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# L-theanine: potential use as a therapeutic agent for psychiatric conditions

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Thesis

**L-THEANINE: POTENTIAL USE AS A THERAPEUTIC  
AGENT FOR PSYCHIATRIC CONDITIONS**

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## **DEDICATION**

I would like to dedicate this work to my advisor, Dr. Hee-Young Park, and to my second reader, Dr. Gwynneth Offner. It is an understatement in acknowledging the mentorship, instruction, wisdom, and support that Dr. Park has given me in my aspirations to become a physician. Throughout my academic career, I have not met with such faculty which had such a proactive, sincere, and wholehearted role in encouraging and giving thoughtful advice not just about medicine, but in ways that truly foster personal growth and development. It is something that I am truly grateful for. To Dr. Gwynneth Offner, whose expertise in providing mentorship for all MAMS students is never unappreciated by all, and her ability to give outstanding lectures, individualized attention, and encouragement is humbling as well as sincerely appreciated. I shall say that it must be continually acknowledged that my educational experience at the Boston University School of Medicine has been personally life changing and transformative in ways more than these two outstanding faculty members know. With much sincerity, I thank both of you with a lifetime gratitude.

**L-THEANINE: POTENTIAL USE AS A THERAPEUTIC AGENT  
FOR PSYCHIATRIC CONDITIONS**

**DAVID CHA**

**ABSTRACT**

Psychiatric conditions including attention disorders, mood disorders, anxiety disorders, and schizophrenia pose some of the most debilitating effects on the patient population worldwide. Treatments currently used to combat such illnesses have been a significant area of research in the medical community. As more molecular mechanisms are elucidated and a deeper pathophysiologic basis is discovered for such ailments, newer pharmacologic modalities pave way to provide greater symptomatic relief and treatment with fewer side effects. Enter L-theanine, a non-essential amino acid found in green tea leaves which has been touted to have anxiolytic and cognitive enhancing properties on a wide variety of patient demographics. Furthermore, it has been recently studied for its neuroprotective qualities and antihypertensive effects. This study delves into the current understanding of common psychiatric conditions, as well as providing a summary into the current understanding of L-theanine in its potential to a wide variety of psychiatric and neurologic conditions. The apparent potential in utilizing L-theanine as a treatment modality is promising, and the limited studies available warrant continued research to provide a safe, non-toxic way in alleviating psychiatric and neurologic conditions.

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## LIST OF ABBREVIATIONS

|       |  |
|-------|--|
| 5-HT  | Serotonin  |
| ADHD  | Attention Deficit / Hyperactivity Disorder                   |
| AMPA  | $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid |
| ANOVA | Analysis of Variance   |
| BZD   | Benzodiazepine   |
| CD    | Conduct Disorder   |
| CNS   | Central Nervous System                                       |
| DSM   | Diagnostic Statistical Manual                                |
| DAT   | Dopamine Active Transporter                                  |
| DBH   | Dopamine Beta Hydroxylase                                    |
| DM    | Diabetes Mellitus  |
| DRD   | Dopamine Receptor  |
| DRI   | Dopamine Reuptake Inhibitor                                  |
| EEG   | Electroencephalogram   |
| ERK   | Extracellular Signal-Related Kinase                          |
| GABA  | $\gamma$ -Aminobutyric acid                                  |
| GAD   | Generalized Anxiety Disorder                                 |
| HTN   | Hypertension   |
| MAPK  | Mitogen-Activated Protein Kinase                             |
| MAOI  | Monoamine Oxidase Inhibitor                                  |

|              |  |
|--------------|--|
| MDD.....     | Major Depressive Disorder                                      |
| MPH.....     | Methylphenidate  |
| NDRI.....    | Norepinephrine Dopamine Reuptake Inhibitor                     |
| NF-kB.....   | Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B cells |
| NE.....      | Norepinephrine   |
| NET.....     | Norepinephrine Transporter                                     |
| NKCC.....    | Sodium-Potassium-Chloride Cotransporter                        |
| NT.....      | Neurotransmitter   |
| OCD.....     | Obsessive-Compulsive Disorder                                  |
| ODD.....     | Oppositional Defiant Disorder                                  |
| PMDD.....    | Premenstrual Dysphoric Disorder                                |
| PTSD.....    | Post-Traumatic Stress Disorder                                 |
| RT-PCR.....  | Reverse Transcriptase-Polymerase Chain Reaction                |
| SANS.....    | Scale for the Assessment of Negative Symptoms                  |
| SERT.....    | Serotonin Transporter  |
| SNAP-25..... | Synaptosomal Associated Protein, 25kDa                         |
| SSRI.....    | Selective Serotonin Reuptake Inhibitor                         |
| TCA.....     | Tricyclic Amines   |
| VMAT.....    | Vesicular Monoamine Transporter                                |
| VTA.....     | Ventral Tegmental Area   |

