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Review Article

A REVIEW ON ANALOGUES OF BETA ODAP IN TREATMENT OF NEUROLATHYRISM SHOWING DOCKING AFFINITY

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ABSTRACT

Lathyrism or neurolathyrism is a neurological disease of humans and domestic animals, caused by eating certain legumes like Lathyrus sativus also known as Grass pea, containing the toxin β-oxalyl-L-α,β-diaminopropionic acid (ODAP). This consumption containing high concentrations of the glutamate analogue neurotoxin beta ODAP causes paralysis by binding at AMPA selective ionotropic glutamate receptors and blocking glutamate transport in the neural milieu and triggering excitotoxic degeneration of neurons, and may involve pyramidal tracts producing signs of upper motor neuron damage. The toxin may also cause aortic aneurysm. ODAP is a poison of mitochondria, leading to excess cell death, especially in motor neurons Children can additionally develop bone deformity and reduced brain development. Recent research suggests that sulfur amino acids have a protective effect against the toxicity of ODAP by applying docking property some researchers have proved to minimise the effect of toxic by developing analogues of beta ODAP with competitively binding to the respective receptor and decrease the neurotoxicity Carboxymethyl alpha, beta-diaminopropanoic acid (CMDAP) N-acetyl-alpha, beta- diaminopropanoic acid (ADAP), Carboxymethylcysteine (CMC). Ligand binding studies demonstrated that all the three compounds were effective to in displacing glutamate. The maximum inhibition was 92% for CMDAP, 61% for ADAP, 65% for CMC. These data indicate that analogues of beta-ODAP may interact with glutamate receptors without producing neurotoxicity.

KEYWORDS: *Neurolathyrism, Docking, Motor degeneration, Beta ODAP.*

INTRODUCTION

It is a neurological disease which is most commonly affects humans and less often in animals; it is caused by indigestion of certain legumes of the genus *Lathyrus*, it also knows with names such as grass pea, chickling pea, Kesari dal and to a lesser degree with *Lathyrus cicera, Lathyrus ochrus*. This is also associated due to over-consumption of *Lathyrus sativus* containing a neurotoxin known as Beta ODAP (β-oxalyl-L-α,β-diaminopropionic acid), Which exert its effects through mitochondrial toxicity [1].

History:

This was the first record in the ancient Hindu work called Bhavaprakasa, but Hippocrates also described it around 400 BC in Greece. Cantani in Italy named the condition as lathyrism.

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Epidemiology:

The seeds of lathyrism can be cultivated in any of the both conditions (flood and drought) where no other food crop cultivates. It has been one of the traditional survival food of the poor in some developing India. One placed named Gondar region of Ethiopia in the 1970s left 1% of the population permanently crippled due to consumption of laythrium [2]. Victims of second warfare displayed signs of chronic lathyrism following a period daily dietary intake of 400 g of *L. sativus* peas roasted in water and 200 g bread manufactured from barley and straw [3].

It is cooked as a vegetable, eaten as gruel, or ground into flour to make bread. In the west and northwest of the People's Republic of Bangladesh, grass pea could be a staple a part of the diet - agricultural labourers eat rutee or chapati manufactured from grass pea. Signs of illness usually seem whenever a food consisting of 1 third to 1 half *L. sativus* seed is consumed for three to six months. Men square measure affected a lot of typically than ladies, notably those within the 25-40-year-old age vary [4].

Risk Factors:

Following risk factors are associated in developing neurolathyrism:- Cooking with clay implements, Eating green unripe and boiled pea forms [5] and also patient having blood group O.

Protective Factors:

It is prevented by following some main steps before consuming green pea are soaking the green peas before cooking with fresh water, Eating with antioxidants (most preferable) or mixed with cereals rich in sulfur-based amino acids to treat neurolathyrism [6].

Mechanism:

Beta-N-Oxalyl amino-L-alanine (L-BOAA); equivalent word beta-N-oxalyl-alpha,beta-diaminopropionic acid (beta-ODAP) may be a present non-protein organic compound gift within the chickling pea from the plant khesari grown in drought-prone areas. Ingestion of L-BOAA as a staple diet ends up in a progressive neurodegenerative condition, neurolathyrism, a style of nerve cell illness that affects the higher motor neurons and anterior horn cells of the lumbar spinal cord. L-BOAA is an excitatory acid and acts as an agonist at the AMPA receptor. Exposure to L-BOAA causes mitochondrial dysfunction as evidenced by loss of complex I activity in lumbosacral cord by concurrent loss of glutathione. The suppressed advanced I activity in mitochondria isolated from the lumbosacral cord of animals treated with L-BOAA rebounded once incubation with the thiol-reducing agent dithiothreitol, indicating that oxidation of protein thiols to disulfides was responsible for enzyme inhibition. The inhibition of complex I may be abolished by pre-treatment with inhibitor thiols like glutathione organic compound and alpha-lipoic acid [7].

