

A possible role of GDNF expression by which cabergoline use affects corpus callosum

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Abstract

A variety of malformations have been associated with cabergoline use during gestation. Recently we had a preterm male infant referred to our Neonatal Intensive Care Unit diagnosed with corpus callosum agenesis confirmed by brain ultrasound and brain magnetic resonance imaging. The mother was on medication with cabergoline, due to a pituitary prolactinoma, only for the first month of pregnancy. The exact possible mechanism by which cabergoline may have a negative effect on corpus callosum development is still unknown. Discovery of neurotrophic brain factors has opened a new chapter in the understanding of neurogenesis and synaptic plasticity mechanisms. To our knowledge, this is the first suggestion of a possible role of glial cell line-derived neurotrophic factor (GDNF) expression on corpus callosum agenesis after the administration of cabergoline in women during pregnancy.

Keywords

Corpus callosum, agenesis, cabergoline, GDNF.

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Introduction

The corpus callosum is the major interhemispheric fiber bundle in the brain, comprised of approximately 180 million axons, extending from the frontal lobe, anteriorly, to above the quadrigeminal plate, posteriorly. In humans, the

development of the corpus callosum begins by week 8 of fetal life and completes about weeks 12 to 13 of fetal life. By the end of the 20th week of gestation, the corpus callosum is well established, but with less myelination, reaching adult size by the age of 2 years. From anterior to posterior part, it comprises 4 parts (rostrum, genu, body and splenium) [1]. Given the complexity of corpus callosum formation, the causes of hypoplasia or agenesis can be multiple and are usually associated with other diverse defects [1].

A very recent study by Karaca et al. associated neural tubes defects and microcephaly with maternal cabergoline use [2]. A variety of malformations have been associated with cabergoline use during gestation. So, dopamine agonists are recommended to be discontinued after confirmation of pregnancy in women with diagnosed pituitary adenomas, unless there is an invasive prolactinoma at risk of tumor expansion.

Personal experience

Recently, we had a preterm (34 weeks of gestational age) male infant referred to our Neonatal Intensive Care Unit diagnosed with corpus callosum agenesis confirmed by brain ultrasound and brain magnetic resonance imaging. The infant was born weighing 1,590 g by cesarean section due to intrauterine growth restriction (IUGR). The mother was on medication with cabergoline, due to a pituitary prolactinoma, only for the first month of pregnancy.

Discussion

Cabergoline is a dopamine D₂ receptor agonist, which also possesses a significant affinity for the D₃, D₄, 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, α_2 B receptors, and moderate/low affinity for the D₁ and 5-HT₇ receptors. Cabergoline acts as an agonist at all of the above-mentioned receptors except for 5-HT₇ and α_2 B receptors, where it acts as an antagonist [3]. The exact possible mechanism by which cabergoline may have a negative effect on corpus callosum development is still unknown.

Cabergoline, in *in-vitro* rat studies, shows a direct inhibitory effect on the prolactin secretion in the pituitary's lactotroph cells and also decreases serum prolactin levels in reserpinized rats. Recent studies on rats found that cabergoline reduces voluntary alcohol consumption, possibly by increasing glial cell line-derived neurotrophic factor (GDNF) expression in the ventral tegmental area. Previous

studies showed that cabergoline treatment increases GDNF levels and secretion of GDNF in cultured astrocytes, while more recent data demonstrate that cabergoline up-regulates GDNF mRNA and protein levels in the dopaminergic-like SH-SY₅Y neuroblastoma cell line. In addition, activation of dopaminergic receptors by the nonselective agonist apomorphine or selective D₃R agonists was found to stimulate GDNF synthesis in mesencephalic neuronal cultures. Therefore, activation of the dopaminergic receptors might contribute to the up-regulation of GDNF levels by cabergoline [4, 5].

