Fasoracetam as a treatment for ADHD: A systematic review of available clinical data

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Abstract

Fasoracetam is a nootropic compound of the racetam class. It is a derivative of Piracetam, the first synthetically created nootropic. It has been suggested that Fasoracetam is potentially effective for the treatment of ADHD, as well as related learning difficulties and cognitive disorders. However, there are few meta-analyses examining this potential use of Fasoracetam; much of the "evidence" relies on inference from studies looking at Piracetam. Furthermore, as a relatively new racetam, there is very little available evidence on the long-term risks associated with Fasoracetam use. This article looks at the available clinical data on Fasoracetam to ascertain its safety and efficacy as a treatment for ADHD. Ultimately, Fasoracetam is unlikely to help 90% of ADHD sufferers, and its efficacy as a nootropic remains unproven.

Keywords: Fasoracetam, Piracetam, racetams, nootropics, ADHD

1. About Fasoracetam

Fasoracetam is a nootropic agent of the racetam class. Like all racetams, it is a derivative of Piracetam; the "mother" racetam and the first synthetically created nootropic. Fasoracetam is a relatively new racetam. The compound was discovered by pharmaceutical company Nippon Shinyaku; researchers took Fasoracetam through phase III clinical trials for vascular dementia, but it was found to be ineffective in the context of that condition and ultimately abandoned as a subject of clinical trials.

Due to its structural similarity to Piracetam, Aniracetam and Oxiracetam, it has been hypothesized that Fasoracetam must have similar mechanisms of action, and as such must have positive effects on memory, learning, and attentional performance.

2. Mechanisms and pharmacokinetics

Like all racetams, Fasoracetam is a glutamate receptor agonist. Specifically, Fasoracetam seems to be a powerful agonist of all three metabotropic glutamate receptors, or rather all three metabotropic glutmate receptor groups (mGluRs)[1]. The importance of mGlurRs in the regulation of cognitive performance cannot be overstated; these receptors are highly prevalent in the central and peripheral nervous systems, and they are implicated in the regulation of most executive cognitive functions, including focus, information processing, learning, memory function, and muscle tone. Activating glutamate receptors would also increase neural excitation, with glutamate the most abundant excitatory neurotransmitter in the human brain.

It has been posited that racetams have several other mechanisms of action, from increasing cerebral circulation to increasing acetylcholine availability by inhibiting reuptake. The evidence supporting these various hypotheses ranges from weak to practically non-existent. It is highly likely that all of the observed cognitive benefits of racetam use stem from their glutamate receptor agonism. However, in the case of Fasoracetam, there is good reason to believe that it acts as a sort of cholinergic. A 1999 study found that Fasoracetam

increased the release of acetylcholine in the cerebral cortex whereas other racetsm did not:

"Furthermore, effects of NS-105 on in vivo release of acetylcholine (ACh) in the cerebral cortex, high-affinity choline uptake (HACU) of the cerebral cortex in rats with lesion of NBM, HACU of the hippocampus in rats treated with pentobarbital and activity of choline acetyltransferase (ChAT) of the cerebral cortex in rats with lesion of NBM were examined. NS-105 showed antiamnestic actions in a variety of animal models of cholinergic dysfunction employed in this study. Aniracetam improved memory disruption caused by scopolamine, but bifemelane, idebenone, and indeloxazine did not. NS-105 (10 mg/kg) showed the increase of ACh release from the cerebral cortex and the enhancement of HACU both in the cerebral cortex and hippocampus".[2]

If Fasoracetam does indeed increase acetylcholine release in the cerebral cortex and hippocampus, then it should have some efficacy as a treatment for ADHD, as elevated acetylcholine levels is correlated with improved attentional performance and learning capacity.

3. Fasoracetam and ADHD

Since 2016, Fasoracetam has been studied as a potential treatment for ADHD. There is a great deal of interest in finding alternatives to the standard pharmacological ADHD treatments, such as Adderall and Vyvanse, as these are non-specific and typically cause a range of adverse effects[3].

To date, there is no clear evidence that it is effective at improving the symptoms of ADHD in most patients.

Most of the claims regarding Fasoracetam and ADHD are based on a 2018 study looking at Fasoracetam and its effects on adolescents with ADHD. In this study, researchers gave 30 adolescents up to 400mg of Fasoracetam for 5 weeks and found that it significantly improved their cognitive performance[4].

