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Review article

Role of glutamate and nitric oxide in onset of motor neuron degeneration in neurolathyrism

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ABSTRACT

Neurolathyrism is associated with a complex pattern of alterations in the glutamatergic system of the cortical motor region of brain. It is a neurological disorder consorted with excessive consumption of *Lathyrus sativus* (Grass pea), comprising large amounts of the neurotoxin, β-N-oxalyl-L-α,β-diaminopropionic acid (ODAP). ODAP being a potent agonist of ionotropic glutamate receptors enhances their activity and also blocks the astrocytic glutamate/cystine transporters, abutting the neurons. This leads to the sustained increase in the concentration of Glutamate in the synapse which triggers excitotoxicity. *L. sativus* also contains high levels of arginine and homoarginine which are natural substrates of nitric oxide production, when NO levels increases, it forms peroxynitrite radicals which cause irreparable damage to mitochondria and cellular macromolecules leading to motor neuron degeneration. This review brings together all the molecular events reported so far, emphasizing on the possible role of glutamate and nitric oxide mediated cell death.

Contents

1. Introduction

1.1. Neurolathyrism—its prevalence

Neurolathyrism, a form of spastic paraparesis, is a disease associated with the excessive intake of the seeds of *Lathyrus sativus* (grass pea, Khesari dal) (Rao, 2011). Grass pea is a high yielding, drought tolerant legume that is produced and consumed in Bangladesh, china, India and parts of Africa such as Ethiopia,

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Table 1
Incidence of lathyrism in Bhopal state of India (Shourie, 1945).

Age group	Number of cases	Percentage
4–10	13	18.0
11–20	19	28.4
21–30	21	29.1
31–40	11	15.2
41–50	7	9.7
51–60	1	1.3

Somalia etc. that are susceptible to drought (Stodolak et al., 2008). It is a cheap source of protein for human and animal consumption (Barceloux, 2008). The uninterrupted consumption for 2–4 months of an exclusive (300–400 g/day) diet of grass pea can give rise to the crippling neurolathyrism, irreversible paralysis of the lower limbs (Spencer and Schaumburg, 1983). It affects more men than women of low socioeconomic (nutritionally compromised) classes (Lambein et al., 2001). The *L. sativus* seeds and the foliage comprise large amounts of β-N-oxalyl-L-α,β-diaminopropionic acid (ODAP), a non-protein, neuroexcitatory amino acid which is widely accepted as the likely causative agent of neurolathyrism (Warren et al., 2004).

During the periods of drought-triggered famines neurolathyrism was rampant in few regions of Ethiopia, Bangladesh and India. The incidence of lathyrism reported on the basis of age, sex of the cases studied and the season of incidence in Bhopal state in Central India in 1945 (Shourie, 1945) (Table 1).

The incidence of neurolathyrism has decreased gradually in Indian topographical scenario because of a few corroborative reasons. The elemental ground for this is the ban (Rule 44-A of the Prevention of Food Adulteration Rules, 1955) on the Lathyrus pulse. The second cause is the descent in the consumption of grass pea as a monotonous diet on the account of developing socio-economic standards of living masses.

Recently in Woreda district of Ethiopia 424 cases of lathyrism were reported. Out of all the affected cases, 19.8% were females and 80.2% were males. The majority (43.3%) were in the 10- to 20-year age group (Table 2) (Haimanot et al., 2005).

Economically backward sections were forced to eat *L. sativus* monotonously during recurrent Famines and droughts due to the insufficiency and dearth of food. Grass pea withstands prolonged drought during grain-filling and heavy rains in early growth stages (Campbell et al., 1994) and, can be grown on wide range of soil types (Abd El Moneim et al., 2001) without expensive inputs (Croft et al., 1999). Excessive consumption triggered the outbreak of lathyrism in many countries. *L. sativus* should be consumed exclusively for 2–3 months for the appearance of disease symptoms. Government of India has initiated several food programs like 'Mid day meal to school children', 'BPL (Below Poverty Line) ration cards for poor sections', 'Public distribution system of Cereals, Rice, Wheat' these helped in mitigating the incidence of lathyrism. Sale of Lathyrus is banned in India under Rule 44-A of the Prevention of Food Adulteration Rules, 1955, in the States/U.Ts. All these factors contributed to decline in incidence of lathyrism in India.

