

Do we need more research on neurolathyrism?

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It is nearly four decades since the discovery of ODAP as the major neurotoxic constituent of *Lathyrus sativus* seeds. However, several basic questions relating to neurolathyrism still remain unanswered. We are unable to convince several governments to ban the cultivation of the pulse and to take on a more serious approach to introducing the low toxin varieties. Meanwhile, farmers continue to grow the traditional varieties and the consumption of the pulse continues. We still do not have a straightforward method to produce a convincing animal model to study the disease. We do not even have an acceptable mechanism for the toxicity of ODAP. While we are concerned that the disease affects the poorest of the poor, we do not know how the majority of the *Lathyrus* consuming population escape from the disease. The precise enzymatic pathway and its characterisation for the biosynthesis of ODAP are still needed before genetic engineering principles can be applied to produce genetically modified ODAP free *Lathyrus*. It is rather intriguing how these seemingly simple questions relating to a human disease of nutritional origin remain unsolved. I am certain that there are reasons that most *Lathyrus* researchers would agree upon.

ODAP is deceptively a dicarboxylic amino acid chemically related to glutamate (aspartate). However, to date, no direct effect of ODAP on any of the enzymes associated with the metabolism of either glutamate or aspartate has been demonstrated and also it does not have any substrate activity with any of these enzymes. A number of studies have shown that ODAP acts as an agonist at the AMPA preferring glutamate receptors^(5,7). But in spite of our best efforts, we have been unable to demonstrate any significant specific binding of ³H ODAP to synaptic membranes of the chick or rat⁽¹⁾. This crucial evidence thus fails to establish antagonistic property for ODAP at glutamate receptors. Moreover, we have now shown that even free diaminopropionate (DAP) and carboxymethyl DAP (CMDAP) another synthetic glutamate/ODAP analogue which are non-neurotoxic (acute study) exhibit a far greater excitotoxic potential

than ODAP⁽⁶⁾. Even if one were to consider agonistic activity of ODAP at glutamate receptors as a plausible mechanism of toxicity, it simply cannot explain the extreme species differences in susceptibility to ODAP. Thus can the adult rat and the BALB/c mice which are resistant to ODAP possess a different disposition of glutamate receptor subpopulations than the susceptible species the chick? Vexed by this inconsistency, we came up with the most surprising finding that the C57BL6J black mice are easily susceptible to ODAP while the BALB/c white mice are resistant to it but would become susceptible if pretreated with tyrosine⁽³⁾. This, further led us to establish the first ever stereospecific inhibition of an enzyme activity by ODAP, namely, that of tyrosine aminotransferase. Over the years we have been so enamoured by the "structural relatedness" of ODAP with glutamate that no one dreamt that it may inhibit the aromatic amino acid transferase. Our molecular modelling studies with ODAP (to be published) show that ODAP is indeed conformationally cognate more with tyrosine and less with glutamate (Fig. 1). We have shown that ODAP administration results in a significant increase in brain dopa and dopamine levels, only in black mice, as a fallout of TAT inhibition and not in white mice. Further studies are needed to pinpoint the toxic metabolites of dopa and dopamine that may be the real culprits of neurotoxicity as a result of oxidative damage⁽³⁾.

One of the more puzzling features of neurolathyrism relates to how and why a large majority of the *Lathyrus* consuming subjects escape from the disease, which is quite evident even in the recent Ethiopian epidemic. To my knowledge, no one has attempted to explain this feature although some newer thoughts appear to be emerging in evaluating the incidence of the disease. Since most laboratory animal studies, including those with monkeys, show that orally administered ODAP is excreted in the urine largely unchanged, it has generally been assumed that ODAP would have a similar fate in humans. I would like to share some of our recent yet unpublished findings on this aspect. In a survey of a *Lathyrus* consuming population, the overnight urine samples collected following a *Lathyrus* meal showed very little urinary excretion of ODAP (less than 2-5%), this was confirmed on several occasions. We have confirmed this finding in controlled studies with human volunteers wherein the ODAP excretion was less than 1% of the dietarily consumed ODAP. This suggests that, as opposed to the findings in experimental animals, humans have an ability to metabolise/detoxify orally ingested ODAP. While we

