Avipaxin and Modulation of the Immune System

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ABSTRACT

Avipaxin is a dietary supplement that contains huperzine A (HupA), L-alpha-glycerylphosphorylcholine (α-GPC), and acetyl-L-carnitine to support acetylcholine levels and function. HupA is a powerful central nervous system (CNS) acetylcholinesterase (AChE) inhibitor and has been proposed as a natural agent to promote healthy immune system function. α-GPC is a natural choline compound, and acetyl-L-carnitine acts as an acetyl donor to support the synthesis of acetylcholine. The immunomodulatory effects of Avipaxin may be mediated by support of acetylcholine levels and activity. Avipaxin appears to regulate systemic immune activation by supporting the cholinergic immune-regulating pathway to ultimately reestablish homeostasis following an immune challenge. The following overview will present research on the features of Avipaxin and the functional significance of muscarinic receptors, nicotinic receptors, the vagus nerve, and the splenic nerve. The mechanism for which Avipaxin promotes a healthy immune system is reviewed with focus on how a centrally acting agent can modulate peripheral immune system activity.

Avipaxin is a dietary supplement that contains huperzine A (HupA), L-alpha-glycerylphosphorylcholine (α-GPC), and acetyl-L-carnitine to support acetylcholine levels and activity. Increasing acetylcholine levels can be beneficial for learning, memory, and attention (Himmelheber et al., 2000). In addition, evidence suggests that increasing acetylcholine may be protective by controlling the immune response, thereby minimizing immune-mediated neurological alterations (Rosas-Ballina & Tracey, 2009). This overview will explain the mechanism of action of Avipaxin and its relationship with the cholinergic immune-regulating pathway.

FEATURES OF AVIPAXIN

HupA, isolated from the Chinese herb *Huperzia serrata*, is a potent, highly specific, and reversible acetylcholinesterase (AChE) inhibitor (Tang et al., 1989). AChE exists in multiple forms (Brimijoin, 1983) and HupA appears to preferentially inhibit the tetrameric G4 acetylcholinesterase enzyme (Zhao & Tang, 2002). The G4 AChE is primarily localized in the central nervous system supporting HupA’s selective increase of acetylcholine in the brain (Bon et al., 1979; Grassi et al., 1982).

α-GPC acts as a cognitive enhancer by providing free choline for the synthesis of acetylcholine in the brain (Gatti et al., 1992). Research has demonstrated that α-GPC helps to reverse learning and memory deficits in humans and animals (Amenta et al., 1993; Drago et al., 1992; Canal et al., 1991).

Acetyl-L-carnitine can function as an acetyl donor for the synthesis of acetylcholine (White & Scates, 1990). The transfer of the acetyl moiety from acetyl-L-carnitine to acetylcholine is dependent on the concentration of acetyl-L-carnitine and requires the presence of coenzyme A (CoA), which acts as an acetyl carrier (White & Scates, 1990). Acetyl-CoA, which consists of a molecule of CoA carrying an acetyl group, is important for the synthesis of acetylcholine (White & Scates, 1990). Research has revealed that acetyl-L-carnitine, through the support of acetylcholine, may be beneficial in reversing age-related cholinergic deficits (Chan & Shea, 2007).
Overall, Avipaxin supplies three ingredients that increase acetylcholine levels and activity. Increasing acetylcholine has implications beyond enhanced cognitive function. Immunomodulation is a key feature of acetylcholine activity and these actions are mediated by the vagus nerve (Pavlov et al., 2003). The subsequent sections will provide information regarding the potential mechanism for which Avipaxin acts as an immunomodulator.

**MUSCARINIC AND NICOTINIC RECEPTORS**

In order to fully comprehend the immunomodulatory role of Avipaxin, the acetylcholine receptors need to be considered.

The biochemical functions of acetylcholine are determined by the presence of nicotinic and muscarinic acetylcholine receptors. Research has indicated that the effects of HupA are dependent on the presence of both receptors. More specifically, CNS muscarinic receptors and peripheral nicotinic receptors are necessary for HupA to modulate cytokine production (Pavlov et al., 2009). Pavlov and colleagues (2009) administered intraperitoneal HupA following pretreatment with atropine sulfate, a centrally acting muscarinic antagonist, to endotoxemic mice. Endotoxemia can occur with excessive amounts of gram-negative bacteria, such as *Escherichia coli*, being present in the blood. Interestingly, atropine sulfate blocked the effects of HupA, whereas atropine methyl nitrate, a peripherally acting muscarinic receptor antagonist, did not block the immunomodulatory effects of HupA (Pavlov et al., 2009). This study suggests that HupA’s, and therefore Avipaxin’s, immunomodulatory effects are dependent on CNS muscarinic activity.