GDNF, discovered in 1991, is a protein encoded by the *GDNF* gene in humans and belongs to the family of transforming growth factors b (TGFb). GDNF has a biologically active pro-form (proGDNF), which is expressed in most parts of the brain and is found in astrocytes as well as in dopaminergic neurons (DANs). GDNF was originally isolated from glioma cell culture, and it was predominantly found in astrocytes, being the major producer of cells, while more recent data recognize GDNF as a necessary factor for the development, survival, protection and function of the nigrostriatal DANs [6]. GDNF was first characterized as a survival-promoting molecule for DANs. Afterward, other cells were also discovered to respond to GDNF not only as a survival factor but also as a protein supporting other cellular functions, such as proliferation, differentiation, maturation, neurite outgrowth and other phenomena. During development, GDNF favors the commitment of neural precursors towards dopaminergic, motor, enteric and adrenal neurons; in addition, it enhances the axonal growth of some of these neurons. GDNF also induces the acquisition of a dopaminergic phenotype by increasing the expression of tyrosine hydroxylase, Nurr1 and other proteins that confer this identity and promote further dendritic and electrical maturation. In motor neurons, GDNF not only promotes proliferation and maturation but also participates in regenerating damaged axons and modulates the neuromuscular junction at both presynaptic and postsynaptic levels [7]. In cell culture, GDNF increased the size of cell bodies and the number and length of 5-HT neuron axons. Moreover, GDNF increases the expression of the gene encoding 5-HT_{2A} receptors in the frontal cortex, but decreases it in the hippocampus.

GDNF mRNA is detected at week 7 of fetal life and reaches the highest level at week 9 of fetal life, before decreasing at week 10. In a recent study Ikeda et al. attested that GDNF is expressed in the

corpus callosum at early postnatal periods of high axon branching, but in this case the exact role of this trophic factor is unknown [8]. Some functions of downstream genes related to axonal growth and guidance have been identified following the activation of GDNF signaling and analysis of gene expression. GDNF down-regulates genes associated with cortical layer development, cytoskeletal reorganization and axonal stabilization, but up-regulates proteins related to the extracellular space and cell surface, axonal sprouting, neurite outgrowth and spine formation, which might contribute to the ability of axons to sense the extracellular environment and continue growing. GDNF participates in proliferation and the acquisition of a dopaminergic phenotype. The mechanism by which GDNF interacts with other factors to promote this phenotype is still a matter of study. In a very recent study conducted by Cortés et al. higher urinary levels of GDNF were found in neonates with lower than expected motor development [7]. However, when there is an insult of the CNS, an up-regulation of neurotrophic factors may occur acting as a repair mechanism [9].

Discovery of neurotrophic brain factors has opened a new chapter in the understanding of neurogenesis and synaptic plasticity mechanisms. To our knowledge, this is the first suggestion of a possible role of GDNF expression on corpus callosum agenesis after the administration of cabergoline in women during pregnancy. GDNF interacts with the 5-HT system of the brain through feedback mechanisms engaged in autoregulation of the complex involving 5-HT system and neurotrophic factors. So, excess concentration of 5-HT decreases GDNF expression, thereby weakening mesencephalic neuronal differentiation. There are insufficient data about positive or negative feedback mechanisms in the interaction of these systems. However, this complex functional relationship is undoubtedly a factor of neuroplasticity and a possible mechanism by which cabergoline may have a negative effect on corpus callosum development.

There are still studies demonstrating that cabergoline treatment at the time of conception appears to be safe for both the pregnancy and the neonate, as the frequency of spontaneous and induced abortions and major congenital malformations were found comparable with rates in the general population [10-13]. More data are still needed on a larger number of pregnancies because long-term effects of cabergoline on developing fetal brain are not well-known. Our aim was not to prove the safety

of cabergoline use during pregnancy, but to propose a possible mechanism on how cabergoline might affect corpus callosum malformations and lead to long-term neurological development of offspring whose mothers were treated.

Declaration of interest

Authors have no conflicts of interest and received no financial support for the research, authorship, and/or publication of this article.

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