Intelligence 39 (2011) 100–107

Contents lists available at ScienceDirect

Intelligence

Improving general intelligence with a nutrient-based pharmacological intervention

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ARTICLE INFO

Article history:
Received 17 August 2010
Received in revised form 28 January 2011
Accepted 31 January 2011
Available online 15 March 2011

Keywords:
Intelligence
Huperzine A
Vinpocetine
Acetyl-L-carnitine
Alpha-lipoic acid
Rhodiola Rosea, raven progressive matrices

ABSTRACT

Cognitive enhancing substances such as amphetamine and modafinil have become popular in recent years to improve acute cognitive performance particularly in environments in which enhanced cognition or intelligence is required. Nutraceutical nootropics, which are natural substances that have the ability to bring about acute or chronic changes in cognition have also been gaining popularity in a range of settings and applications including the workplace, driving and in the amelioration of age related cognitive decline. Huperzine A, Vinpocetine, Acetyl-L-carnitine, *Rhodiola Rosea* and Alpha-lipoic Acid are popular nutritional supplements that have shown promising benefits in improving a range of biological (e.g., blood flow, anti-inflammatory, anti-oxidant, and direct neurotransmitter effects) and cognitive processes from *in vitro*, animal and human clinical research. We report here the first human randomized clinical trial for cognition in which we administer a combination of Huperzine A, Vinpocetine, Acetyl-L-carnitine, *R. Rosea* and Alpha-lipoic acid (called Ceretrophin) vs placebo. Sixty participants (40 females and 20 males, with a mean age of 45.4 years, SD = 12.6) completed either the odd or even items from the Raven Advanced Progressive Matrices (APM) at baseline and the opposite odd or even items at week 4 after consuming either the combination nootropic or placebo. A significant study visit (time) × treatment condition interaction was found: $F(1, 57) = 7.279$, $p = 0.009$, partial $\eta^2 = .113$, with paired samples t-tests revealing a significant improvement in mean APM score from baseline to retest (week 4) ($t(34) = -4.045$, $p < .001$) for the Ceretrophin™ group. Improvements in APM scores could be attributed to the active intervention over the placebo, indicating that the treatment improved general intelligence. Implications for improving our understanding of the biological basis of intelligence and pharmacologically improving human cognition are discussed.

1. Introduction

There are many pharmacologically active substances available that claim to enhance cognitive functioning such as learning and memory. Many of these have not been subjected to scientific analysis, some have been subjected to preliminary animal work, and a few have been subjected to carefully controlled human clinical trials. The use of nootropic or cognitive enhancing substances whether they be naturally occurring or synthesized is increasing in western societies as the pressures to achieve and to enhance individual levels of intelligence increases (Sahakian & Morein-Zamir, 2007). Despite this trend, there is little research scientifically examining the efficacy of these substances and particularly the mechanisms by which they exert their claimed effect.

The term nootropic was first coined by Giurgen (1973) who used it to propose a class of pharmacologically active

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doi:10.1016/j.intell.2011.01.003

substances that improve cognition or intelligence without side-effects and which should protect the brain from damage. Therefore it may be better to describe common pharmaceuticals (such as modafinil and amphetamines) that improve cognition as cognitive enhancers and refer to nutraceuticals or natural medicines that improve cognition as nootropics. Most cognitive enhancers or nootropics work acutely to improve the functioning of a narrow range of neural processes such as is the case with specific neurotransmitter systems that may underpin narrow elements of cognition. Examples of acute cognitive enhancers that have been subjected to research are: modafinil (Turner et al., 2003), *Ginkgo Biloba* (Kennedy, Scholey, & Wesnes, 2000), amphetamines (Silber, Papafotiou, Croft, Ogden, et al., 2005; Silber, Papafotiou, Croft, & Stough, 2005), Ginseng (Scholey et al., 2010) and *Schizandra Chinesis* (Panossian & Wikman, 2008).

Even fewer substances have been shown to improve cognition or intelligence after chronic administration in non-clinical populations. In contrast to acute cognitive enhancers they usually exert a gradual biological effect over time on different neural targets. Instead of a direct change in neurotransmitter activity they may gradually improve blood flow to the brain, increase energy metabolism, improve anti-oxidant defence, provide anti-inflammatory effects, or increase membrane fluidity usually requiring weeks or longer of administration. There are several examples of chronic nootropics. Vitamin–mineral supplementation has been shown to modestly raise the non-verbal intelligence of some groups of Western schoolchildren (Schoenthaler, Bier, Young, Nichols, & Jansenns, 2000) and supplementation with creatine (which plays a pivotal role in brain energy homeostasis) in vegetarians was shown to produce a significantly positive effect on both working memory (backward digit span) and intelligence (Advanced Progressive Matrices; Rae, Digney, McEwan, & Bates, 2003). Chronic administration of both *G. Biloba* (e.g. Stough, Clarke, Lloyd, & Nathan, 2001) the Indian herb Brahmi, particularly CDRI08 (e.g. Stough, Lloyd, et al., 2001; Stough et al., 2008) as well as the pine bark extract Pycnogenol® (Ryan et al., 2008) have also been shown to improve cognitive processes in healthy participants.