Experiments were done in mice shows that male mice, but not female mice, with L-BOAA resulted in the loss of complex - I activity and dendritic swelling of neurons in the motor cortex and lumbar cord, leading to biochemical effects on CNS mitochondria. These results support the view that thiol oxidation and joint mitochondrial dysfunction occurring downstream of the glutamate receptor activated by L-BOAA, are first events leading to neurodegeneration. Researchers suggest that maintenance of protein thiol homeostasis by thiol delivery agents could potentially offer protection against excitotoxic insults such as those seen with L-BOAA.

(i) ODAP and excitotoxicity: ODAP is an uncommon compound in this it's one in all the foremost anionic amino acids best-known and is additionally a decent metal cheater, and a few of its options particularly, in vitro systems could also be associated with this property [8].

One of the very early studies by Watkins et al. [9] had identified ODAP as one of the most excitatory substances in spinal interneurons and Betz cells of cats. Several in vitro cell culture studies have established that L-ODAP is α-amino-3-hydroxy-5-methyl-4-isoxazole carboxylic acid (AMPA) receptor agonist (glutamate receptor agonist) and this has been investigated extensively [10]. This excitotoxic theory has been wide command chargeable for all the toxin properties of ODAP. Also, any receptor interaction has to exhibit significant specific binding, but L-ODAP fails to show any significant specific binding to glutamate receptors [11].

(ii) Oxidative stress in neurolathyrism: Some studies recommend a radical element species generation as a mechanism of ODAP toxicity in rats following its focal hippocampal application [12]. Also, in vitro studies with mouse brain slices treated with ODAP recommend associate inhibition of mitochondrial complex - I (NADH dehydrogenase) [13]. Although oxidative damage from free radicals is a generally accepted mechanism of toxicity, some of the studies with ODAP have not been confirmed by other workers [14].

(iii) Inhibition of tyrosine aminotransferase (TAT) by L-ODAP: Most mechanisms instructed for ODAP toxicity come short of explaining the species variations in condition to ODAP. during this context, the reportable inhibition of TAT by ODAP both in vivo and in vitro suggests another attention-grabbing mechanism of neurotoxicity [15]. TAT is that the single protein known to date that's considerably reserved by L-ODAP. It's possible that excessive generation of hormone metabolites like 6-OH amino acid that are renowned neurotoxins may be the cause for neurodegeneration [16]. TAT inhibition by ODAP will, therefore, make a case for the species distinction in condition to ODAP a minimum of between black and white mice.

(iv) Metabolism of ODAP in humans and animals: The reasons for the low incidence of neurolathyrism in cohorts subsisting on grass pea dal haven't been explained. Even inside a family, not everyone seems to be liable to neurolathyrism. The fate of orally ingested ODAP from *L. sativus* had not been examined in detail. Since ODAP was not metabolised in experimental animals as well as primates [17], the same had been extended to humans also without any validation. A study administrated by the US in healthy volunteers and subjects commonly intense *L.sativus* established that humans could almost quantitatively detoxify/metabolise orally ingested ODAP in sharp contrast to animals [17]. This established for the first time that humans have a unique ability to metabolise ODAP. This raises the question as to how humans can be susceptible to ODAP toxicity when it is being detoxified while all animals examined so far are not susceptible even when they cannot metabolise/detoxify ODAP. This contradiction raises the likelihood which will be some people within the population area unit unable to detoxify ODAP and that they could also be liable to neurolathyrism. However, in a small group of individuals, no individual has been identified so far who exhibits this trait and calls for a study involving a larger group [18]. The precise biochemical mechanism of metabolism of ODAP in humans, however, remains to be elucidated. Oxalate is one of the end products in humans. It is possible that humans alone have a singular ability to oxidise eaten ODAP fully. This could also be the reason for not finding cases of neurolathyrism when *L. sativus* was getting used by large populations as a part of their daily diet. A deficiency of sulfur amino acids has been proposed as a contributing factor in precipitating neurolathyrism [19].

Clinical Presentation:

The onset of neurolathyrism is sometimes unforeseen and coincident with the monsoon season. Early symptoms include: walking difficulties, intolerable cramps, leg weakness
It may also be associated with developing of spastic paralysis which becomes irreversible.

Pyramidal tract involvement causes: Motor weakness, accumulated tone, A staggering scissoring gait caused by engagement of the thigh extensors and adductors and striated muscle, skeletal muscle region responses, terribly brisk knee and ankle sinew reflexes, usually convulsion, Hoffmann's sign and exaggerated skeletal muscle and/or striated muscle sinew jerks within the most severely affected.