## INTRODUCTION

Psychiatric disorders are some of the most unique medical illnesses known due to the subjectivity of individuals in what they perceive, think, or feel<sup>1</sup>. Defining the disease or disorder from a symptomatic point of view has been a conceptual dogma in describing and diagnosing the disease, and ascertaining key features of each illness is a dynamic process, with advances in each edition of the Diagnostic and Statistical Manual of Mental Disorders and the International Statistical Classification of Diseases and Related Health Problems<sup>1</sup>. Such advances in diagnostic information help clinicians accurately diagnose and treat mental disease. The subjectivity in many disorders helps one to recognize the exigence in understanding the biology behind Mood disorders, Anxiety Disorders, and Attention Deficit Hyperactivity Disorder. These common psychiatric disorders are discussed and expounded upon due to the high prevalence and co-morbidities of these disorders in the United States and worldwide.

### **Major Depressive Disorder: A Worldwide Health Problem**

Major Depressive Disorder (MDD) is one of the most common psychiatric disorders worldwide and its prevalence is evident by the multitude of pharmacological agents available to treat the condition<sup>2</sup>. Understanding the etiology of MDD has been an extensive and substantial area of scientific research in the medical community. The

complexity of its causation from a biological standpoint has proved to be difficult due to the intricate nature of overlap involving genetic and environmental factors<sup>3</sup>.

### **Monoamine Hypothesis: The First biological theory of Depression**

Mechanistic theories to elucidate the biological cause of depression originated with the Monoamine Hypothesis. During the discovery of a potential new drug to treat tuberculosis in the 1950s, iproniazid, it was observed that patients had an uplifted mood and became inappropriately happy<sup>4</sup>. Additionally, the use of an alkaloid, reserpine, used for treatment for hypertension and psychotic symptoms, would induce depressive-like symptoms in certain patients<sup>5</sup>. These unexpected side effects helped to shed light onto the biological mechanisms which would contribute to the understanding of the pathophysiology of MDD.

The basis of the monoamine hypothesis is that a chemical imbalance of monoamines, norepinephrine, dopamine, and serotonin, have a direct effect in potentiating mood disorders<sup>6</sup>. For example, a deficiency of norepinephrine can lead to depression, likewise, an excess of norepinephrine can induce mania<sup>6</sup>. Such an imbalance of these monoamines provides the basis of the monoamine hypothesis in elucidating the underlying pathophysiology of major depressive disorder<sup>6</sup>. Iproniazid, a non-selective, irreversible monoamine oxidase inhibitor, could induce manic symptoms due to an excess of monoamines<sup>7</sup>, whereas reserpine, which irreversibly blocks the vesicular monoamine transporter, VMAT, could induce depressive like states in patients<sup>8</sup>.

Anecdotal evidence of the side effects of these early pharmacotherapies paved way to produce the first pharmacologic agents, monoamine oxidase inhibitors (MAOI), which were approved to treat MDD<sup>4</sup>. The treatment of depression with a specific pharmacologic agent proved to be helpful in alleviating depressive symptoms, however, the dietary interactions and side effects associated with MAOIs, specifically foods and beverages with a high tyramine content such as wine and cheese, could cause a hypertensive crisis in patients<sup>9</sup>. Tyramine, as a pressor amine, would exacerbate the sympathetic pressor response and potentiate a hypertensive crisis<sup>9</sup>.

### **Tricyclic Amines**

The next class of medications which were used to treat depression were the tricyclic antidepressants (TCA). During the time in which neuropharmacology research was experiencing rapid growth and discovery, the development of a drug by the French chemist Paul Charpentier developed chlorpromazine, which was one of the first widely used antipsychotic drugs. Chlorpromazine is used currently as an antipsychotic to treat schizophrenia, and its utility for clinical therapy prompted the further discovery of other derivatives of chlorpromazine. This led to the first TCA used to treat MDD, imipramine, which was not initially developed for the condition. Clinical observations of manic effects in patients paved way for it to be tested on depressed patients.