Alpha 7 nicotinic acetylcholine receptors ($\alpha_7$nAChRs) are found on immune cells and in the spleen, and when triggered by the binding of acetylcholine, lead to decreased synthesis and release of cytokines (Wang et al., 2003). Furthermore, $\alpha_7$nAChR knockout mice have been shown to be resistant to the neuromodulatory effects of centrally acting AChE inhibitors (Pavlov et al., 2009). Previous studies illustrated that the spleen is the primary organ that integrates the cholinergic immune-regulating effects as described in the following section (Huston et al., 2006).

**VAGUS AND SPLENIC NERVE**

The immunomodulatory effects of HupA are dependent on the vagus nerve and the splenic nerve. One study showed that surgical transection of the right cervical vagus nerve, which innervates the celiac ganglia, reduced the immunological effect of AChE inhibitors (Berthoud & Powley, 1993). This study suggests that HupA, and therefore predictably Avipaxin, can modulate immune activation by enhancing vagal nerve activity descending from the CNS.

The vagus nerve modulates immune system activation indirectly by stimulating the splenic nerve, which innervates the spleen (Rosas-Ballina et al., 2008). Therefore, the spleen may be essential to the immunomodulatory effects of HupA. This is supported by research demonstrating that splenectomy abolished the decrease in cytokine levels following vagal nerve stimulation (Huston et al., 2006). Upon stimulation of the descending vagus nerve from the brain, acetylcholine is released at the celiac-superior mesenteric plexus ganglion causing activation of the splenic nerve (Rosas-Ballina et al., 2008). The splenic nerve innervates the spleen and
releases catecholamines, leading to attenuation of cytokines by binding to β-adrenergic receptors (Rosas-Ballina et al., 2008). In addition, it has been proposed that catecholamine release from the splenic nerve can enhance acetylcholine levels in the spleen, which can act on α7nAChRs to attenuate cytokine production (Huston et al., 2006; Rosas-Ballina et al., 2008).

**PILOT STUDY ON AVIPAXIN**

A recent study conducted by NeuroScience, Inc. (2009) assessed the immunomodulatory effects of Avipaxin by evaluating serum cytokine levels and urinary neurotransmitters in healthy participants. Serum cytokine measurements were evaluated for seven participants before and after ingesting Avipaxin. Four hours after ingesting 2 capsules of Avipaxin, the cytokines interleukin-1β (IL-1β), IL-6, IL-8, IL-12, IL-17, tumor necrosis factor-α (TNF-α), and interferon-γ (IFN-γ) decreased significantly from baseline. After utilizing 2 capsules twice daily of Avipaxin for one week, these same cytokines drastically decreased from baseline and the 4-hour post-dose measurements (NeuroScience Inc., 2009).

Urinary neurotransmitters were evaluated in eight participants before and after ingesting Avipaxin over a one day period. The mean values for norepinephrine decreased at 1, 2, 4, 5, and 6 hours following Avipaxin ingestion with statistical significance observed at 5 and 6 hours. Serotonin levels increased at all time points and statistical significance was observed at 5 and 7 hours post-dose. Taurine levels increased at 1, 4, 5, 6, and 7 hours, but decreased at 2 hours. Statistical significance was only observed at the 6 hour time point for taurine (NeuroScience Inc., 2009).

This pilot study supports that Avipaxin had immunomodulatory actions by decreasing certain cytokines, thereby minimizing neurological alterations associated with immune activation.

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<th>Cytokines</th>
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**Table 1.** Significant cytokine and chemokine changes were observed following 4 hours and 1 week of Avipaxin ingestion, n=7 (A). Significant changes were observed in urinary neurotransmitters during one day of Avipaxin ingestion compared to a control day, n=8 (B). Down arrow= decrease, up arrow= increase, one arrow= p≤0.05, two arrows=p≤0.01.

**SUMMARY**

Avipaxin may increase brain acetylcholine by preventing its metabolism (with HupA) and by increasing synthesis (by supplying α-GPC and acetyl-L-carnitine). Subsequently, acetylcholine binds to muscarinic receptors to increase descending vagal nerve activity from the CNS. The vagus nerve, which innervates the celiac ganglia, can then activate the sympathetic splenic nerve, and causes the release of norepinephrine from splenic nerve endings in the spleen. Norepinephrine can then bind to β-adrenergic receptors to decrease the production of certain cytokines. Additionally, norepinephrine may also increase the release of acetylcholine in the spleen, which can bind to α7 nicotinic receptors to further decrease cytokine production.
In conclusion, Avipaxin can be used as a dietary supplement to modulate immune system activation by increasing acetylcholine levels and activity in the brain. The primary function of the cholinergic immune-regulating pathway is to attenuate systemic expression of certain cytokines following an innate immune response (Tracey, 2009). The cholinergic immune-regulating pathway is a reflex pathway which functions to reestablish homeostasis and prevent systemic immune activation. Avipaxin supports the cholinergic immune-regulating pathway to prevent systemic release of cytokines and can limit the potential damage by cytokines under acute and persistent conditions.

REFERENCES


