Matters arising

Arginase deficiency and phenylketonuria

Hyland et al. report clinical similarities between arginase deficiency and phenylalanine hydroxylase deficiency, two inborn errors causing progressive neurological damage. The similarity in the changes of homovanillic acid (HVA) and 5-hydroxyindoleacetic acid (5HIAA) levels in cerebrospinal fluid and plasma of the deficient patient reported was striking.

We have measured the dihydropteridine reductase (DHPR) activity in rats loaded with phenylalanine and rats loaded with arginine. Inborn DHPR deficiency is responsible for the "atypical" phenylketonuria (PKU) which unlike its classical variant is not controllable by strict dietary regimes. The effect on the brain and blood DHPR activity of loading phenylalanine or arginine was in both cases a similar dramatic reduction.

Brain tyrosine can be synthesised from phenylalanine by tyrosine hydroxylase. Lowered brain tyrosine of untreated PKU is therefore not explicable by amino acid competition for brain entry. We suggest that the action of hyperargininaemia and hyperphenylalaninaemia on catecholamine and serotonin metabolism may be indirectly reduced in DHPR activity.

References


CSF and plasma levels of pro-opiomelanocortin-related peptides

Sir: Of great interest was the report by Nappi et al demonstrating increases in CSF beta-endorphin levels in patients with ischaemic attacks and strokes. The authors suggested that the increase of beta-endorphins was possibly related to augmentation of 5-HT release or to the unknown phenomenology of diachisis or in some more direct way to hypoxia, acidosis or hypercapnia. We believe that whatever the mechanism of beta-endorphin release, their actions in this setting serve primarily the protection of neurons at risk from hypoxic or ischaemic demeise. Although it has been suggested, that administration of naloxone may be beneficial in improving stroke outcome, this may as we have recently proposed, actually be detrimental to survival of neurons at risk due to metabolic stressors. Indeed, Claperson et al have shown an apparent deleterious effect of naloxone on rat brain hypoxic insults, and Cutler et al have reported worsening of neurological defects following administration of naloxone in humans with stroke.

The effects of opioids on neuronal function include reduction in voltage-dependent calcium transport, increase potassium conductance and presynaptic inhibition of neurotransmitter release. Thus they diminish electrophysiological (neuronal and synaptic) activity and may also depress neuronal metabolism by inhibiting cyclic AMP directly, and indirectly through inhibition of noradrenergic locus coeruleus mechanisms. Thus the net result of opioid action would be expected to reduce neuronal metabolic demand. Indeed, opiates are known to reduce CMRO2 by 85% with a lesser reduction of CBF. In addition, areas rich in opioid receptors have been shown to have their oxygen consumption specifically decreased by low-dose morphine. Thus it is quite conceivable that the dramatic increases in the release of beta-endorphins during ischaemic act to modulate neuronal activity and oxygen consumption. This may possibly represent an extension of a physiological modulatory role of the intrinsic opioids during periods of metabolic stress.

References