Although MAOI's and TCA's were some of the front-line medications in

pharmacologic advancement in the treatment of mood disorders in the 1950's and 1960s, the widespread non-selective pharmacodynamic effects, side effect profile, which included the lowering threshold of seizures<sup>10</sup>, and high potential for toxicity with food interactions, prompted researchers to ascertain and hone on a new class of medications which would have a lower side effect profile, did not have such a stringent diet restriction, and didn't exhibit such broad, non-selective effects<sup>11</sup>.

### **Selective Serotonin Reuptake Inhibitor: Pharmacologic Breakthrough in Treatment of Mood Disorders with Selective Action**

Selective serotonin re-uptake inhibitors (SSRI) were developed in the 1970s in response to the unfavorable side effect profile and dietary interactions associated with MAOIs and TCAs<sup>11</sup>. The development and discovery of SSRIs were a pharmacologic breakthrough, for many reasons. First, they were the first to validate the principal role of the inhibition of a neurotransmitter re-uptake as a therapeutic modality<sup>11</sup>. Second, SSRIs paved way to provide evidence that Serotonin (5-HT) has a central, pathophysiologic role in mediating the causality and severity of affective and mood disorders. Third, SSRIs were the first class of medications in the treatment of mood disorders developed through rational design. Meaning, the development of a new pharmacologic agent with intention of effecting a known biological target<sup>12</sup>.

SSRIs are used to treat a variety of mood disorders including major depressive disorder (MDD), obsessive compulsive disorder (OCD), premenstrual dysphoric disorder



(PMDD), panic disorder, and social anxiety disorder<sup>11</sup>. They are currently recommended as a first-line agent in treating MDD by the National Institutes of Health, with less of a side effect profile than MAOIs or TCAs<sup>10</sup>. Some examples include citalopram, escitalopram, fluoxetine, paroxetine, and sertraline.

SSRIs were a breakthrough in pharmacologic research because of their selectivity in inhibiting the serotonin transporter, with negligible effects on the dopamine transporter or norepinephrine transporter. Inhibition of the 5-HT binding to the serotonin transporter increases the concentration of 5-HT in the synaptic cleft, increasing postsynaptic receptor binding of 5-HT receptors, manifesting as an alleviation of depression symptoms<sup>13</sup>.

It is interesting to note that although noticeable increases of 5-HT in the synaptic cleft can be experimentally observed soon after one starts the medication, it usually takes a few weeks to alleviate the symptoms and receive the clinical benefit and therapeutic effect of SSRIs<sup>13</sup>. One possible explanation is that although SSRIs increase the amount of 5-HT in the synaptic cleft by binding to the serotonin transporter and subsequently prevent degradation and metabolism in the presynaptic neuron by MAOI, the increased amount of 5-HT leads to a desensitization of the 5-HT<sub>1A</sub> autoreceptors on the presynaptic neuron. This desensitization of the autoreceptor increases the impulse flow of 5-HT leading to an enhanced release and greater aggregate of 5-HT in the synaptic cleft. Desensitization of the autoreceptors takes some time compared to the noticeable increase of 5-HT soon after taking SSRIs, which is thought to be the main reason for the 2-3 week delay in observing therapeutic effects of SSRIs<sup>13</sup>.

### **Serotonin-Norepinephrine Reuptake Inhibitors**

Serotonin-norepinephrine reuptake inhibitors (SNRIs), like SSRIs inhibit the reuptake of Serotonin Transporter, but additionally inhibit the reuptake of norepinephrine transporter (NET)<sup>14</sup>. As a result, the pharmacologic effect of inhibiting the reuptake of both the SERT and NET have possibly contributed for using SNRIs to not only treat mood disorders, but also its utility in treating other conditions such as Attention Deficit Hyperactivity Disorder (ADHD), Fibromyalgia, Generalized Anxiety Disorder (GAD), and Post Traumatic Stress Disorder (PTSD)<sup>15</sup>.

