



CILTEP™

WHITEPAPER

BY: ABELARD LINDSAY

**A natural dietary supplement for
motivation, concentration and memory.**

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By Abelard Lindsay (@ciltep on Twitter)

INTRODUCTION

Starting in late 2011 I began exploring mechanisms for inhibiting PDE4 with the intention of improving my ability to learn and remember. Through self-experimentation and reading of the scientific literature I discovered that a combination of artichoke extract and forskolin produced what I considered to be substantially beneficial results.

In April 2012 I shared my results with the Longectiy.com community. Through feedback and discussion with the community we developed a deeper understanding of the theory behind the stack.

In this document I have put together the theory that led me to the stack as well as the theories behind the additions to the stack that I have adopted to help adapt nutritionally to the epigenetic changes that the stack is theorized to activate.

No placebo controlled double-blind studies have been done with the stack to date. However, what follows is a synopsis of the scientific basis in the literature of my understanding that has led me to the current formulation of the CILTEP stack which I have been taking in one form or another almost continuously since late 2011.

LONG TERM POTENTIATION AND PDE4

There has been a significant amount of research into the benefits of PDE4 inhibitors. In animal models synthetic PDE4 inhibitors have been shown to enhance object memory¹, and reverse deficits to learning, working and reference memory induced by scopolamine²³, NMDA antagonists⁴⁵ and under conditions of depleted tryptophan and serotonin⁶.

The primary means by which PDE4 inhibitors are theorized to improve learning and memory is by lengthening the duration during which the secondary messenger cyclic-adenosine monophosphate (cAMP) is present in cells⁷ where it can activate CREB⁸ and thus increase CREB's gene transcription activities in the nucleus⁹ and mitochondria¹⁰¹¹.

These gene transcription activities are what are theorized to lead to long term potentiation (LTP) activity which is crucial to learning and memory¹². Additionally, Increased transcription of BDNF by CREB has been linked to improved short-term memory in studies¹³.

FORSKOLIN'S EFFECTS ON CAMP

Forskolin is a chemical derived from the plant *Coleus forskohlii* which has been widely used in

traditional Ayurvedic medicine¹⁴. It has also has been extensively studied due to it's ability to increase the levels of intracellular cAMP¹⁵. It has been paired with PDE4 inhibitors to enhance its effects on LTP activity¹⁶

HERBAL PDE4 INHIBITORS

There have been several PDE4 inhibitors identified in herbal preparations including luteolin¹⁷, quercetin¹⁸, hesperidin¹⁹, resveratrol²⁰, biochanin a²¹, genistein²² and mesembrenone²³. Among them luteolin, which is present in artichoke extract²⁴, has proven to be the most subjectively beneficial in my personal experimentation. It also inhibits PDE 1 through 5²⁵. PDE 1 and PDE 5 inhibition have both shown beneficial activity with regards to synaptic plasticity^{26,27}.

PUTTING IT ALL TOGETHER

In late 2011, influenced by the forskolin and rolipram “chemically induced LTP” studies²⁸ I replaced rolipram with artichoke extract and combined it with forskolin. After taking this combination I was able to study for longer periods of time and retain more information. I also experienced an improvement in mood and motivation.

AUGMENTATION OF THE STACK WITH DOPAMINE PRECURSORS AND COFACTORS

CREB's activities in the cell have been shown to increase the transcription of enzymes such as tyrosine hydroxylase²⁹ which are key enzymes in dopamine metabolism. Increased transcription of these enzymes leads to increased processing of dopamine precursors³⁰. I added the essential amino acid L-Phenylalanine which is converted into L-Tyrosine by Phenylalanine Hydroxylase and then converted into L-DOPA by Tyrosine Hydroxylase³¹. I added B6 to the stack to support the conversion of L-DOPA to Dopamine by DOPA Decarboxylase³².

COUNTERACTING INCREASED TRANSCRIPTION OF AChE

I experienced problems with afternoon sleepiness and a temporary decrease in short term memory while taking the stack. Studies have provided evidence that forskolin³³ increases transcription of acetylcholinesterase (AChE). Acetylcholinesterase breaks down acetylcholine in the brain. Sleepiness is a common symptom of medicines that are anti-cholinergic³⁴ so it would follow that excess acetylcholinesterase would lead to lower acetylcholine levels and thus sleepiness. Acetyl-L-carnitine has been shown to increase the levels of acetylcholine in the brain³⁵ and thus would theoretically help counteract increased transcription of acetylcholinesterase by forskolin.

I added acetyl-L-carnitine to the stack in an amount determined by self-experimentation in a ratio proportional to the amount of forskolin taken. After adding this component to the stack I noticed that afternoon drowsiness and short-term memory issues were largely mitigated.

EXPLORATION OF ADDITIONAL PDE4 INHIBITORS

Substantial self-experimentation with quercetin, hesperidin and mesembrenone were performed. Quercetin was abandoned largely because of its subjectively more negative effects on working memory compared to Artichoke Extract and because its effects lasted for an excessively long amount of time leading to night time insomnia. Mesembrenone from kanna and the extract Zembrin® proved highly effective in my trials. Zembrin® has been shown to completely inhibit PDE4 in clinical trials³⁶. It's subjective effects on mood, motivation and social anxiety were judged by myself and others to be subjectively less beneficial than Artichoke Extract.

NON-COGNITIVE BENEFITS OF PDE4 INHIBITION

There are a significant number of potential uses for PDE4 inhibitors that have been examined in studies. CILTEP should be further investigated as a means of achieving these previously investigated PDE4 inhibition benefits.

PDE4 Inhibition has been proposed as the mechanism of action of resveratrol's anti-aging properties³⁷. This mechanism of action is theorized to be triggered through cAMP activated signaling pathways that result in the activation of SIRT1 genes³⁸. In fact, rolipram produced similar results to resveratrol with respect to anti-aging effects.

FUTURE DIRECTIONS

Developing further synergistic interactions with the basic CILTEP mechanism is something that remains to be explored. Processes upstream of LTP that might be explored such as allosteric NMDA receptor modulation, CAMKII phosphorylation, and AMPA receptor trafficking would all be interesting areas to look for synergies in. Providing essential nutrition to support increased transcription and neuronal cell development would also be an interesting avenue for development and experimentation.

CONCLUSION

We have discussed the proposed mechanism of action of the CILTEP stack. The combination of the cAMP increasing effects of forskolin along with the PDE inhibiting effects of luteolin are theorized to produce LTP enhancing effects via prolonging CREB activation. Acetyl-L-carnitine has been theorized to provide a mitigating effect with regards to the increased acetylcholinesterase

transcription that forskolin triggers. L-phenylalanine and vitamin B6 are theorized to provide support for increased dopamine metabolism generated by CREB's heightened transcription of tyrosine hydroxylase.

The link between herbal PDE4 inhibition and cognitive enhancement in combination with forskolin lay unexplored in the literature for a significant amount of time. Through careful examination of clinical research, self-experimentation and community feedback the CILTEP stack has been developed into its present form. It's my hope that with continued careful understanding of the scientific literature, community input, and experimentation CILTEP stack theory can be further explored, refined and validated.

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