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Gene Expression Related to Cognitive Function in Growth Hormone-treated Mice with Prader-Willi Syndrome

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Prader-Willi syndrome (PWS) is a rare genetic disorder often caused by a deletion of the chromosome 15q11-q13 region inherited from the father or by maternal disomy 15. Growth hormone deficiency with short stature, hypogonadism, cognitive and behavioral problems, analgesia, decreased gastric motility and decreased ability to vomit with hyperphagia are common in PWS leading to severe obesity in early childhood, if not controlled. The goal of this study is to investigate the effects of recombinant human GH (rhGH, henceforth designated GH) on the gene expression related to cognitive function in the brain of PWS mouse model (*Snord116*del). GH restored the mRNA expression level of several genes in the cerebellum. These data suggest the effect of GH on the expression of cognitive function related genes in cerebellum may provide a mechanism for the GH-induced brain function in PWS patients.

Keywords: Prader-Willi syndrome, Snord116del mice, Cognitive function, Growth hormone

Introduction

Prader-Willi syndrome (PWS) is a rare genetic disorder often caused by a deletion of the chromosome 15q11-q13 region inherited from the father or by maternal disomy 15[1]. PWS is characterized by a dysregulation of growth hormone (GH)/insulin-like growth factor I axis, as the consequence of a complex hypothalamic involvement[2]. GH therapy is able to ameliorate the phenotypic appearance of the syndrome, as well as to improve body composition, physical strength, and cognitive level[3,4]. However, the physiological and molecular mechanisms underlying the improvements in cognitive function after GH treatment still remains unclear in PWS. GH/insulin-like growth factor (IGF)-1 axis is important for the growth, development and function of the central nervous system (CNS)[5]. Another mediator of GH effects, IGF-2, has been proposed as a novel cognitive enhancer[6]. The presence of binding sites for GH and IGF-1 in the brain has been suggested that GH crosses the blood-brain barrier[7,8], although the mechanisms behind the actions of GH on brain function remain unclear. Gamma-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the CNS, acts via $GABA_A$ and $GABA_B$ receptors. The functional $GABA_B$ receptors consist of two subunits, $GABA_{BR1}$ and $GABA_{BR2}$[9], which are responsible for the neuromodulatory effect of GABA[10,11]. Recently, exogenous GH has been reported to increase the abundance of the $GABA_B$ receptor in the area of the rat brain[12] and $GABA_{BR1}$ gene expression in hypophysectomised rat[13]. These findings suggest the possible correlation between GH-induced cognitive function and the GABAB receptor. Since GH is an important regulator of developmental and cognitive functions in the CNS, we investigated the effects of GH on the expressions of $GABA_B$ receptor subunits as well as the GH/IGF axis gene in specific brain regions known to be affected by GH treatment[14,15] in *Snord116del* mice.

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1. *Snord116del* mice exhibited PWS symptoms

Compared to the WT mice, the *Snord116*del mice with GHD exhibited reduced body weight. And also the expression of six genes related to cognitive function (*Gabbr1*, *Gabbr2*, *Igf-1*, *Igf-1r*, *Igf-2* and *Igf-2r*) in the brain was compared between WT and Snord116del mice. In the cerebellum, Gabbr1 mRNA was significantly reduced in PWS mice. There was also a significant difference between two genotypes regarding the *Igf-1r*, *Igf-2* and *Igf-2r* expression in the cerebellum. These data demonstrated that in comparison to WT, both the expression of $GABA_{BR1}$ and IGF-1R transcripts are markedly decreased in the cerebellum of *Snord-116*del mice.

2. Growth hormone (GH) treatment altered the expression of $GABA_B$ receptor subunit and GH/IGF-1 axis genes in PWS mice

Reduced body weight in *Snord116del* mice with GHD was significantly rescued after GH treatment. This indicates that the administered GH was physiologically active and had an expected systemic effect on body growth. In the cerebellum, there were significant differences between the treatment groups regarding the mRNA expression of *Gabbr1* ($P<0.05$) where both the PWS+ GH and WT groups showed increased *Gabbr1* mRNA expression compared with the PWS group, but no effect on the *Gabbr2* expression was observed. The results from the gene expression analysis of *Igf-1*, *Igf-1r*, *Igf-2* and *Igf-2r* in the cerebellum were also shown after GH treatment. There was a significant difference between the treatment groups regarding the *Igf-1r*, *Igf-2* and *Igf-2r* expression in the cerebellum. Decreased *Igf-1r* mRNA was recovered after GH administration ($P<0.05$). In addition, the PWS + GH group had increased the *Igf-2* and *Igf-2r* expression ($P<0.05$).

By comparing the expression of the gene transcripts for IGF-1R, IGF-2 and IGF-2R with those of the GABAB receptor subunits, a significant positive correlation was observed in cerebellum, between the level of IGF-1R mRNA and the level of the transcript for the *Gabbr1* ($r^2=0.62$, $P<0.05$).

These data demonstrated that both the expression of $GABA_{BR1}$ and IGF-1R transcripts are rescued in cerebellum of GH treated PWS mice. $GABA_B$ receptor has been shown to be important for neuronal excitability and plasticity and is suggested to be involved in the regulation of long term potentiation, which is the cellular mechanism for learning and memory. We also detected a significant positive correlation between the mRNA level of IGF-1R and $GABA_{BR1}$ in the cerebellum. This finding, indicative of an IGF-1R-mediated effect on the function of the $GABA_B$ receptor, is in agreement with a recent observation that the activation of the $GABA_B$ receptor induces IGF-1R transactivation leading to survival signaling in the cerebellum. Thus, several studies have suggested that the $GABA_B$ receptor protects the brain from ischemic damage and improves memory, providing evidence that stimulation of the $GABA_B$ receptor may be involved in a mechanism by which GH regulates brain function, including a cognitive and neuroprotective effect. Also our data suggest the possibility that IGF-2/IGF-2R signaling could have an important role in GH-induced cognitive function in *Snord116*del mice.

Conclusion

This is the first study to demonstrate that GH restores the gene expression of $GABA_{BR1}$ and IGF-1R and increases IGF-2 and IGF-2R in the cerebellum of *Snord116*del mice. The alterations of $GABA_{BR1}$ and IGF-1R observed in *Snord116*del mice could, at least partly, account for cognitive impairment. Because GHD during early life could impair proper brain development, thereby leading to cognitive deficits, it is suggested from the present study that a modulatory effect of GH on the expression of $GABA_{BR1}$ and GH/IGF-1 axis genes in brain may provide a mechanism for the GH-induced brain function in *Snord116*del mice, genetic models of PWS.

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