### **Norepinephrine Reuptake Inhibitors**

Norepinephrine reuptake inhibitors inhibit the action of the NET transporter, thus increasing concentrations of Norepinephrine and Epinephrine in the synaptic cleft. This is manifested as an increase in adrenergic transmission, and has been favorably used in the treatment of ADHD, Anxiety Disorders, MDD, Panic Disorders, and Narcolepsy due to its sympathomimetic effects. Since NRI medications do not affect the dopamine reuptake inhibitor (DRI), these class of drugs do not have the potential of abuse as other drugs that inhibit both the NRI and the DRI<sup>16</sup>. Some drugs in this class include atomoxetine and bupropion, which are FDA-approved to treat ADHD and Depression, respectively.

## **Etiology of Anxiety**

Anxiety is an emotion described as an unfavorable state of inner dissonance, and often manifested with nervous behavior, in which one anticipates pending danger or threat. It is a complex emotion in which the individual subjectively perceives a circumstance or situation as overly threatening, and the accompanying behavior can include fatigue, restlessness, problems concentrating, and muscular tension. Although some level of anxiety is considered normal, when it is pathologically over-experienced by the individual, he or she may be suffering from an anxiety disorder<sup>17</sup>.

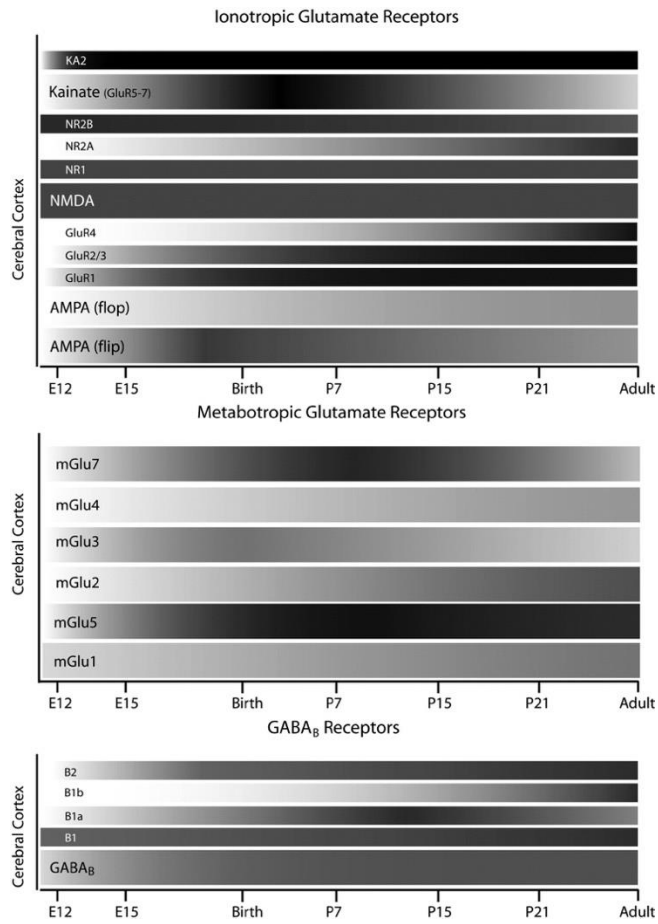
## **Biological Origins of Anxiety**

There is much scientific evidence which provides information on the biological origins of anxiety. From an anatomical perspective, the amygdala, which regulates emotions like anxiety and fear, and the hippocampus, which processes emotional memory, are thought to be the main contributors to anxiety<sup>18</sup>. From a biochemical level, the neurotransmitter g-aminobutyric acid (GABA) plays a central role in the pathophysiology of anxiety and anxiety disorders<sup>19</sup>.

GABA is a primary inhibitory transmitter in the central nervous system (CNS) of mammals, modulating neuronal excitation in the CNS<sup>20</sup>. Derived from the amino acid glutamate through glutamate decarboxylase, GABA functions as an excitatory neurotransmitter during the neonatal stage of brain development, whereas it functions as an inhibitory transmitter in the adult brain<sup>21</sup>. The switch from an excitatory to an inhibitory NT is influenced from the concentration of chloride ions in the brain. When

the neuronal chloride concentration is at a high level, GABA acts as an excitatory NT, and as it decreases to a certain level it acts as an inhibitory neurotransmitter<sup>21</sup>. Chloride concentration is modulated by the Na<sup>+</sup>K<sup>+</sup>Cl<sup>-</sup>Cl<sup>-</sup> cotransporters (NKCC), with NKCC1 increasing chloride concentration and NKCC2 decreasing chloride concentration<sup>19</sup>. GABA is also known to have a crucial role in the developing brain acting in both an autocrine and paracrine fashion<sup>22</sup>. Although for many years it was known that glutamate is the primary excitatory NT and GABA is the primary inhibitory transmitter in the adult brain, recent evidence has shown that both NT's are important in modulating embryonic development of the brain<sup>23</sup>. Glutamate and GABA mediate their action through activation of ionotropic (ligand gated ion channels) and metabotropic (G-protein coupled) receptors<sup>23</sup>.