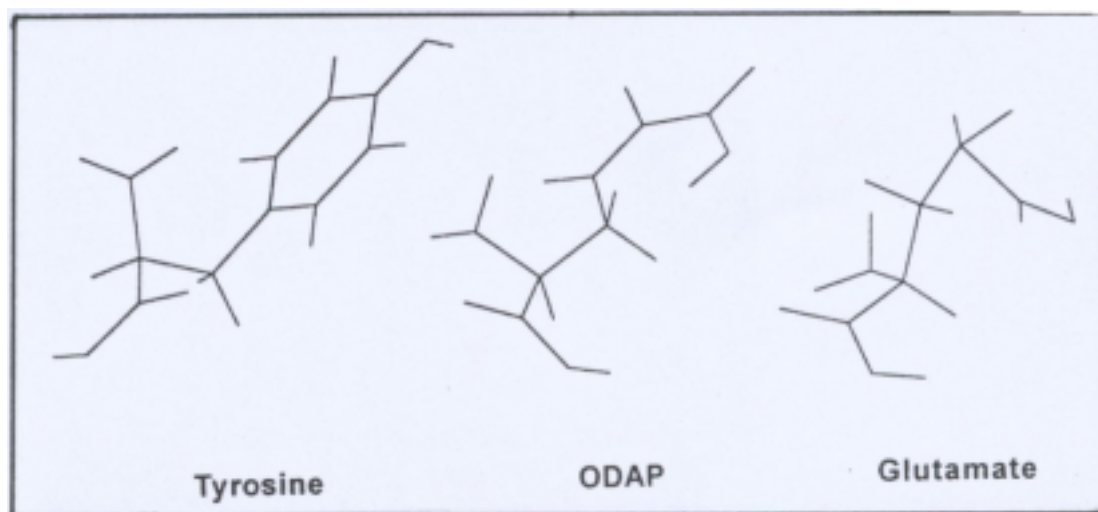


Fig. 1: Energy minimised structures of tyrosine, ODAP and glutamate.

are yet to establish the pathway in humans, our studies with chicks, rats and mice indicate that orally administered ^{14}C ODAP does undergo some oxidation, albeit to a limited extent, resulting in the appearance of $^{14}\text{CO}_2$ in the expired air. It is likely that in humans a similar pathway may operate to a greater extent and

lead to near complete metabolism/detoxification of ODAP ⁽²⁾. This finding opens up the interesting possibility that this pathway could be deficient in certain individuals or under certain conditions such that these individuals may run the risk of the disease. Identifying such individuals and the metabolic/detoxification pathway should receive high priority in future investigations.

I am certain that readers of Lathyrus Lathyrism Newsletter would agree with me that further research on these lines would go a long way in clearing up some of the grey areas of *Lathyrus* toxicity. Further, as pointed out by Dr. Fernand Lambein ⁽⁴⁾ in the previous issue of this newsletter, there is a need for a coordinated effort on the part of different *Lathyrus* researchers in solving the mystery associated with this pulse and the disease.

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**Following commentary by Fernand Lambein,
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Professor SLN Rao was at the cradle of *Lathyrus* research with the publication of the structure and chemical properties of ODAP in 1964⁽³⁾. The ever popular "Rao-method" for the quantitative analysis of ODAP is still an important tool for breeders and for other *Lathyrus* researchers⁽²⁾. As Prof. Rao continues with surprisingly innovative and thorough research, he can rightly be considered the godfather of *Lathyrus* researchers. Those who were present at the festivities and the scientific symposium at the occasion of his retirement witnessed the signs of extraordinary sympathy and respect he received from colleagues and students⁽⁴⁾. We wholeheartedly welcome SLN Rao as contributor to the renovated Lathyrus Lathyrism Newsletter.

As a man of dialogue, he will understand that among his students and friends different opinions can emerge. Or perhaps we use only different words to express the same conviction. Banning the sale of *Lathyrus* but not the consumption has been a controversial topic and probably will remain as such, while propositions to lift the ban has achieved nothing but raising blood pressures. In Europe, it took at least two generations for the ban on *Lathyrus sativus* to take effect (edicts in 1671, 1705 and 1714 for the same Wurtemberg area)⁽¹⁾. Yet 300 years later consumption still persists and bloomed during the Second World War. After crop failures due to drought in Eastern Poland and Northwest China, grass pea was reintroduced recently. Grass pea and lathyrism become an acute problem in periods of drought-triggered famine, when other food grains are not available and grass pea seed forms a survival food from which up to 95% of the people suffer no ill consequences. Considering this one should not be surprised that a ban on grass pea has no immediate effect.

As Prof. Rao points out the lathyrism victims are the poorest of the poor. The depressing socio-economic environment where lathyrism thrived among subsistence farmers also promotes a low socio-political status of the victims, which may be responsible for the under-financing of much *Lathyrus*/lathyrism research. It is cynical that so much research money is spent on diseases such as cancer and cardio-vascular diseases of which a sizable portion can be prevented by a poorer diet. Yet so little money is spared for diseases such as lathyrism, konzo

and diarrhoea that can easily be prevented by a better balanced diet. Imposing a ban on grass pea in areas where it is an essential part of the survival economy may only solve the problem on paper while furthering the neglect of the victims and of research. On the other hand, lifting unconditionally an existing ban might only benefit grain traders and give totally wrong signals to the consumers if no proper nutritional education is in place. Until now, researchers did not voice a single and convincing opinion on how to prevent lathyrism.

During the last decade, Prof. Rao and others have added some exciting new features to the increasingly complex biochemistry and physiology of this simple molecule ODAP, in the producing plant as well as in the consuming human or animal. The remarkable variability of the plant and the remarkable variability in the susceptibility of species and individuals to this molecule make it increasingly difficult to draw the simple conclusions that are needed to educate the people at risk and so prevent lathyrism.

Undoubtedly, the environment affects the level of ODAP and other secondary metabolites in the plant. Can the environment also affect human susceptibility? Under the term environment we also need to consider our internal environment or intestinal flora, which is much more variable than our genetic blueprint and may be prone to dietary or environmental effects. We very much hope that Prof. Rao can continue to unveil the intricacies of ODAP metabolism leading to the oxidative damage and probably apoptosis of some specific neuronal cells. Only from a complete and probably very complex picture, we will be able to derive the simple advice that can prevent lathyrism and protect the consumers.

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