Semax, an analogue of adrenocorticotropic (4–10), is a potential agent for the treatment of attention-deficit hyperactivity disorder and Rett syndrome

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Summary
Psychostimulants, such as methylphenidate, are currently the most common used drug therapy for children with attention-deficit hyperactivity disorder (ADHD). However, a number of patients with ADHD either fail to respond to these drugs or experience side effects that preclude their use. The heptapeptide Semax is an analogue of the N-terminal fragment (4–10) of adrenocorticotropic hormone, but is completely devoid of any hormonal activity. It has been found to stimulate memory and attention in rodents and humans after intranasal application. Evidence from animal studies revealed that Semax can augment the effects of psychostimulants on central dopamine release and also stimulates central brain-derived neurotrophic factor (BDNF) synthesis. In addition, Semax could improve selective attention and modulate brain development. Since ADHD is likely to be a neurodevelopmental disorder with disturbance in dopamine and BDNF function, it is proposed in this paper that Semax may have good therapeutic potential in ADHD. Furthermore, increased BDNF activity is found to improve Rett syndrome, a severe neurodevelopmental disorder which is, in the majority of cases, caused by mutations in the gene encoding methyl-CpG-binding protein 2 (MECP2). The potential therapeutic effect of Semax in Rett syndrome by increasing central BDNF activity may be of interest for further exploration in animal models of Rett syndrome.

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from animal, genetic, pharmacological and neuro-radiological studies has all suggested primary involvement of the dopaminergic system, particularly the dopamine transporter (DAT) [2]. For the past four decades, the main treatment for ADHD has been with psychostimulant drugs (e.g. methylphenidate and amphetamine), which are potent DAT inhibitors [3]. Up to three quarters of all children with ADHD respond well if two different stimulants (amphetamine and methylphenidate) are used, nonetheless a subset of ADHD patients will either fail to respond to these psychostimulants, or have side effects that preclude their use (e.g. severe loss of appetite, nausea, headache, marked insomnia) [4]. Thus the discovery of new agents using novel strategies may help to develop more effective and safer treatments for this disorder.

Semax, a heptapeptide (Met-Glu-His-Phe-Pro-Gly-Pro) and an analogue of the N-terminal fragment (4–10) of adrenocorticotropic hormone (ACTH), is completely devoid of any hormonal activity present in the full-length ACTH molecule. It is developed by the Institute of Molecular Genetics; Russian Academy of Sciences, Moscow, Russia, and has undergone all essential stages of development from fundamental investigations to practical application (For review see Semax International Website: http://www.semaxint.com/index.htm and Ref. [5]). Semax penetrates the brain after intranasal application and the Pro-gly-Pro fragment of Semax is responsible for its metabolic stability and the relatively long duration of effects [6]. Currently, Semax is used as a remedy for the treatment of cognitive disorders and ischemic stroke [5].

Given recent findings in animal as well as in human studies, I propose that Semax could be an effective therapeutic agent for ADHD. Several lines of evidence led to the formulation of this hypothesis and these are discussed below.

Firstly, Semax has been shown to stimulate the processes required for learning and memory formation in animals and is capable of stimulating operant memory and attention in humans [7,8], one of the key ADHD deficits.

Secondly, brain-derived neurotrophic factor (BDNF), a member of the neurotrophic factor family, has been suggested to play a role in the therapeutic process and hence pathogenesis of ADHD [9]. This hypothesis is further supported by recent genetic studies that associate BDNF genetic variation with ADHD susceptibility (e.g. Ref. [10]). Drawing on evidence from studies which show a drugs for ADHD are associated with increased central BDNF expression, BDNF knockout mice have hyperactivity, BDNF affects midbrain dopaminergic function, and the known close association between BDNF and DAT, it is further proposed that decreased central BDNF activity, particularly in the midbrain region, may play an important role in the pathogenesis ADHD [11]. Study of BDNF gene expression in primary cultures of glial cells isolated from the basal forebrain of newborn rats, demonstrated an eight-fold increased BDNF mRNA level following in vitro treatment with Semax [12]. Similarly, a recent study demonstrated that nasal application of Semax increased BDNF protein, both in the rat hippocampus and the basal forebrain [13]. From the above findings, it seems likely that Semax could have a therapeutic effect in ADHD by increasing central BDNF levels.

Thirdly, ADHD is a common childhood-onset neurodevelopmental disorder [14]. Studies in rats demonstrated that neonatal Semax administration during the first three weeks of life diminished anxiety and improved the learning ability of adult rats [15]. These data suggest that Semax may modulate brain development and so have a therapeutic effect for ADHD.

Finally, psychostimulant drugs, such as dextroamphetamine, are currently the most commonly used agents in the treatment of ADHD. The potential mechanism of action of psychostimulants involves the enhancement dopamine and norepinephrine release from the midbrain [16]. A recent animal study showed that Semax alone failed to alter tissue and extracellular concentrations of dopamine, however, Semax injected 20 min prior to dextroamphetamine administration dramatically increased the effects of the latter on extracellular dopamine levels [17]. These findings suggest Semax may improve the therapeutic effects of psychostimulants in ADHD, and thus could be employed as an effective supplement in ADHD treatment. This would mean that either a lower dose of psychostimulant could be used, or an enhanced therapeutic effect could be achieved at a given dose.

The above evidence suggests that Semax may have a useful therapeutic effect for ADHD, particularly by improving attention. The therapeutic mechanism may act by augmenting central dopamine release or increasing central BDNF levels. Furthermore, since Semax increases central BDNF [12,13], it may also have therapeutic potential in Rett syndrome (RTT) — a severe neurodevelopmental disorder — in the majority of cases caused by mutations in the gene encoding methyl-CpG-binding protein 2 (MECP2) [18]. A recent report demonstrated that deletion of BDNF function in Mecp2 mutants caused earlier onset/accelerated disease progression, whereas BDNF overexpression in the Mecp2 mutant brain led to later onset/slower disease progression [19]. This evidence
suggests that increasing BDNF expression/signaling in the brain could be a novel therapeutic strategy for this disease [19,20]. The potential therapeutic effect of Semax in RTT subjects could be easily tested in known RTT animal models, such as Mecpt2 KO mice before clinical application [21].

References