The variety of subclasses of ionotropic glutamate receptors are named after the agonists 1)  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) 2) *N*-methyl-d-aspartate (NMDA) 3) kainate receptors<sup>24</sup>. The metabotropic glutamate receptors are known to have at least eight different subtypes based on homology of their sequence and transduction pathways<sup>25</sup>. Group I comprise of mGlu<sub>1</sub>, mGlu<sub>5</sub> and their [splice variants](#) (mGlu<sub>1 $\alpha$</sub> ,  $\beta$ , c, d and mGlu<sub>5a,b</sub>); group II receptors include mGlu<sub>2</sub> and mGlu<sub>3</sub>; and group III consists of mGlu<sub>4</sub>, mGlu<sub>6</sub>, mGlu<sub>7</sub> and mGlu<sub>8</sub>, and some splice variants<sup>23</sup>. The GABA ionotropic receptors, GABA<sub>A</sub> receptors, display even more diversity in their composition with eight subunit families 21 subclasses. The metabotropic G coupled protein GABA receptors (GABA<sub>B</sub> receptors) have 2 subunits of GABA<sub>B1</sub> and GABA<sub>B2</sub>.



**Figure 1: The different classes and subtypes of Glutamate and GABA receptors**

Hollmann M, Heinemann S. Cloned glutamate receptors

## **Pharmacologic Agents of Anxiety**

Specific pharmacologic agents possessing anxiolytic effects have helped hone in on the molecular mechanisms which contribute to anxiety. Specifically, benzodiazepines and barbiturates, with known anxiolytic effects, have allowed researchers to ascertain specific molecular receptors which help explain a neurobiological basis for anxiety.

### **Benzodiazepines**

A class of medications known as benzodiazepines (BZD) has been around since the 1960's, and has been used as therapeutic agents for alleviating anxiety<sup>26</sup>. Such pharmacologic agents increase the amount of GABA, and clinical observations have shown that BZDs have positively therapeutic effects of anxiolytic and anti-convulsive effects<sup>27</sup>. BZDs have been paramount agents of clinical utility, still being currently used for treatment of anxiety disorders, insomnia, and as a sedative<sup>28</sup>.

BZDs allosterically potentiate the GABA<sub>A</sub> receptor, dually increasing the amount of GABA and potentiating its effects, decreasing the excitability of neurons, which is correlated with the anxiolytic effects associated with BZDs<sup>28</sup>. The GABA<sub>A</sub> receptor allows chloride ion influx resulting in hyperpolarization of the neuron, causing an inhibition of neurotransmission and neuronal activity<sup>19</sup>. It is interesting to note that BZD's do not decrease the K<sub>m</sub> of GABA binding to the GABA<sub>A</sub> receptor as other positive allosteric modulators do, but rather by increasing the conductance of Cl ions across the cell membrane when GABA is already bound. The increased conductance

hyperpolarizes the neurons and decreases excitability through increasing the gap of resting membrane potential and the threshold potential<sup>29</sup>.

Although BZDs are common in their short-term use to treat anxiety and insomnia, long-term use of BZDs have been associated with negative health effects and risks<sup>30</sup>. Physical dependency of BZDs can develop and individuals who have taken BZDs for a considerable amount of time. Such patients need to be tapered off dose to prevent physical and mental withdrawal symptoms, often manifested as tremors, dizziness, irritability<sup>31</sup>. Such physical dependence can occur only after a few weeks of use, and studies have shown the utility of mood stabilizing medications to help attenuate negative, adverse withdrawal effects with discontinuing BZD use in patients who have been prescribed BZDs for a considerable amount of time<sup>32</sup>.

