. It is a carbonyl polymer of thymoquinone, isolated from black cumin seeds; less toxic than thymoquinone [2]. It is in comparatively low concentrations is very effectual in inhibiting histamine release. The machinery of action appears to be through diminishing intracellular calcium by inhibiting its uptake and activating the efflux, and by an inhibition on protein kinase C [3].

Histamine was identified in 1910 by Dale and Laidlaw, and it was recognized as a moderator of anaphylactic reactions in 1932. It belongs to the biogenic amines and is made by the pyridoxal phosphate –containing L-histidine decarboxylase (HDC) from the amino acid histidine. It is synthesized by many cells, counting, mast cells, basophils, platelets, histaminergic neurons, and enterochromaffine cells, where it is stored intracellularly in vesicles and discharged on stimulation. It is a powerful mediator of numerous biologic reactions. Moreover the well-known triggering of degranulation of mast cells by crosslinking of the FcεRI receptor by specific allergens, numerous other nonimmunologic stimuli, for example neuropeptides, complement factors (ie, C3a and C5a), hyperosmolarity, cytokines, lipoproteins, superoxidases, adenosine, chemical and physical factors and hypoxia (e.g., traumas, extreme temperatures,) or alcohol and certain drugs and food, may stimulate mast cells [4].

DISCUSSION

Study done by Masuda K *et al*., [5] showed that aryl hydrocarbon receptor (AHR) negatively regulates IL-6 production via H1R signaling through the suppression of histamine production in macrophages following LPS stimulation.

The result concerning the role of histamine in allergic regulation, carcinogenesis, and even behavioural ruling highlight it as an extraordinary therapeutic target. But, as histamine receptors are broadly expressed in the body and alter during cell differentiation and ageing and even differ between genders, multifaceted histamine/receptor agonism/antagonism should be exploited for therapeutic approaches with caution [6].

Histamine is highly implicated in cancer development, growth, and metastasis through interactions with distinct HRs [7]. We suggest that cytosol contains antagonistic receptors (HRs) aryl hydrocarbon receptors and histamine receptors. The first one maintains the homeostasis inside the human body and the second one acts after failure of AHR to fix the cause of the disorder. Furthermore, histamine is not present in all body cells like AHR which exists in all body cells.

Study done by Tuomisto L *et al*., [8] showed that, histamine appears to be necessary for the maintenance of the circadian rhythmicity of the adrenocortical hormone release, locomotor activity and food intake, and the sleep-wakefulness cycle. Also, a role for histaminergic neurons in the light entrainment is concerned. Another study done by *et al*., [9] suggested that aryl hydrocarbon receptor (AhR) influences amplitude and phase of rhythms in circadian clock genes, hormones, and behaviour.

We suggest that the intracellular calcium concentration plays a key role in secretion of histamine and activation of AHR. Study done by Chakravarty N and Yu WJ [10] suggested that Calcium seems to have two opposing effects on histamine secretion from mast cells. An augment in the cytosol calcium concentration starts the chain of reactions leading to histamine release. Conversely, calcium appears to have a regulatory role, limiting the secretion.

Regulation of genes targeted by the ligand-activated aryl hydrocarbon receptor (AhR) has been shown to be controlled by calcium (Ca^{2+}) changes induced by AhR agonists [11].

Dioxins lead to increase in intracellular free calcium and activation of cyclooxygenase -2expression [12]. Cyclooxygenase, an enzymes catalyze a key step in the conversion of arachidonate to PGH2, the immediate substrate for a series of cell specific prostaglandin and thromboxane synthases [13].

The prostaglandins are a cluster of lipids synthesized at sites of tissue break or infection that are concerned in dealing with injury and illness. They control processes such as inflammation, blood flow, the formation of blood clots and the induction of labour [14].

Sustained increased ICF Ca+2 leads to activation of intracellular self-destructive lysosomal enzymes that destroy the mitochondrial membrane, cellular membrane and other organelle membranes [15].

This increase occurs as a response to a chemical, electrical, or physical stimulus interaction with a cell surface receptor, intracellular calcium concentrations rise from an influx of extracellular calcium or from intracellular calcium stores such as the endoplasmic or sarcoplasmic reticulum [16].

Study done by Shukla S *et al*., [17] showed that the calcium channel blockers, 1,4-dihydropyridines, are substrates of the multidrug resistance-linked ABC drug transporter, ABCG2, and AHR regulated ABCG2 via directly binding and transcriptional activation [18]. So we hypothesized that exhaustion of AHR leads to a defect in ABCG2 that appears as an increase in intracellular calcium, and we will discuss many physiological and pathological conditions to explain our hypothesis.

AN increase in intracellular calcium is the key trigger for contractile activity in pregnant human myometrium. It is hypothesized that key proteins concerned in myometrial calcium homeostasis are gestationally controlled and play a significant role in the preparation for labor.

Study done by Tribe RM *et al*., [19] showed that the activity of the sarcoplasmic reticulum Ca ATPases (SERCAs) isoforms becomes increasingly important in the maintenance of regular contractile activity throughout labor and may recompense for the functional loss of other calcium control pathways at term.

Maternal S-cortisol was higher during vaginal delivery compared to elective caesarean section [20]. Study done by Hyde GN *et al*., [21] showed that cortisol rapidly reduces intracellular free calcium and suppresses L-type voltage-gated ion channel activity in events that lead to reduced PRL release.

