International Journal of Scientific Research and Engineering Development-– Volume 5 Issue 4, July- Aug 2022

Available at www.ijsred.com

REVIEW ARTICLE OPEN ACCESS

Involvement of D-Aspartate in Releasing GnRH, LH and Stimulation of Testosterone Production

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Abstract:

D-Aspartic acid is a non-essential amino acid which is present in vertebrates and invertebrates for stimulating the different hormones in endocrine system. Its nature to rotate the plane polarized light in right direction deter it to act as building block of proteins.

This review is focuses on the contribution of D-Aspartic acid in Hypothalamus, Pituitary and Leydig cell of vertebrate's testis for the production of GnRH, LH and Testosterone respectively. In hypothalamus gland, it is elucidated that D-Aspartic acid is transform into NMDA (n-methyl D-aspartate) by reacting with SAM-CH_3 molecule. Furthermore, the NMDA will activate the KISS-1 neuron to stimulate the gonadotropin releasing hormone (GnRH). The D-Aspartic acid action activate the NMDA-R along with glycine to facilitate the calcium ion movement after depolarization to form gonadotropin (**luteinizing hormone LH and follicle-stimulating hormone FSH**) in pituitary gland. In vitro, the direct action of D-Aspartic acid in Leydig cell initiate intracellular signalling through second messenger cAMP and MAPK by binding with NMDA-R to stimulate pregnenolone. There is an limited research available about the direct action of D-aspartic acid in Leydig cell to finish the dependence of testosterone production on neuronal activity of brain (mental causation). The male infertility will eradicate by the chemical treatment of D-aspartic acid instead of surgery.

Keywords —D-Aspartic acid, NMDA, SAM-CH_3 , KISS-1, NMDA-R, GnRH, gonadotropin, LH, FSH.

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I. INTRODUCTION

The transfer ribonucleic acid(t-RNA) does not recognized the D-Aspartate. So that, it will not be able to carry D-aspartic acid in messenger ribonucleic acid (m-RNA) for protein synthesis according to gene information. The overall nature of D-Aspartate is acidic due to the attachment of ethanoic acid. D-aspartate mainly serves as neurotransmitter and main constituent of endocrine system for the exchange of information among neurons and regulation of hormones [12]. There is a complex mechanism involve in the inter and intra-cellular signalling pathways for the regulation of the diversity of hormones. Withimmunocytochemistry, the D-aspartate is observed inHypothalamus gland, Pituitary gland and Leydig cell. The considerable high concentration is present in testis of vertebrates specially rat species [13].

The solid correlation between the concentration of D-aspartate and Testosterone (T) level have been observed in rat tests, which was considerable increase from birth to the level of maturity.At 80 days after birth, testis levels of d-aspartate and Testosterone are about 150–200 nmol/g [2] .

Several study reported that the increase in D-aspartate will increase the testosterone but the result difference is huge in vitro and vivo. Recent study reveals that the rise in testosterone concentration observed with respect to D-aspartate in inactive human but very minor and limited in active human [4]. Additionally, the vitro study supports the direct-action argument of D-aspartate in Leydig cell. In cultured rat testis, D-aspartate alone signalling into the Leydig cell through bind NMDA-R

and upregulates Testosterone synthesis by stimulating gene and protein expression of the steroidogenic acute regulatory protein (STAR), a transport protein that regulates cholesterol transfer within the mitochondria [1]. The experiment in isolated rat hypothalamus shows that D-aspartate elicited the release of GnRH (gonadotropin releasing hormone) which lead toward releasing LH in pituitary gland [5].On the basis of the above findings, D-Asp seems to play a crucial role in reproduction because it is involved in biosynthesis and the release of sexual hormones.

Here we review the signalling pathway and the affect of D-aspartate in endocrine system of testosterone production with focuses in Hypothalamus gland, Pituitary gland and Leydig cell of tests.