Additionally, long term use of BZDs have been shown to cause a decline cognitive function, manifested as memory problems (anterograde and retrograde amnesia), attention deficits, and psychomotor dysfunction<sup>33</sup>. These effects on cognition can exacerbate the decline in cognitive dysfunction, especially in elderly patients<sup>34</sup>. Although the deficits in cognitive function associated with long-term use are often reversible with improvement to baseline function, often times such decline in cognition can be permanent<sup>35</sup>. Thus, the long-term impact on cognition is not clear and must be taken into consideration when prescribing such medications, and particularly in the elderly<sup>35</sup>. Such improvements of returning cognition to baseline function are most noticeable after 6 months, but often take a few years to improve<sup>35</sup>.

The decline in cognitive function associated with elderly patients poses a

significant concern, as many elderly patients are on antihypertensive medication not only affects the cholinergic system, but also can potentiate symptoms of ataxia, vertigo, and fatigue associated with orthostatic hypertension<sup>36</sup>. One of the biggest concerns for BZD use in the elderly is that such side effects of ataxia and vertigo can increase the chances of falls, which are potentially dangerous<sup>37</sup>. Furthermore, concurrent treatment with BZD's and antihypertensives has been associated with a strong correlation of drug-induced dementia in the elderly<sup>38</sup>. Fortunately, studies have shown that cessation of BZD use in the elderly who use the medication for treatment of insomnia restores psychomotor function and improves cognition, while not exacerbating the insomnia<sup>39</sup>. Such evidence requires prescribers to consider and acknowledge the long-term effects of BZD use, and recognize that the utility of treatment of anxiety and insomnia with BZDs is best used as a short-term pharmacologic agent.

### **Barbiturates**

Barbiturates are derivatives of barbituric acid and are pharmacologic agents primarily used as anesthetics, anticonvulsants, and analgesics<sup>40</sup>. Although they possess anxiolytic and hypnotic qualities, their potential for side effects and lethal overdose has greatly decreased their use as an anxiolytic in preference of benzodiazepines for short-term treatment of anxiety and insomnia<sup>41</sup>. Thus, their main utility in current clinical application is as an anticonvulsant and as an anesthetic<sup>42</sup>.

Like BZDs, barbiturates potentiate the effects of GABA on the CNS. Barbiturates are allosteric modulators of the GABA<sub>A</sub> receptor, but at higher doses, they can act like as



a direct agonist of the GABA<sub>A</sub> receptor<sup>43</sup>. The binding sites of barbiturates to ionotropic GABA<sub>A</sub> receptors are distinct from the binding sites of BZDs<sup>43</sup>. Like BZDs, the effects of allosteric modulation of the GABA<sub>A</sub> receptor potentiates the effect of GABA once bound to the GABA<sub>A</sub> receptor<sup>44</sup>. It is interesting to note that BZDs increase the frequency of the GABA<sub>A</sub> receptor receptor from opening the chloride ion channel, whereas barbiturates can prolong the opening of the chloride ion channel<sup>45</sup>. This is referred to as increasing potency of GABA for BZDs and increasing the efficacy of GABA for barbiturates.

Not only do barbiturates increase the efficacy of GABA, leading to a prolonged state of chloride conduction, but at higher doses, barbiturates can directly open the chloride channel in the absence of GABA binding. Furthermore, at increased concentrations of barbiturates, they also have an inhibitory effect on AMPA and kainate ionotropic glutamate receptors, leading to a synergistic effect of barbiturates having an enhanced effect on CNS depression than BZDs, which only have an effect on the GABA<sub>A</sub> receptor<sup>45</sup>. Lastly, at higher concentrations of barbiturates, as often used during the induction phase of anesthesia, they can modulate the calcium dependent release of glutamate through its effects on P/Q type voltage-dependent calcium channels<sup>45</sup>. These widespread effects of barbiturates including allosterically modulating GABA<sub>A</sub> receptors, acting as a direct agonist of GABA, acting on AMPA and kainate receptors, and modulating release of the excitatory transmitter glutamate facilitate the much stronger effect of barbiturates causing CNS depression than BZDs<sup>45</sup>. Thus, prescribers need to be much more cognizant when dosing barbiturates due to potential of lethal overdose<sup>45</sup>.

## **Etiology of ADHD**

Attention deficit hyperactivity disorder is a complex, neurodevelopmental disorder which is defined as one having as attentional and neurocognitive deficits, specifically with problems regarding attentional control, working memory (known as executive function), as well as hyperactive and impulsive behavior. This disorder is estimated to affect more than 30 million people<sup>46</sup>.

