Reviewer's report

Title: Plasma Prolyl Endopeptide Activity in Children with Autistic Spectrum Disorders

Version: 3  Date: 24 October 2004

Reviewer: Lonnie Zwaigenbaum

Reviewer's report:

General
The authors argue convincingly that Prolyl Endopeptidase (PEP) are of interest in the study of autism, given that altered PEP activity is associated with other neuropsychiatric disorders, and PEP is involved in the metabolism of proteins (particularly oxytocin and AVP) that may play an important role in the autism phenotype. However, there are a number of concerns with the study methodology and interpretation of data.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. No hypothesis is stated, and cited literature on PEP in other disorders suggests the primary hypothesis would be that the mean PEP would differ between children with ASD and controls. It would seem, therefore, that this paper is presenting a secondary finding (that the variance in PEP is higher, even though the means are roughly equal). This needs to be presented in a more straightforward fashion, and the authors must consider factors that might have led to increased variability (including measurement error - see below)

2. Details regarding sample selection are needed. How were children with ASD recruited and selected? What medical treatment (under general anaesthesia) were these children receiving? What were the procedures for confirming the diagnosis - ie, what is meant by 'diagnosed with DSM-IV criteria'? The controls are not matched by age or gender - how were the controls selected?

3. Potential measurement issues. The reliability and validity of the procedures needs to be described - few readers will have access to reference [15 - Scand J Clin Lab Invest]. Is it possible that the GA or the treatment the ASD children received might have altered measurement of PEP? Is it known whether there are gender differences in children's PEP?

4. The Discussion doesn't really give a plausible explanation for how increased variability in PEP might be involved in the development of ASD - what would be the biological effect of extreme values (both high and low)?

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Page 4, The last sentence of first paragraph should be referenced to [16], not [4].

Page 4, paragraph 2. Several of these examples, while findings in autism, are not 'disorders' e.g., hyperserotoninemia, increased level of opiod, increased AVP

Page 7, Statistical analysis - should list all the analyses that were done, not just the analysis that is reported.

Page 8, line 2 - it appears that the SD values are reversed; ASD group should be higher.

Some discussion of methodological limitations and how these might be addressed in future work.

Discretionary Revisions (which the author can choose to ignore)

The authors could clarify what they mean on page 9 by: "We intend to perform further investigations regarding PEP activity in CSF and blood plasma in ASD children. It is essential to control for
subgroups within the ASD spectrum and we intend to do so using an index capturing differences on a perceptual level."

**Which journal?:** Not appropriate for BMC Medicine: an article of only archival interest, but might be suited to a subject-specific BMC journal

**What next?:** Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

**Quality of written English:** Acceptable

**Statistical review:** No

**Declaration of competing interests:**

None