had greater axial lengths than their normal fellow eyes (range 0.1–11.5 mm, mean 2.48 mm).[6] Interestingly, the patient with an injured eye 11.5 mm longer than the normal fellow eye had suffered the injury at age 3 years.

The authors believe that the reported case appears to be the first reported case of severe macrophthalmos following trauma in a juvenile. This could be due to gradual stretching of a biomechanically weakened sclera from previous trauma in response to raised intraocular pressure and extraocular muscle tension. This case suggests that since the dynamic process of emmetropisation continues after the age of 7 years, the axial length might remain malleable, if this process is interrupted by trauma and visual impairment.

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Sir,

Glutamate excitotoxicity in glaucoma: throwing the baby out with the bathwater?

The recently published study by Kwon *et al* provides some interesting and valuable data concerning the possible role of glutamate in neuronal cell death in glaucoma.[1] As pointed out in the accompanying editorial, this is a field of study that has been bedevilled by conflicting results and even scientific fraud.[2] The editorial[2] is right to draw attention to these matters and to state that 'it is important to re-evaluate the evidence for and against glutamate being causal in the development of glaucoma.' Additionally, the editorial goes on to imply that there is thus no role for glutamate and its receptors (particularly NMDA receptors) in glaucomatous neuronal death. However, it may be wise to urge caution in the interpretation of these new data, as the lack of vitreal glutamate elevation does not necessarily mean that there is no role for glutamate and its receptors in glaucoma. Indeed, Kwon *et al*[1] clearly discuss some of the relevant issues. Although an elevation of vitreal glutamate *might* be expected in glaucoma models, there is no *a priori* reason for assuming that this must be so, and indeed it may be that such an increase is not as central to the disease as implied in the editorial:[2] there is a danger here of throwing the baby out with the bathwater.

It is well known that glutamate is an amino acid that is abundant in all cells and that it is intimately involved in many metabolic processes, with only a relatively small proportion being involved in neurotransmission and the activation of the receptors involved in this.[3] This compartmentalisation of glutamate, maintained by active transport processes, makes it difficult to measure changes in tissue levels of glutamate related to activation of glutamate receptors unless relatively noninvasive sampling techniques with good temporal resolution are applied close to the source of glutamate (eg micro-dialysis or push–pull perfusion). Thus, sampling of retinal tissue post-mortem or sampling of vitreal glutamate, as performed by Kwon *et al*,[1] might not yield information directly relevant to the activation of glutamate receptors on threatened neurones.

A second issue is the nature of the NMDA receptor (the glutamate receptor that is thought to be involved in the neurodegenerative aspects of glutamate pathophysiology) itself. A feature of the NMDA receptor is that its ion channel is largely blocked by magnesium ions when cell membranes are maintained at a healthy resting membrane potential.[4] If tissue is compromised (eg injury or anoxia), then the membrane potential will depolarise and this will then relieve the magnesium ion block of the NMDA receptors: the consequence of this is that even relatively 'normal' levels of glutamate will have a much greater effect and there will be a substantial inward current into cells carried by sodium and calcium ions. Thus, large increases in glutamate levels may not be

necessary in order to have sustained enhanced activation of NMDA receptors leading to the start of neurodegenerative processes.

Therefore, looking for increases in vitreal or retinal glutamate levels in glaucoma or glaucoma models may not be the correct question. What will be more telling and significant is to see whether antagonists of NMDA receptors are effective treatments in such conditions. Experimental work shows some promise in this regard,[5] and the forthcoming clinical trials data with memantine will be of great significance here.

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Sir,

Reply to: Glutamate excitotoxicity in glaucoma: throwing the baby out with the bathwater?

We appreciate the opportunity to respond to the letter by Salt and Cordeiro. We agree that there are less invasive means of continuously measuring the vitreous glutamate level in an experimental model of retinal ischaemia (eg, microdialysis). As discussed in our report,[1] several studies have used such technique to measure the vitreous glutamate level in various animal models of ocular ischaemia. Briefly, one study found gradual elevation of vitreous glutamate following ocular ischaemia to the peak of 6.7 times the preischaemia level in the cat.[2] Another study found only transient elevation of vitreous glutamate up to seven times the preischaemia level in the rabbit.[3] However, a third study failed to show any increase in the vitreous glutamate in a rabbit ocular ischaemia model.[4] Another study not cited in our report monitored retinal glutamate levels continuously in real time using a dialysis electrode in a rat model of ocular ischaemia, and also failed to find glutamate elevation.[5] In fact, the retinal glutamate level decreased during ischaemia, which is consistent with our results (see Table 1[1]). Interestingly, in the same experiment, the authors induced brain ischaemia simultaneously and measured almost five-fold elevation in the brain glutamate level.[5] The authors concluded that slower depletion of ATP in the retina compared to the brain allowed the retina to maintain the physiologic glutamate level and a longer tolerance to ischaemia.

How do we reconcile these disparate results? We have outlined some of the possible reasons in the report.[1] One plausible explanation lies in the ability of the retinal cells' reuptake of released glutamate through glutamate transporter. If there is sufficient reuptake into the neurons and glia during ischaemia, one may not observe elevated glutamate levels. On the other hand, if the ischaemia overwhelms the reuptake mechanism through ATP depletion and depolarization, one may see a rise in glutamate levels. In our primate model of central retinal artery occlusion, ischaemia affects only the inner retina and spares the outer retina and choroid. Such partial retinal ischaemia may allow sufficient reuptake of glutamate through intact functioning of glutamate transporter system in the retina. Indeed, there is evidence that retinal glutamate transporter activity can persist in mild ischaemic conditions *in vitro*.[6]

In our report, we limited the scope of discussion to glutamate excitotoxicity and acute retinal ischaemia. The accompanying editorial by Lotery[7] and the letter by Salt and Cordeiro extend the discussion into glutamate excitotoxicity and *glaucoma*. Unlike the large body of literature supporting the role of glutamate excitotoxicity in acute ischaemia, the role of glutamate excitotoxicity in glaucoma was based on a handful of reports that showed elevation of vitreous glutamate levels in human and animal models of glaucoma.[8,9]