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EDITORIAL

Global Neurology

The Therapeutic Utility of L1-79

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Introduction

We believe we have found a novel mechanism for treating a variety of diseases including autism, diabetes, PTSD, and potentially others. It is predicated in an imbalance between catecholaminergic neural systems and those systems that oppose them.

In 2015 some colleagues and I pursued an idea that the symptoms of Autism Spectrum Disorder (ASD) might result from an imbalance in catecholaminergic neurotransmission. The core symptoms of ASD include difficulties in cognition and cognitive development, socialization and language expression, and ASD is associated with changes in regions of the CNS associated with these functions as well as non-core symptoms including anxiety and agitation [1-3]. Similarly, changes in the periphery associated with the autonomic nervous system (ANS) and cranial nerve functions seen in autism such as heart rate changes and arrythmias, "fight or flight" type responses, leaky gut, and other signs and symptoms associated with catecholamines have been reported. Dopamine (DA) is a key mediator in many of the CNS systems associated with ASD and alterations the genetics of DA are associated with ASD [3-11]. ASD patients' manifest changes in DA levels and the enzymes associated with DA metabolism [12-15]. These changes correlate with the alterations in executive functions seen in ASD [16]. So, for these and other reasons we chose to look at a novel method of manipulating catecholamines in autism.

We knew from the literature that high levels of both nerve growth factor (NGF) and brain derived nerve growth factor (BNGF) are associated with the synaptic release of catecholamines and are essential to the maintenance of the catecholaminergic synaptic architecture [17]. We hypothesized that if, for any reason, an imbalance occurred between catecholaminergic systems and those systems that oppose them, such as the cholinergic arm of the ANS, that an elevated release of growth factors commensurate with an elevated release in catecholamines might result in growth and budding of these synapses. Further, if this new architecture was supported tonically by elevated levels of catecholamines and growth factors the hypertrophy of catecholaminergic synapses would result in a chronic neurologic imbalance; not only in the ANS, but in the CNS, the gut and other sites that catecholamines mediate. We ruled out a post-synaptic mediation utilizing receptor blocking agents because these would not influence the pre-synaptic release of growth factors.

L-α-methylparatyrosine (metyrosine, L-AMPT) is approved for the inhibition of tyrosine hydroxylase, the rate limiting enzyme for the synthesis of catecholamines, and it inhibits synthesis, storage and release of these agents. Metyrosine is used in very high doses to eradicate, as much as possible, catecholamines in the adrenal medulla prior to surgery for pheochromocytoma, and as therapy for patients for whom surgery is not an option. It is indicated in doses of 1-4 g/d, which are quite high and associated with moderate-severe toxicity. It's half-life is reasonably short (~3.5 h) and is therefore given in divided doses. As it was our intent not to eradicate catecholaminergic transmission, but to bring it back into balance with opposing forces, it became apparent that the label regimen was not appropriate for our intended use. Upon further study we concluded that the racemate used in much lower doses might be efficacious as it is known that the L-amino acid transport mechanisms in the body will allow for a low level of D-amino acid carriage, and that the D form of the drug might competitively inhibit the utilization of the L form. We therefore hypothesized that a low dose of racemic AMPT (L1-79) might improve the therapeutic AUC and because intent was to only tweak the system to bring it back into balance, that a low dose of the racemate might be enough. We subsequently found the half-life of racemic AMPT is ~11.5 hours (Yamo Pharmaceuticals published data).

We treated 8 patients in a proof of concept open label study and saw dramatic improvements in the core symptoms of ASD in 7 of 8 patients. We observed adolescent boys kiss their parents for the first time, speech and attention improved in most patients, socialization improved significantly in some patients, as did expressive language. Changes were noted by parents, bus drivers, teachers, therapists and others. This work is currently in press [18]. A second prospectively randomized, placebo controlled, and double blinded study was conducted and is currently being analyzed. We are currently planning a large phase 2b study.

Subsequently, we have found reasons to apply this therapy to other indications. As with ASD, there is ample evidence of catecholaminergic mediation of virtually all the events that underlie energy metabolism and diabetes. These include; insulin synthesis and release from the pancreatic islets, mediation of insulin receptor sensitivity, uptake of various insulin mediating nutrients from the gut, synthesis storage and release of hematologic mediators of insulin release such as nutrients and local tissue mediators, modulation of endocrine influences on insulin release such as glucose like peptide 1, adiponectin, secretin and others, central nervous stimulation from the striatum and other sites that govern energy metabolism centrally, and so forth. Bile acids, which have effects on mediators of gene transcription underlying glucose and lipid homeostasis such as LXR, FXR, PPARα and PPARγ

have been found to be crucial mediators of energy metabolism and are regulated by catecholamines. It is interesting to note that bile acids are the predominant steroid in the brain; the organ with the highest glucose consumption [19-22]. In the few diabetic patients treated thus far, anecdotal reports of benefit are consistent with our hypothesis and we are preparing a clinical development program for L1-79 in diabetes.

PTSD is another indication in which benefit has been seen. This is a syndrome clearly associated with hyperarousal associated with a fight or flight responses associated with an overabundance of catecholamines and induced by stress. Preliminary insights into the use of racemic AMPT appear to show therapeutic utility in this indication also.

We believe that these results reveal the potential for self-perpetuating imbalance in catecholaminergic transmission may play a role in many different indications. This heretofore undescribed imbalance that can arise between catecholaminergic systems and those oppositional systems that are required to maintain homeostasis balance can have far reaching effects in many disease states as it has the potential to affect every tissue in the body at the highest levels of functional integration. Most importantly, we have found this system to be druggable and amenable to therapeutic intervention. Preliminary reports in a few widespread indications suggest this may become an important therapeutic mechanism.

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