I have read with interest the article recently published in *CNS Spectrums* by Tayeb et al., in which they have given an overview of the available literature on the schizophrenia metabolome with the aim of "uncovering potential selective biomarkers for the disease that may change how the disorder is diagnosed, and how patients are stratified and treated." In the section entitled "Metabolomics and Schizophrenia Pharmacotherapy" of this article, it has been mentioned, while citing an article I have published in the journal *Medical Hypotheses* in 2011, that "subcutaneous administration of insulin-growth factor-1 (IGF-1) has been tried therapeutically in an attempt to increase the reported lower levels of IGF-1 in schizophrenia patients." However, the cited reference is a theoretical perspective through which arguments in favor of administering IGF-1 for patients with schizophrenia have been exposed. This hypothesis has been followed by another more recent development on the subject through which schizophrenia and autism spectrum disorder (ASD), 2 mental disorders that share many commonalities on the clinical and neurobiological levels, have been considered to potentially benefit from a treatment with IGF-1. Accordingly, it would be important to remind the readers of the rationale supporting the administration of IGF-1 in both disorders and the difficulties that such a treatment might face.

IGF-1 may reduce neuronal hyperexcitability seen in patients with schizophrenia and/or ASD. It is also an important regulator of oligodendrocytes function, which may compensate the myelination defect classically encountered in those patients. In addition, ASD and schizophrenia are both considered to be linked to de novo mutations in the 22q13, a gene coding for the SH3 and multiple ankyrin repeat domains 3 (SHANK3), that connects neurotransmitter receptors, ion channels, and other membrane proteins to the actin cytoskeleton and G-protein-coupled signaling pathways. IGF-1 has proved its efficacy in reversing the effects of SHANK3 deficiency whether in preclinical or clinical studies. Finally, neuro-inflammatory processes involved in the pathogenesis of schizophrenia and/or ASD may be improved with IGF-1 potentially due to its known modulatory role on the PI3-AKT-mTOR pathway.

IGF-1 is being considered as a therapeutic option for many neurodevelopmental disorders, such as Rett syndrome, fragile X syndrome, Phelan-McDermid syndrome, and ASD. Despite all evidence relating schizophrenia with other neurodevelopmental disorders, IGF-1 has not been considered for the treatment of schizophrenia patients yet. Patients treated with a long-term treatment of subcutaneous injections with human recombinant IGF-1 report hypoglycemia as one of the most frequent adverse drug reactions. Hair loss and its replacement with a thicker, curly hair reflect an accelerated hair turnover. Injection site lipohypertrophy has been frequently described. Tachycardia may develop due to the inotropic effects of IGF-1. Benign intracranial hypertension may develop, as well as parotid swelling and lymphoid tissue, tonsillar and adenoid hypertrophy. Weight gain, dyslipidemia, and an increased risk for the development of a metabolic syndrome have been noticed. Less frequent but serious adverse drug reaction such as coarsening of facial features and a potential mitogenic effect increasing the risk of cancer have also been described. Accordingly, the systemic administration of IGF-1 seems to impose several undesirable side effects, especially in the population of patients with schizophrenia and/or ASD who might receive the treatment on a daily basis for an unlimited duration. Local or paracrine/autocrine IGF-1 might be more interesting for future research in this domain, since local IGF-I may lead to brain overgrowth in the absence of elevated circulating IGF-1 levels. Astrocytes seem to be...
the IGF-1-secreting cells of the central nervous system. Accordingly, the administration of intranasal IGF-1 might be more interesting in patients with schizophrenia and/or ASD, since this treatment formulation may bypass the blood–brain barrier and become available more directly and rapidly to brain cells than the subcutaneous injections with the same agent.

In summary, while evidence supports the administration of IGF-1 to patients with schizophrenia and/or ASD, future studies would be more interested in trying intranasal IGF-1 rather than the subcutaneous injections of the same agent.

**REFERENCES:**