II. D-ASPARTATE AND HYPOTHALAMUS GLAND

NMDA (n-methyl d-aspartate) are excitatory neurotransmitter found excessively in blood vessel which is a product of non-essential amino acid (d-aspartic acid) carry the signals across the synapse in order to reach the next neuron [14]. Occurrence of S-Adenosyl-L-methionine (SAMe) are abundantly in body that react with d-aspartic acid to form NMDA (n-methyl d-aspartate) and SAM by Nucleophilic substitution reaction, suggesting that D-aspartic acid is an endogenous precursor of NMDA biosynthesis (Figure 1).

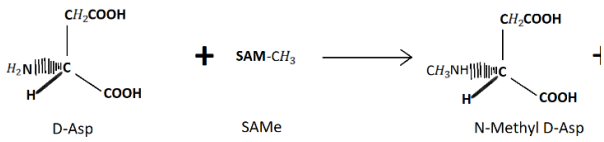

Figure 1. Synthesis of NMDA. The methyl from S-Adenosyl-L-methionine substitute with hydrogen of N-terminal (D-aspartic acid). The N-terminal of D-aspartic acid act asnucleophile due to nitrogen lone pairs.

The cell membrane of KISS 1 neuron have NMDA-R which actuate by the binding of NMDA to release Kp (Kisspeptin) protein encoded by kiss 1 gene was originally identified as a human metastasis suppressor gene that has the ability to suppress melanoma and breast cancer metastasis [20,21]. GnRH (gonadotropin releasing hormone) neuron begins to active by the binding of Kp in GPR-54 (KISS1R) receptor [2,3].

Several pieces of evidence indicates that the GnIH (gonadotropin inhibitor hormone) neuron release GnIH (gonadotropin inhibitor hormone) by requisition of stress, which will hug the GnIH receptor (GnIH-R) in the cell membrane of GnRH (gonadotropin releasing hormone) neuron. In the interface between the neural and peripheral endocrine systems where gonadotropin inhibitor hormone and gonadotropin releasing hormone converge to release GnRH on to the portal capillary system that vascularizes the anterior pituitary gland named (ME) median eminence (Figure 2).

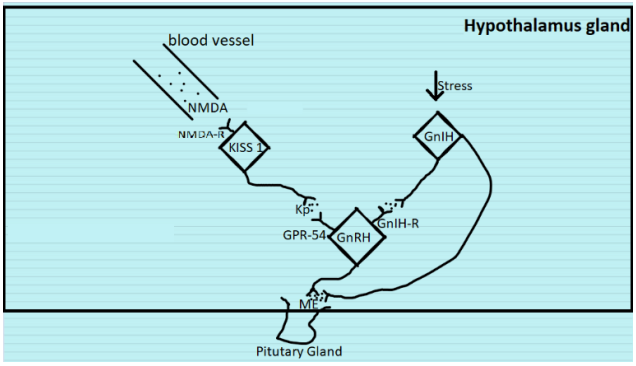

Figure 2: Signalling Pathway of releasing GnRH from GnRH neuron by the action of neurotransmitter and the reception of receptor in hypothalamus gland. The excitatory neurotransmitter NMDA excite the KISS 1 neuron and cause it to fire off the Kp that continues to be passed along to the next cell (GnRH).Gonadotropin releasing hormone and inhibitor hormone converge at ME to vascularizes the anterior pituitary gland by depart the releasing hormone (GnRH).

III. D-ASPARTATE AND PITUITARY GLAND

Explicit receptors of d-Aspartic acid have not yet been identified, a number of reports indicate that NMDA-R has an affinity for D-Aspartic acid. Interestingly, GnRH-R (Gonadotropin releasing hormone receptor) belongs to the family of GPCR (G protein coupled receptor), that arouse theGonadotropic cells due to the GnRH binding leads to the intracellular signalling through second messenger cAMP (cyclic adenosine monophosphate). It is known that the Membrane potential in the closed position of NMDA-R (N methyl d-aspartic acid receptor) is -70mV which states more anions inside the cell, the binding of D-aspartic acid and Glycine on the dedication site of receptor will remove the magnesium upon depolarization. The calcium moves into the cell that responsible for 0mV membrane potential.