There are not any objective sensory signs however perverse sensations within the legs area unit frequently reported at the onset. Walking difficulties usually begin suddenly however might also seem sub acutely or perniciously.

Some folk's expertise part reversible symptoms implicational a diffuse CNS excitation of bodily, motor and involuntary operate [20]. Spasticity may be a lot of marked than the motor weakness [21].

Lathyrism isn't merely a paralytic syndrome, as neurolathyrism causes sudden death: the poisonous substance changes the snap of the artery inflicting aneurism that will rupture.

Osteolathyrism affects skeletal development: cartilages and bones grow abnormally departure the body unshapely [22]. Children suffer skeletal deformity and poor cerebral growth.

Management:

The disease is usually nonprogressive but irreversible. , a muscle relaxant which is centrally acting tolperisone, has been shown to produce a significant reduction in treating patients with neurolathyrism [23].

Prevention:

Public health education regarding the risks of lathyrism is vital however the harsh reality is that folks could face an alternative between lathyrism or starvation. Food preparation measures can help:

Boiling in water or recurrent steeping in a predicament and discarding the extracts will detoxify the laythrisum.

Barbecuing the seeds at 140*C for 15 to 25 minutes ends up in 80-90% destruction of the neurotoxins.

Soaking the seeds or pigeon pea night long and decanting the water before preparation eliminates concerning 90th of the poison.

The dangers of lathyrism are often seen along with knowledge of how to detoxify Lathyrus, but drought conditions can lead to fuel and water shortages preventing the necessary steps from being taken.

One goal for the bar is to develop a plant with the resilience of chickling pea to extreme atmospheric condition, with its nutritional content and taste but without toxin ('zero BOAA' strains). Genetic modification might supply safer food and therefore the use of marginal farming land. Some types of chickling pea that contain a far lower quantity of poison are developed and will become additional wide cultivated [24].

To learn other regarding the mechanisms underlying Lathyrism 3 structural analogues of beta-ODAP were synthesised by using docking or molecular docking.

It is a method which predicts the preferred orientation of one molecule to a second when bound to each other to form a stable complex [25]. Knowledge of the preferred direction, in turn, is also accustomed to predicting the strength of association or binding affinity between two molecules exploitation, for example, scoring functions.

Molecular docking is one of the most frequently used methods in structure-based drug design, due to its ability to predict the binding-conformation of small molecule ligands to the appropriate target binding site. Characterisation of the binding behaviour plays a vital role in the rational style of medicine likewise on elucidating elementary organic chemistry processes [26].

Molecular docking analysis focuses on computationally simulating the molecular recognition method. It aims to realise associate optimised conformation for each the macromolecule and matter, and relative orientation between macromolecule and ligand such the free energy of the system is minimised.

Applications:

A binding interaction between a little low molecule substances an accelerator supermolecule might lead to the activation or inhibition of the accelerator. If the supermolecule may be a receptor, substance binding might lead to agonism or antagonism. Docking is most typically utilised in the sphere of drug style most medication is tiny organic molecules, and moorage could also be applied to:

By using the above molecular docking property researches have designed three structural analogues with are similar to beta ODAP

1. Carboxymethyl-alpha,beta-diaminopropanoic acid (CMDAP) induced inward currents that were offended by APV (30 microM), however not by CNQX (10 microM).
2. N-acetyl-alpha,beta-diaminopropanoic acid (ADAP) induced no detectable ionic currents however potentiated N-methyl-D-aspartate (NMDA)-activated currents. The synergism of NMDA currents by ADAP was blocked by 7-chlorokynurenic acid.
3. Carboxymethylcysteine (CMC) failed to activate any detectable ionic currents [27].

None of the three beta-ODAP analogues created visible symptoms of toxicity in day previous chicks once administered for 2-3 consecutive days.

Ligand binding studies incontestable that everyone the 3 compounds were useful to in displacing [3H]glutamate.

The maximum inhibition was ninety-two (92) for CMDAP, sixty-one (61) for ADAP, sixty-fifth (65) for CMC and ninety-nine for beta-ODAP. These knowledge indicate that analogues of beta-ODAP could act with glutamate receptors while not manufacturing neurotoxicity [27].

By using these analogues we can design the drugs with are similar to beta ODAP with binds to the same receptor and ultimately inhibits the action (neurolathyrism or neurotoxicity) caused it

CONCLUSION

It's been decades in which many people have been effecting from neurolathyrism, but only symptomatic treatment has been given, by using various new technique's like docking and different other drugs can be synthesized to prevent the attachment of beta ODAP at the target receptor site thereby resulting in treatment of neurotoxicity, multiple approaches have been shown through docking mechanism like fit mechanism to synthesize molecules like CMDAP which has higher affinity to bind with the glutamate receptor and inhibit the action thereby resulting in inhibition of neurotoxicity caused by Beta ODAP.

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