Significant correlation between cerebrospinal fluid nitric oxide concentrations and neurologic prognosis in incomplete cervical cord injury (N. Hosaka et al.)

Khai S. Lam

Accepted: 17 September 2007 / Published online: 6 October 2007
© Springer-Verlag 2007

This is an interesting, important and appears to be the first study of its kind attempting to correlate the concentrations of the small, free radical molecule nitric oxide (NO), with the severity of spinal cord injury and its relationship to neurological prognosis. Many studies have described the increased presence of stable metabolites of NO (i.e. nitrites and nitrates or NOx) in inflammatory neuro-degenerative and inflammatory disorders, and hence an indirect involvement of NO; a major ubiquitous pleiotropic biological mediator that is involved in cellular signal transduction in neurons and the immune system.

Although I would entirely agree that there is insurmountable evidence that NO plays a pivotal role in spinal cord injury; however the biochemical pathways for its protective (physiological) versus destructive (pathological) roles have yet to be fully elucidated. As such NOx concentrations in the cerebrospinal fluid (CSF) may be an important biochemical marker of the severity of the neurotoxicity processes associated in spinal cord injury and perhaps its sequel; the subject of this investigation.

In the afore-mentioned manuscript, the authors have investigated patients with incomplete cervical spinal cord injury and ascertained a significant inverse correlation between NOx and neurologic recovery, i.e. the higher the levels of NOx, the less chance of recovery and thus NOx could potentially be used as a biochemical prognosticator in this group of patients.

Despite the interesting associated findings, still there are yet unanswered issues. The entire premise of this study hinges upon NO production via inducible or nitric oxide synthase (iNOS) and we are lead to believe that all NOx are derived from the activity of iNOS; the presence of NO being deleterious to the spinal cord.

Therefore interesting enquiries raised relates to:

- (a) Can the authors be wholly certain that the total NO concentrations are derived from iNOS and not from cellular or cNOS [neuronal (nNOS) or epithelial (eNOS)]; gene upregulation of cNOS also have been shown to occur in the early hours of spinal cord injury that has been described as protective?
- (b) Can the authors therefore also discern the ratio of production of NOx (hence NO) that is derived from either iNOS or cNOS and the clinical relevance of each?
- (c) Does NO production differ depending on the level of spinal cord injury, i.e. cervical versus thoracic versus thoraco-lumbar cord injuries (despite the fact that the thoracic cord injury group have now been removed from the re-analysis). This is particularly important since all major trauma centres typically are exposed to injuries affecting all spinal levels.
- (d) What were the injury severity scores of the cohort of patients investigated? Were there associated traumatic brain injuries that are commonly seen in the CCI group? And how do the authors suppose these factors could affect the NOx concentrations in these groups of patients, particularly from the upregulation of nNOS that typically occurs following traumatic brain injury?
- (e) The investigation only looked at an “incomplete” neurological group of patients. Therefore, in order that these results could have any meaningful

This comment refers to the article
<http://dx.doi.org/10.1007/s00586-007-0477-9>

K. S. Lam (✉)
Guy's Hospital, St Thomas' Street, London SE1 9RT, UK
e-mail: khai.lam@gstt.nhs.uk; DocKS Lam@aol.com

interpretation, I strongly believe that it is essential to compare them with a “complete” or Frankel A group; as this latter group will act as a “positive control”.

My other concerns relate to the standardisation of timing of CSF collection and that the patient numbers investigated remains somewhat modest. Notably, one is far from

understanding the physiology let alone patho-physiology of NO in spinal cord injury. Therefore, I would view this investigation as an especially preliminary introduction to the involvement of NO in spinal cord injury. Additionally it seems rather premature to conjecture over iNOS blockers in the treatment of SCI.