Histamine is regarded as a neurotransmitter, as it is exist in hypothalamus and pituitary gland. It has been reported to stimulate prolactin (PRL) release in rats and humans [22]. We hypothesized that cortisol prevents PRL release

by lowering free intracellular calcium and subsequent release of histamine. Furthermore, it affects the activity of aryl hydrocarbon receptor [23], or actually it decrease the action of AHR.

Cortisol secretion can be affected by circadian rhythms, physical activity, food consumption, smoking, caffeine, alcohol, and steroid medications [24]. Miscarriages were 2.7 times more likely among women with increased cortisol levels [25].

Increased cortisol availability involved nearly all placentas of women suffering from preeclampsia [26]. The rate of secretion of cortisol by maternal adrenals is not increased in pregnancy, but the rate of clearance is decreased [27].

Cigarette smoking is associated acutely with elevated cortisol levels [28]. Study done by Wang K *et al*., [29] showed that although smoking during pregnancy may lead to many adverse effects, such as fetal growth restriction, placental abruption, stillbirth, and preterm labor, smoking is the merely environmental exposure identified to consistently decrease the danger of preeclampsia and gestational hypertension.

Study done by Walter S *et al*., [30] suggested that cigarette smoking causes histamine release. And study done by Szewczyk G *et al*., [31] established that preeclampsia group compared to the control group had a higher mean histamine concentration.

Wang K *et al*., [29] proposed that cigarette smoke decreases the risk of developing preeclampsia via direct activation of AhR system in placenta, and impairs *cortisol* response to stress [32]. But we hypothesized that high levels of histamine lead to many adverse effects, such as foetal growth restriction [33], placental abruption, preterm labor [34], and stillbirth [35].

Study done by Barnett KR *et al*., [36] showed that in addition to mediating toxicity of environmental chemicals, the Ahr is required for normal ovulation.

Study done by Küchenhoff A *et al*., [37] demonstrated that Aryl hydrocarbon receptor was expressed in 43% of the endometria studied and was correlated with the day of the cycle. The most of immunopositive endometria was establish around the time of ovulation. Immunostaining reduced with rising age of the patients. The receptor protein was restricted completely in the apical part of the cytoplasm in the epithelial cells of the endometrial glands. In women positive for arylhydrocarbon receptor, aryl hydrocarbon receptor mRNA was expressed in the cytoplasm of endometrial epithelial cells.

Study done by Hernández-Ochoa I *et al*., [38] suggested that AHR may be involved in regulation of ovarian function by controlling the number and growth of antral follicles, as well the ability to produce steroids and to reach ovulation; providing a optimum environment for fertilization, nourishing the embryo and maintaining pregnancy; regulating fertility; and controlling reproductive senescence.

Study done by Englund-Ögge L *et al*., [39] showed that women adhering to a “prudent” or a “traditional” dietary pattern during pregnancy were at lower risk of preterm delivery compared with other women. Though these result cannot establish causality, they support dietary advice to pregnant ladies to eat a balanced diet counting vegetables, whole grains, fruits, and fish, to drink water. Rising the intake of foods related with a prudent nutritional guide is more significant than completely excluding processed food, junk food, fast food, and snacks.

Current studies have revealed that these toxic heavy metals provoke oxidative stress in the trophoblastic placental tissue by producing reactive oxygen species (ROS) that change the machinery of antioxidants probably leading to preterm birth [40]. And this supports our hypothesis about exhaustion of AHR.

Higher nuclear factor κB (NFκB) expression and activity is observed in preeclamptic placentas [41]. Study done by Vogel CF *et al*., [42] showed that NF-κB RelA is a critical component regulating the expression of AhR and the induction of AhR-dependent gene expression in immune cells.

Dithymoquinone is a carbonyl polymer of thymoquinone [43]. Aldehydes and ketones contain carbonyl groups attached to aryl groups and a hydrogen atom or both. These groups have slight influence on the electron distribution in the carbonyl group; thus, the properties of aldehydes and ketones are determined by the behaviour of the carbonyl group. In carboxylic acid and its derivatives, the carbonyl group is joined to one of the halogen atoms or to groups holding atoms such as oxygen, nitrogen, or sulfur. These atoms do influence the carbonyl group, shaping a novel functional group with distinguishing properties [44] thymoquinone (TQ) played a role in the inhibition of activation of NF-*κ*B [45]. It protects liver from injury via different mechanisms including inhibition of iron-dependent lipid peroxidation, elevation in

total thiol content and glutathione level, radical scavengering, increasing the activity of quinone reductase, catalase, superoxide dismutase and glutathione transferase, inhibition of NF-κB activity and inhibition of both cyclooxygenase and lipoxygenase [46].

We hypothesized that dithymoquinone also has a suppresser influence on NF-κB at less dose and toxicity in comparison to TQ. Furthermore, the low toxicity of dithymoquinone in comparison to thymoquinone is attributed to a long reduction time of it compared to thymoquinone.

CONCLUSION

We hypothesized that dithymoquinone, a polymer of thymoquinone, is useful for the health of both a pregnant lady and her foetus, decreases histamine release, promotes cortisol clearance and prevents exhaustion of aryl hydrocarbon receptor through removal of free radicals and by inhibition of activation of NF-κB. The superiority of dithymoquinone owing to its complexicity compared to thymoquinone.

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