The Potential Use of Insulin-like Growth Factor I (IGF-I) as a Neuronal Rescue Therapy

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Asphyxial or ischemic insults to the brain lead to neuronal loss in two phases—one associated with the insult and a second phase which is delayed for some hours after the injury, termed delayed neuronal death (DND). Recent evidence suggests that provided the initial insult is not excessively prolonged, DND is a major component. The mechanisms of DND are incompletely resolved but include apoptosis. Because of the delay in the onset of DND (generally to 8–72 hours after an insult) there is a window of opportunity in which it may be possible to block the processes initiated by asphyxia that lead eventually to DND. Using a standardised model of hypoxic ischemic injury (HII) in the 21 day rat we have shown using *in situ* hybridisation that insulin-like growth factor I (IGF-I) IGFBP-2 and IGFBP-3 are induced in regions of neuronal loss within 1 to 3 days of injury; induction is seen both in areas of infarction and of selected neuronal loss. In contrast IGF-II is not induced until 7 days after injury and is restricted to the area of infarction. We therefore examined, in the adult rat with unilateral fill, the effect of IGF-I administration via the lateral cerebral ventricle. IGF-I given prior to the insult had no effect. However IGF-I (5 to 50 μ g) given as a single injection 2 hours after the injury markedly reduced ($P < 0.05$) the incidence of infarction and the degree of neuronal loss throughout the injured hemisphere. The histological improvement was associated with improved functional outcome as measured by bilateral tactile responses. Co-administration of IGF-II blocked the effect of IGF-I suggesting that IGF-I was attracted to the region of injury by IGF binding proteins and that this is blocked by saturation with IGF-II. Similarly des-IGF-I was not effective at equimolar doses to IGF-I, perhaps reflecting reduced association with IGFBPs. Alternatively, or in addition, IGF-I may act in part by being the precursor for the N terminal tripeptide, GPE which has some neuroactivity. We examined the effect of GPE (3 μ g) administered similarly 2 hours after HII and found significant ($P < 0.05$) neuroprotection extending throughout the injured hemisphere. The mode of action of GPE is not clear as the effect is not mimicked by MK801, a NMDA receptor antagonist. However it seems unlikely that the entire effect of IGF-I is to act as a precursor for GPE given the induction of IGF receptors after injury and the neuroprotective effect of high doses of insulin. We have further examined the neuronal rescue action of IGF-I in fetal sheep subject to reversible cerebral ischemic injury. A single dose of 100 ng ($n=6$) or 1 μ g ($n=7$) given 2 hours after injury conferred marked neural protection ($P < 0.05$). Thus in two species with markedly different models of brain injury IGF-I is neuroprotective when given after the injury. We speculate that IGF-I acts to interfere with processes leading to the induction of apoptosis. These studies suggest the possibility of the therapeutic use of IGF-I as a neuronal rescue therapy.