Therefore, the intracellular signalling of GnRH and the presence of calcium liable for the synthesis of gonadotropins. It is well known that gonadotropins are directly responsible for luteinizing hormone (LH) and (FSH) follicle-stimulating hormone (Figure 3).

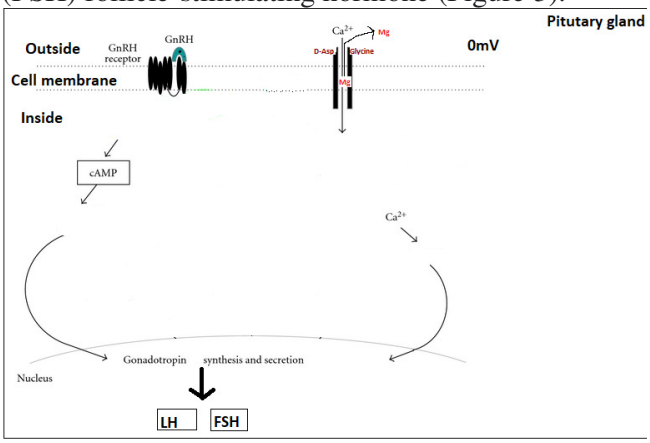

Figure 3: Intra signalling pathway of GnRH in Gonadotropic cellsof pituitary gland. Depolarization of NMDA-R increase the membrane potential of Gonadotropic cells from -70mV to 0mV by equal the concentration of cations and anions on outside and inside the cell. The formation of gonadotropin in the nucleus of gonadotropic cell leads to releasing of LH and FSH. The motivated LH through blood vessel on the way to the Leydig cell of testis.

IV. D-ASPARTATE AND TESTOSTERONE PRODUCTION IN TESTIS

The vitro study shows the direct action of D -aspartic acid in NMDA-R (N-methyl d aspartic acid receptor) of Leydig cell, upregulated the Testosterone (T) by stimulating the STAR (steroidogenic acute regulatory protein) protein expression through second messenger cAMP [7]. A transport protein STAR regulates cholesterol transfer into inner mitochondria membrane. Mostly, low density lipoprotein (LDL) cholesterol converted into cholesterol (free) in the action of Acetate [16,17].Further, several pieces of evidence shows the NMDA-R (n-methyl d aspartic acid) activation by the binding of D-aspartic acid induces phosphorylation of MAPK (Mitogen-activated protein kinase), a well-known signal transduction pathway in intracellular signalling of cells. The activation of cAMP (cyclic adenosine monophosphate) and MAPK (Mitogen-activated protein kinase) pathways by the binding of D-Aspartic acid to NMDA-R could be involved in steroidogenesis [8].In Leydig cell, the mitochondria have honour of centrality to embarks steroidogenic pathways. The STAR protein mediated the translocation of LDL-cholesterol from intracellular sources (across the outer mitochondrial membrane) to the inner mitochondrial membrane. The cytochrome P450 cholesterol side-chain cleavage enzyme (CYP11A1) converted the Cholesterol into the pregnenolone that converted to testosterone (T) by the chain of reaction [1,9] (Figure 4).