Table 2
Age and sex distribution of cases of lathyrism in Legambo Woreda 2004/2005 (Haimanot et al., 2005).

Age distribution	Male	Female	Total
0–10	29	19	48
11–20	148	36	184
21–30	60	15	75
31–40	40	7	47
41–50	32	3	35
51–60	13	3	16
61–70	11	1	12
70+	7	–	7
Total	340	84	424
%	80.2	19.8	100.0

1.2. Neuropathology of neurolathyrism

Neurolathyrism is a motor cortical neuron disorder characterized by paralysis of the lower extremities. It predominantly targets the upper motor neurons (beta cells and the corticospinal tracts) of the cortex of the brain (Lipton, 2007) anterior horn cells and axons in the pyramidal tracts of the lumbar region and the pyramidal tract neurons of the spinal cord (Ravindranath, 2002; Hirano et al., 1976). Ingestion of the seeds and foliage (containing high amounts of ODAP) of *L. sativus* as a staple diet results in the progressive neurodegenerative condition (Ravindranath, 2002).

The pathological conditions of neurolathyrism include bilateral atrophy in the distal pyramidal tract in the lumbar cord, degenerative changes in the spinocerebellar tracts and the dorsal columns. The pathology is more pronounced in the longest CNS fibers. The central distal axonopathy is caused by the degeneration of the longest corticospinal tracts, with lesser involvement of shorter pyramidal pathways serving the upper extremities of the immune compromised individuals. The pathological changes in the spinal cord predominantly include distal symmetrical degeneration of lateral, ventral corticospinal tracts and distal degeneration of spinocerebellar, gracile tracts and changes in lumbar anterior horn cells, including swelling, diminished Nissl substance, and Hirano bodies (Zaninovic, 2001).

1.3. Clinical symptoms

Clinically, lathyrism symptoms often commence with complaints of pain or cramps in the legs or in the region of the lumbar spine, weakness of lower extremities evolving into permanent spastic paraparesis. The cramping pains and the sphincter dysfunction usually subside when the intoxication ceases and spasticity develops (Zaninovic, 1999). Susceptibility for neurolathyrism varies among individuals and communities, and an increased risk of paralysis is associated with male sex and young age (Getahun et al., 2005).

1.4. Etiological factors involved in neurolathyrism

The anti nutritional factors and neurotoxic non-protein amino acid, ODAP is present in the seeds of *L. sativus* (Adiga et al., 1962). Malnutrition in population consuming Lathyrus as sole diet has been considered as contributing factor for the cause of neurolathyrism (Getahun et al., 2005) the action of β-ODAP is subtle; it hyper-excites the neurons causing spastic movements of the legs and leads to paralytic neurolathyrism. Naturally occurring ODAP exists in two isomeric forms, α and β (Bell and O'Donovan, 1966) with α-isomer being less toxic (De Bruyn et al., 1994). The concentration of the β-ODAP is about 95% of the total ODAP. Isomerization of β-ODAP to α-ODAP depends on temperature (Padmajaprasad et al., 1997).

Excitatory neurotransmission is required for normal brain function, and NMDA receptor stimulation with calcium influx is required for neonatal and immature brain development (Gustafsson and Wigstrom, 1990; Durand et al., 1996), but excess of Glutamate excitotoxicty is the major etiological factor in many neurodegenerative disorders. The link between the excitatory amino acid neurotransmitter glutamate and neuronal excitotoxic brain damage is well established (Choi and Rothman, 1990). Glutamate, the endogenous neurotransmitter required for