Pharmacology is an important strategy in understanding the biological basis of intelligence because it offers the possibility of understanding more about intelligence at the cellular and neuronal levels. Although there have been some promising models describing neural imaging studies of general intelligence which have indicated the role of frontal–parietal networks (Deary, Penke, & Johnson, 2010; Jung & Haier, 2007), these studies are not able to describe processes at the cellular level that may underpin cognition or intelligence. There have been several studies that link neurotransmitter activity to discrete components of cognition or intelligence, such as dopamine and working memory (Dickinson & Elvevåg, 2009); or acetylcholine and information processing speed (Stough, Thompson, Bates, & Nathan, 2001). However, these studies do not describe more wide-spread cellular influences that have accumulating long-term effects on the integrity of neuronal structures.

To date, much of our understanding of the processes underpinning human cognition at the neuronal level derive from studies in which age-related changes in the brain have been characterised (for reviews see Buckner, 2004; Hedden & Gabrieli, 2004). These studies have shown that the integrity of both white matter and grey matter structures are reliably correlated with differences in the cognitive ability between young and old individuals, with the largest age-related changes observed in the frontal and temporal cortices (Fjell & Walhovd, 2010). A number of cellular processes have been implicated in causing impairments to brain function and cognition, with accumulated damage becoming most noticeable with advanced age. These processes include oxidative stress due to free radicals (Halliwell, 1992), chronic systemic inflammation (Sarkar & Fisher, 2006), and decreased mitochondrial efficiency (Kidd, 2005).

As such it is unlikely that one mechanism at the cellular level will completely contribute to individual differences in human intelligence. As a consequence strategies in which combinations of compounds with different cellular mechanisms may be most efficacious in developing nootropic compounds for chronic consumption. In order to fulfil these criteria we tested a combination nootropic agent in which Huperzine, Vinpocetine, Alpha lipoic acid, Acetyl-L-carnitine, and *Rhodiola Rosea* were combined. We briefly present relevant research on the mechanisms and efficacy of each of these substances. These substances have been selected because of well validated biological mechanisms which target processes at the cellular level (such as those described above) or their solid clinical data showing improvement in cognition after chronic administration.

1.1. Huperzine A (HupA)

Recent studies have revealed that Huperzine A (HupA) functions as a potent reversible inhibitor of Acetylcholinesterase (Wang & Xi, 2005). There is evidence to suggest that HupA has better penetration of the blood-brain barrier, higher oral bioavailability, and longer duration of AChE inhibitory activity compared with the pharmaceutical ChEIs tacrine, donepezil and rivastigmine (Bai, Tang, & He, 2000). HupA has also been found to reverse or attenuate cognitive deficits in a broad range of animal models (Wang, Zhang, & Tang, 2001); and numerous clinical trials have demonstrated that HupA is effective in relieving memory deficits associated with the elderly and Alzheimer's disease (AD) without any serious adverse side effects (Wang, et al., 2001) and is considered to be safe (Xu et al., 1995). A recent Cochrane's review of HupA in the treatment of AD (Li, Wu, Zhou, Liu, & Dong, 2008) concluded that a dosage of between 0.2 and 0.4 mg per day resulted in significant improvement to global cognitive function at 6–12 weeks.

1.2. Vinpocetine (VIN)

VIN has been highly researched as a neuroprotective agent (Dezsi, Kis-Varga, Nagy, Komlodi, & Karpati, 2002; Pereira et al., 2003; Santos, Duarte, Moreira, & Oliveira, 2000; Vas & Gulyás, 2005). Due to inhibition of cyclic nucleotide phosphodiesterases type 1, VIN causes vasodilation of cerebral smooth muscle and increases blood flow to the brain (Hagiwara, Endo, & Hidaka, 1984). In addition to enhancing cerebral vascular blood flow, VIN has also been found to increase brain energy metabolism (Gulyás et al., 2002; Szakács, Veres, & Vereczkey, 2001; Vas & Gulyás, 2005; Vas et al., 2002) and increase the neuronal uptake of glucose and