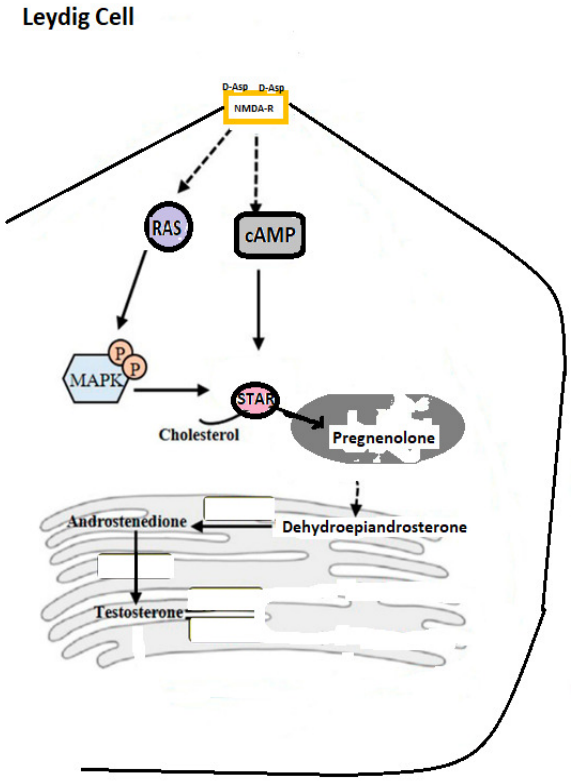

Figure 4: Diagrammatic representation of molecular pathway activated by D-Asp in Leydig cell. The activation of NMDA-R by the binding of D-aspartic acid will up-regulates the Testosterone (T) production in Leydig cell of testis by shoot up the STAR protein expression by the way of cAMP and MAPK pathways. Further, STAR regulates the cholesterol transfer within the mitochondria, where the CYP11A1 enzyme converted it into pregnenolone. It is known that the pregnenolone are the responsible for the synthesis of Testosterone (T) by the chain of reaction.

V. DISCUSSION

There is a mixed results in the previous research on the effects of D-aspartic acid on testosterone concentration, some study reveal that it will increase the testosterone

level but some study opposite to that. One of the study examined the effects of D aspartic acid supplements on the healthy men aged 27-37 for 12 days. This study surface that 20 men out of 23 taking D aspartic acid had successfully increase testosterone about 42%. After the three days, they stopped taking supplements still have 22% higher testosterone than at the beginning of study [2]. Another similar study examined the effects of taking D aspartic acid supplements for about a 90 days, experienced a 30-60% increases in testosterone [22]. On the other side, one study reveal that there is no increase in testosterone level of young adult men who took D aspartic acid for 28 days with performed weight training [23]. One study found that two week of taking high-dose D aspartic acid supplements of 6 grams per day decrease the testosterone level in young men who weight trained [24]. The analysis of above research is that there is no effect of D aspartic acid on muscles and testosterone level combined with weight training. The study on 60 men with infertility problems found a substantially increase the sperm quantity for taking D aspartic acid supplements about three months [22]. Although a limited research is available, but the based on the available research the higher doses of 6 grams D aspartic acid supplements does not appear to be effective. The above explained pathway of testosterone production from LH and D aspartic acid involvement evidences that D aspartic acid improve sperm quality and quantity in infertile men. In Overall, there is a need of more research before recommended D aspartic acid as testosterone booster.

CONCLUSIONS

Synthesis of NMDA from D-aspartic acid and SAMe to activate the NMDA-R of KISS 1 neuron suggest a remarkable role of D-aspartic acid in hypothalamus. D-aspartic acid is known to causes depolarization upon the removal of magnesium by binding with NMDA-R to allow calcium movement. A considerable body of evidence suggest that D-aspartic acid regulate steroidogenesis by induce several intracellular pathways possibly via binding to the NMDA-R. D-aspartic acid stimulate the STAR protein expression thorough cAMP and MAPK pathways. Further, mitochondrial protein STAR favours the cholesterol movement into mitochondria for pregnenolone production, leads to the synthesis of Testosterone (T). In vivo study, Future research should directed to investigate the direct role of D-Aspartic acid in Leydig cell. Recent study demonstrating the affinity of NMDA-R toward D-aspartic acid, but the satisfactory result required the actual receptor of D-aspartic acid. There is need to focus on the effect of D aspartic acid with other forms of exercise (other than weight training) to introduce a better way for boosting testosterone in infertile men.

ACKNOWLEDGMENT

Special thanks to the Mujahid Din for contributing and motivating as a author.

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