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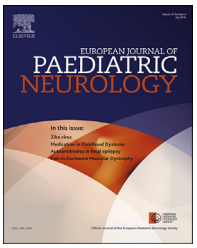

Review article

Treatment of autistic spectrum disorder with insulin-like growth factors

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ABSTRACT

There are no treatments for the core symptoms of autistic spectrum disorder (ASD), but there is now more knowledge on emerging mechanisms and on mechanism-based therapies. In autism there are altered synapses: genes affected are commonly related to synaptic and immune function.

Dysregulation of activity-dependent signaling networks may have a key role the etiology of autism. There is an over-activation of IGF-AKT-mTor in autism spectrum disorders. Morphological and electro-physiological defects of the cerebellum are linked to system-wide ASD-like behavior defects. The molecular basis for a cerebellar contribution has been demonstrated in a mouse model. These have led to a potential mechanism-based use of drug targets and mouse models. Neurotrophic factors are potential candidates for the treatment. Insulin-like growth factor-1 (IGF-1) is altered in autism. It reduces neuro-inflammation: by causing changes of cytokines such as IL-6 and microglial function. IGF-1 reduces the defects in the synapse. It alleviates NMDA-induced neurotoxicity via the IGF-AKT-mTor pathway in microglia.

IGF-1 may rescue function in Rett syndrome and ASD caused by changes of the *SCHANK3* gene. There are recently pilot studies of the treatment of Rett syndrome and of *SCHANK3* gene deficiency syndromes. The FDA has granted Orphan drug designations for Fragile X syndrome, *SCHANK3* gene deficiency syndrome and Rett syndrome.

Contents

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1. Introduction

There are no treatments for the core symptoms of autistic spectrum disorder, but there is now more knowledge on emerging mechanism-based therapies.[1,2]

Autism is a heterogeneous condition, both in its genotype and phenotype. There are hundreds of genetic variants involved in the causation of idiopathic autism. Monogenic diseases include Rett syndrome (RS), Fragile X syndrome, and *SHANK3* gene deficiency (Phelan-Mc Dermic syndrome).

Genes affected are commonly related to synaptic and immune function.[3]

Dysregulation of activity-dependent signaling networks may have a key role in the etiology of ASD.[4]

Diseases and conditions caused by different mechanisms often result in the same pathology at the cellular and molecular levels. Common pathological processes in central nervous system (CNS) disorders involve (1). inflammation of the brain, (2). abnormal microglial function, (3). synaptic dysfunction, and (4). reduced levels of IGF-1. Such disorders are (a) acute brain injury and neurological sequelae, (b) neurological (neurodevelopmental) disorders, and (c) neurodegenerative disorders. Now there are available mechanism-based therapies, for use not only in animals but also in humans, for autism-spectrum disorders which result in improvements in a wide range of symptoms such as memory, anxiety, hyperactivity, seizures and social behavior.

2. Insulin-like growth factor-1 (IGF-1)

IGF-1 is naturally occurring protein containing 70 amino acids. It is important for brain growth. In animals brain growth is extremely sensitive to IGF-1 levels. Insulin-like growth factors and growth hormone (GH) have neuro-protective effects.

IGF-1 and IGF-2 are members of the insulin-gene family that stimulate cellular proliferation and differentiation during embryonic and postnatal development. IGF-1 and IGF-2 are bound to six different binding proteins. These binding proteins are thought to have a role in the modulation of IGF action and targeting of IGFs to certain tissues.[5,6] Both IGF-1 and IGF-2 exert their mitogen effects via the membrane-bound tyrosine kinase IGF-1 receptor.[5,6] IGF-1 and IGF-2 are widely expressed in the central nervous system. However, in contrast to IGF-1, IGF-2 is most highly expressed in non-neuronal tissues of the nervous system: in the choroid plexus, leptomeninges, microvasculature, myelin sheaths and cerebrospinal fluid (CSF).[7,8] The highest expression of IGF-2 is during the fetal and early postnatal development of the human brain. In contrast, IGF-1 mRNA is widely expressed in fetal brain tissue, with more discrete expression postnatally in sites showing ongoing growth and differentiation.

2.1. *Growth hormone (GH)/IGF-1 axis*

GH/IGF-1 axis involves hypophysiotropic hormones controlling pituitary GH release, IGF-1 production in the liver and elsewhere, and tissue responsiveness to GH and IGF-1 release. GH and its receptors are expressed widely in the brain, especially in the hippocampus and frontal cortex which mediate memory and cognitive function.[8] After birth, IGF-1 concentrations rise in response to GH and increase steadily throughout childhood.

An important function of growth hormone (GH) is to promote cell and tissue growth, and a key component of these effects is the stimulation of protein synthesis. GH activates protein synthesis through signaling via the mammalian target of rapamycin (mTOR) and specifically through the rapamycin-sensitive mTOR complex 1 (mTORC1).[9]

GH and particularly IGF-1 have been attributed neuroprotective effects in different in vitro and in vivo experimental

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