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Insulin-like Growth Factor 1 for Healthy Spines and Healthy Minds?

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Spines, as dendritic protrusions, harbor most synaptic contacts and, accordingly, serve as critical indicators of neuronal health and function. Pyramidal neurons comprise the major neuronal constituent and output relay of the cerebral cortex and undergo the process of spine remodeling, with the generation of new spines counterbalanced by an equally dynamic process of spine elimination. This ongoing interplay of spine proliferation, growth, and retraction enables cortical neurons to continually adapt their dendritic spine landscape and synaptic connectivity in response to a myriad of internal and external stimuli, thereby providing a basis for the lifelong process of neuronal plasticity and learning. Unsurprisingly then, alterations in the spine densities and structural characteristics of cortical pyramidal neurons have been reported for a wide range of conditions, from rare monogenic neurodevelopmental syndromes to common psychiatric diseases, including schizophrenia and bipolar disorder (1). Given the central importance of spines in cortical connectivity, cognition, and complex behaviors, a deeper understanding of underlying molecular and cellular mechanisms is a prerequisite to exploring novel treatments for such types of spine disorders.

In this issue of *Biological Psychiatry*, Della Sala *et al.* (2) draw a new link between the cyclin-dependent kinase-like 5 (*Cdkl5*, also known as *Stk9*) gene and overexcessive spine elimination in pyramidal neurons. The findings are important, because mutations in the X-linked *CDKL5* gene [*Online Mendelian Inheritance in Man* (OMIM) entry *300203] have been linked to intellectual disability, autism, seizures, and hypotonia and are referred to in the literature as “atypical Rett syndrome”; this is in contrast to classic Rett syndrome, which is associated with mutations in the chromatin regulator methyl-CpG-binding protein 2, *MECP2* (OMIM entry *300005). Earlier work had already implicated the dendritically enriched CDKL5 protein in stabilizing excitatory synapses, via phosphorylation of postsynaptic density proteins such as the netrin-G1 receptor LGL-1 (3). The study of Della Sala *et al.* (2) extends these previous studies. For example, they applied in vivo two-photon imaging, a powerful technique for monitoring the dynamics and morphologic plasticity of spines in specific areas of the brain. By longitudinally evaluating spines positioned on the apical dendrites of layer V pyramidal neurons over multiple days, the researchers were able

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to pinpoint excessive loss of young spines, rather than insufficient generation of new ones, as the underlying cause for the observed net loss of spine and excitatory synaptic densities in the *Cdkl5*-null mutant mice. These findings, in turn, form the morphologic basis for the observed defects in neurotransmission and impaired long-term potentiation in juvenile and adult *Cdkl5*-deficient cortex.

Next—in arguably the most interesting and effective portion of the study—the researchers treated juvenile and adult *Cdkl5*-null mutant mice systemically with a small protein, insulin-like growth factor 1 (IGF-1). Remarkably, both age groups of the mutant mice responded within days of IGF-1 initiation, resulting in a marked attenuation of the spine deficits in their cortical pyramidal neurons. Importantly, this treatment effect remained statistically significant even 3 weeks after administration of the last IGF-1 dose, suggesting that the net gain in spine numbers is not erased by the underlying disease process, at least within a certain window of time. Consistent with the positive effect of IGF-1 on spine numbers, levels of postsynaptic density protein 95 as a sensitive indicator for synaptic density were increased after treatment. One possible molecular mechanism mediating these therapeutic actions includes a specific, well-defined intracellular signaling cascade that starts with activation of the IGF-1 receptor and the phosphoactivation of the phosphatidylinositol 3-kinase/AKT/mammalian target of rapamycin/S6 pathway, ultimately resulting in the phosphorylation of the S6 ribosomal subunit and consequent upregulation of protein translation (4). Indeed, the phosphorylation of select serine residues of the S6 ribosomal protein was abnormally low at baseline in the *Cdkl5*-null mutant mice, and this deficit was fully rescued by IGF-1 treatment in the Della Sala *et al.* (2) study (Figure 1). Therefore, it is possible that a regulatory deficit in protein translation, causing an abnormal loss of young spines, is at the core of the neuronal disease and defective connectivity affecting the *Cdkl5*-null brain.

