COMMENTARY

Growth hormone and memory

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Abstract

Growth hormone (GH) replacement unequivocally benefits growth, body composition, cardiovascular risk factors and quality of life. Less is known about the effects of GH on learning and memory. The recent paper on ‘early onset – GH deficiency (GHD) results in spatial memory impairment in mid life – and is prevented by GH supplementation’ by Nieves-Martinez importantly adds to this literature. Other data suggest that GH beneficially affects cognitive function in rats. In man, treatment of GHD has been associated with improvements in measures of memory and attention. There are also differences in verbal memory of patients with

childhood onset GHD. Further questions remain, and the beneficial effects or otherwise of treating GHD in different age groups remain to be better defined. Certainly for reasons of maturation of neural connections and their development to young adulthood contemporaneous with rises in GH and IGF1 make these important areas for further study in man. Lastly because of what we already know in terms of cognitive effects of GHD, it is important to replace GH when studying other potential causes of adverse effects on cognition, for example, with radiotherapy.

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Introduction

Much has been written about the effects of growth hormone (GH) replacement therapy in GH-deficient human subjects on growth, body composition, cardiovascular risk factors, bone and muscle development and quality of life. When properly administered and monitored, the effects of GH on all of these parameters are positive. The effects of GH replacement therapy on various aspects of learning and memory have received less attention but are clearly of the utmost importance. The recent paper by Nieves-Martinez *et al.* (2010) nicely addresses this problem in rats and has important implications for humans.

Rats, which are homozygous for the Dw-4 mutation (‘dwarf’), do not exhibit the normal increase in GH at 4 weeks of age, during a time at which, in rats, GH levels normally rise. In this paper, this model was used to mimic early onset or childhood GH deficiency (GHD). There were four groups that were compared as follows: i) Untreated Dw-4 mutation rats (early onset GHD), ii) rats treated from 4 to 14 weeks (replete in childhood but deficient in adults (adult onset GHD)), iii) rats treated from 4 weeks and thereafter (GH replete) and

iv) rats heterozygous for the mutation (controls). Using a water maze test to assess spatial learning ability at 8 and 18 months, it was shown that the early onset GH-deficient group had poor spatial learning compared to the other groups. The suggestion is made that GHD during adolescence has negative effects on learning and memory, and that this effect can be reversed in rats by GH supplementation.

What is known already and how can this be applied to humans?

Kwak *et al.* (2009) have shown that in hypophysectomised female Sprague-Dawley rats given GH, not only was somatic growth enhanced, as predicted, but that cognitive function as assessed by the Morris water maze test was significantly better in the GH-treated animals, suggesting that GH improved the acquisition of spatial memory. GH has also been shown to accelerate recovery of motor function and improve spatial memory in the same water maze test when given to a group of rats in which stroke induction had been carried out (Pathipati *et al.* 2009).

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In humans, there are clear deficiencies in cognitive functions in GHD patients (Van Dam & Aleman 2004, Maruff & Falletti 2005). Thus, impaired hippocampal/medial temporal function has been shown in adulthood of patients with childhood onset GHD (Van Dam *et al.* 2005). This disturbance is also greater in childhood onset GHD than adult onset GHD. In younger patients with GHD, GH treatment has been associated with improvements in measures of memory and attention. Factors associated with an improvement depend on the extent of cognitive impairment at baseline, the dose of GH administered and to some extent the age at onset of GHD (Burman & Deijen 1998). There are differences in verbal memory of patients with childhood onset GHD when compared with age-matched controls (Van Dam & Aleman 2004). Whether this, as opposed to somatic development, is benefited by GH replacement in humans is unclear. Certainly, there is continued maturation of fronto-temporal connections in the second and third decades of life (Lebel *et al.* 2008).

We have looked at the effects of GH on cognitive function in elderly patients with adult onset GHD and, using a battery of psychometric measures, we assessed cognition and mood (Sathiaivegeswaran *et al.* 2007). There were improvements at 6 months from baseline in the GH-treated group for the digit-learning test. There were also small improvements in cognition, but these differences between GH and the control groups were in part due to a decline in performance in the placebo group, as well as improvement in the GH-treated group. At the 12-month assessment, no significant benefits of GH were found. This may relate in part to the small sample size (34 patients).

The brain in man continues to mature and develop in young adulthood. There is evidence of maturation of neural connections (e.g. fronto-temporal; Rice & Barone 2000) in the second and third decades of life; GH and insulin-like growth factor 1 levels normally rise to a peak at around the period of late adolescence. Whether these are related remains unanswered, but the current study certainly suggests the possibility of an important interaction.

Further work clearly needs to be done, particularly in man. Adequate numbers of patients need to be studied, and there are problems with complicating factors such as past radiotherapy which may itself have adverse effects on cognitive function which are not currently clearly delineated (Tooze *et al.* 2009). Thus, any studies on radiotherapy effects on cognitive function need to correct for GHD.

The suggestion that there is an important period of childhood during which, if GHD occurs, there is a significant defect in cognitive development which may be reversible with GH therapy is important. Long-term effects on memory should therefore be added to the list of benefits of childhood GH treatment, as this may be used as an incentive for compliance.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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