This has led many people to claim that fasoracetam is effective for the treatment of ADHD in adolescents generally. However, there are some serious limitations to the claims made by the researchers in the aforementioned study.

The participants in the cited study all had some gene mutation which impaired their mGluR receptor networks. While variants in genes governing mGluR density and activity are more common in people with ADHD than those without it, these mutations are far from the norm among people with ADHD; it is estimated that around 10% of patients suffering with ADHD have some kind of mutation in genes in the metabotropic glutaminergic network compared to 2% of the population at large.

Fasoracetam may therefore be highly effective at improving learning and attention in people with mGluR network gene mutations, but not in people with ADHD who do not have such mutations (i.e. 90% of ADHD sufferers).

3.1 Fasoracetam and focus

There is strong evidence that Fasoracetam acts as a potentiator of acetylcholine. In previously mentioned rodent studies, Fasoracetam clearly and significantly elevated acetylcholine release in the cerebral cortex and hippocampus; two extremely important regions of the brain for the regulating of executive cognitive functions and memory.

Increasing acetylcholine availability in the cerebral cortex would greatly improve behavioral control, decision-making, verbal fluency, and attention span.

Raising the availability of the neurotransmitter in the hippocampus is known to produce measurable improvements in both episodic and semantic memory function. Cholinergic neurons innervate the hippocampus, and impairment or atrophy of cholinergic receptors have been linked with age-related cognitive decline and memory loss[5][6].

While the only clinical trial showing Fasoracetam as having cholinergic effects was conducted on rodents, there is good reason to believe that these effects would be mirrored in humans. Firstly, the cholinergic systems of rats are very similar to the cholinergic systems of humans. But more importantly, other racetams have been found to increase acetylcholine release in the brain, and some have been said to increase acetylcholine receptor density on the neuronal membrane (Noopept is said to increase acetylcholine receptor density although it is not actually a racetam).

However, it remains the case that no clinical trial has ever observed significant improvements in cognitive performance, such as focus, concentration, or learning capacity, after Fasoracetam administration.

3.2 Fasoracetam and depression

One potential use of Fasoracetam with a great deal of potential is as an antidepressant. Rodent studies have found that Fasoracetam has powerful antidepressant properties stemming from novel effects on GABA receptors. As one study found:

"Biochemical data showed that repeated administration of NS-105 increased the number of GABA(B) receptors in rat cerebral cortex without affecting the binding properties of beta-adrenoceptors and 5-HT2 receptors. In contrast to other antidepressants, NS-105 did not inhibit monoamine uptake in vitro, nor did it change monoamine concentrations in brain tissues or extracellular fluids. These findings suggest that NS-105, which lacks an effect on monoaminergic systems, has potent antidepressant activity, which may involve up-regulation of GABA(B) receptors after repeated administration."[7]

What is most interesting about this observed effect of Fasoracetam consumption is that it seems to have no effect on monoamine neurotransmitter systems; this makes it a very promising substance for the treatment of depression in people who do not respond to monoamine neurotransmitter reuptake inhibitors.

Again though, much more work is needed here. Fasoracetam will need to be trialed on human subjects to determine its efficacy as an antidepressant. As it stands, the evidence is not there to support this use case.

4. Fasoracetam safety and contraindications

Generally speaking, Fasoracetam is thought to be safe for human consumption in dosages typical for drugs in the racetam class. None of the available clinical trials report severe side effects or a high rate of participant dropout due to adverse health effects. Racetams are, broadly speaking, well tolerated by most users, and they are not thought to pose any serious toxicity concerns.

5. Conclusion

Fasoracetam is a promising new drug of the racetam class; evidence suggests that it may be useful for the treatment of depression in patients unresponsive to traditional monoamine neurotransmitter modulators, or patients who cannot use SSRIs and antidepressants of that nature. It is also likely that, as a racetam, Fasoracetam positively affects various aspects of executive cognitive function.

However, in the context of ADHD and related attention and/or learning disorders, there is little evidence that Fasoracetam is an effective treatment. ADHD patients with specific mGluR gene mutations may benefit from Fasoracetam, but 90% of ADHD sufferers will be unresponsive. This compares poorly to existing treatments for ADHD which are broadly effective (if prone to causing side effects).

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None of the work presented here would exist without the tireless work of the nootropics community. Together, bio-hackers are paving the way toward better cognitive function. It is through their research and their experimentation that we yield improvements in focus, memory, and productivity.

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