Importantly, the therapeutic effects of IGF-1 on the spine deficits in *Cdkl5*-deficient cortical neurons were apparent, despite the fact that IGF-1 protein levels were indistinguishable between mutant and wild-type cerebral cortex. Thus, the researchers rightly concluded that IGF-1's spine promoting effects cannot simply be interpreted as the restoration of a preexisting deficit in IGF-1 protein levels. Therefore, it is possible that systemic IGF-1 could exert therapeutic actions in a wide range of spine disorders, beyond those that are caused by rare mutations in *CDKL5* and *MECP2* (atypical and typical Rett syndrome genes), to include common psychiatric diseases such as schizophrenia and depression.

Consistent with this claim, systemic IGF-1 treatment exerts beneficial effects in several types of monogenic neurodevelopmental disease. For example, peripheral administration of IGF-1 prolongs the life span and improves autonomic function, cognition, and complex behaviors in juvenile and adult *Mecp2*-null mice modeling Rett syndrome (5). Furthermore, in cultured cells from patients with 22q13.3 (Phelan-McDermid) deletion—a neurodevelopmental syndrome often encompassing the *SHANK3* gene with a clinical phenotype different from typical or atypical Rett syndrome—application of IGF-1 robustly ameliorated the deficits in glutamatergic neurotransmission and spine disease (6). Note that, according to Della Sala *et al.* (2) and Castro *et al.* (5), systemically applied full-length IGF-1 (a 70-amino acid protein) produces significant phenotypic effects in the brain with respect to

synaptic function and spine “homeostasis” and behavior. However, it is quite surprising that neither of these aforementioned studies quantitatively or qualitatively tested whether the systemically delivered IGF-1 protein ultimately reached brain tissue. This is obviously a key question, given that the extent of penetration of IGF-1 across the blood-brain barrier, and functional interrelations between serum IGF-1 levels and centrally produced IGF-1 are still actively being investigated (7,8). It should also be noted that the roles of key molecular regulators of IGF-1 signaling, including insulin growth factor binding proteins 1–5 and the heterodimerization of the IGF-1 receptor with related molecules from the insulin receptor family, remain to be explored in the context of brain disease and systemic treatment with IGF-1 (8).

Moreover, it has been shown that systemic administration of the IGF-1 N-terminal tripeptide glycine-proline-glutamate improves life span and autonomic and motor functions in *Mecp2*-null mutant mice (9), similar to the therapeutic effects of full-length IGF-1 (5). Given that the three-amino-acid conjugate Gly-Pro-Glu is naturally cleaved from IGF-1 in brain tissue and is thought to lack the signaling capacity of full-length IGF-1 (10), the specific mechanisms underlying its therapeutic actions are far from clear. We argue that future studies should directly compare the therapeutic effects of systemically administered IGF-1 and the Gly-Pro-Glu tripeptide. In sum, further preclinical exploration of the promising actions of IGF-1 and its N-terminal tripeptide on spine homeostasis and synaptic signaling (Figure 1) will undoubtedly offer immense opportunities to develop better treatment options for a wide range of psychiatric conditions associated with spine pathologies, from rare neurodevelopmental syndromes, including atypical and typical Rett syndromes and Phelan-McDermid syndrome, to common psychiatric disease, including depression and schizophrenia.

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Figure 1.

Potential mechanism of systemically injected insulin-like growth factor 1 (IGF-1) action on the central nervous system. Subcutaneous injections of IGF-1 may cross the blood-brain barrier, where it binds to the membrane-bound IGF-1 receptor to subsequently trigger the phosphatidylinositol 3-kinase/Akt/mammalian target of rapamycin/S6 cascade. The resulting increase in protein synthesis produces key synaptic players, such as postsynaptic density protein 95, that contribute to the stabilization of spines. This paradigm is in line with the observation by Della Sala *et al.* (2) that IGF-1 rescues excessive spine loss in cortical pyramidal neurons both of juvenile and adult *Cdk15*-null mice. Therapeutic effects have also been observed after systemic delivery of the IGF-1 N-terminal Gly-Pro-Glu tripeptide. Further mechanistic exploration will offer insight into IGF-1 treatment for psychiatric conditions associated with functional or structural spine deficits.