One of the challenges in understanding the etiology and diagnosis of ADHD is that there are no laboratory or conclusive phenotypical tests to confirm the diagnosis. Additionally, there are often other disorders that have overlap of symptomatic features that can make differentiating a conclusive diagnosis particularly challenging. This is even further complicated by the fact that individuals who have ADHD often have co-morbidity of other psychiatric disorders, such as anxiety disorders, mood disorders, narcolepsy, obsessive compulsive disorders, and sleep disorders<sup>47</sup>. ADHD is often known to have a significantly higher rate of diagnosis in boys than girls<sup>48</sup>.

It has been suggested that there are complex environmental factors involving social and behavioral facets as well as genetic predispositions associated with the condition. As a result,

the diagnosis and its treatments are a controversial topic in the medical community<sup>49</sup>. Nevertheless, the associated prevalence and impact of ADHD in the pediatric and adult patient population is indeed real, as it is estimated to affect close to 10% of the pediatric

patient population and that almost half of the pediatric patient population affected pose a significant chance of having the disorder throughout his or her life<sup>50</sup>. Furthermore, conclusive diagnoses of ADHD are difficult and may be underdiagnosed, as individuals with higher cognitive functioning may be able to mask the symptoms of ADHD through performance in academic, personal, and social lives that are on par with what is associated as a normal range<sup>51</sup>.

### **The Complex Task of Differential Diagnosis with ADHD**

One of the challenges in differentiating a diagnosis of ADHD from other mood and panic disorders is that many of the symptoms are often identical, which often may complicate the ability in giving a conclusive diagnosis<sup>52</sup>. Specifically, mood and panic disorders such as anxiety, depression and bipolar disorder often display an overlap and similarity of symptoms<sup>52</sup>. Such overlap could potentially lead to the condition being underdiagnosed or even possibly overdiagnosed. In the United States and Canada, the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV or DSM-V) is primarily used to diagnose patients, while in Europe, the International Statistical Classification of Diseases and Related Health Problems (ICD-10) is used<sup>53</sup>. It is interesting to note that a diagnosis of ADHD is four times more likely using the DSM-IV criteria than with the ICD-10 manual<sup>53</sup>. Thus, an accurate differential diagnosis is paramount when ascertaining the condition and any associated overlap of symptoms. Even known medical conditions not necessarily related to the biologic or physiologic etiology of ADHD can produce symptoms very similar to ADHD<sup>54</sup>. For example, symptoms of low self-esteem,

irritability, and mood swings can occur from abnormalities of the thymus; cyclothymia and dysthymia are known to precipitate such symptomatic behavior<sup>54</sup>. Furthermore, personality disorders such as antisocial personality disorder and borderline personality disorder have been observed to display an overlap of symptoms as well<sup>54</sup>.

### **Co-Morbidities Associated with ADHD**

There is a significant proportion of individuals having co-morbidities of learning, mood, panic, and personality disorders with ADHD. One German study by Walitza et al. found that the majority (66%) of children who have ADHD are co-morbid for other disorders as well<sup>47</sup>. Although ADHD is not considered a learning disability, it has been found to occur in close to one-third of the pediatric patient population who have been diagnosed with ADHD<sup>47</sup>. Behavior disorders, such as Oppositional Defiant Disorder (ODD) and Conduct Disorder, display a significant association of co-morbidity with ADHD<sup>55</sup>. Additionally, Tourette syndrome has a higher incidence within the ADHD population<sup>55</sup>.

Not only is the diagnosis of ADHD difficult due to the overlap of similar symptoms with anxiety disorders and mood disorders, but there is a profound incidence of co-morbidity with anxiety disorders, mood disorders, and substance use in individuals with ADHD<sup>56</sup>. Childhood behavior disorders such as ODD and CD often times manifest throughout adulthood as antisocial disorders in individuals suffering from ADHD<sup>56</sup>.

Symptoms of anxiety increase the complexity of differential diagnoses due to the similarity of overlap of symptoms in anxiety disorders as well as ADD, and without a

doubt there are increased rates of co-morbidity of generalized anxiety disorder and social anxiety disorder with individuals who have ADHD<sup>56</sup>. An increased incidence of individuals who have ADHD having co-morbidity with MDD by two-fold suggests a strong correlation of individuals with ADHD developing a depressive disorder in his or her life<sup>56</sup>. There is evidence that pre-adolescent males diagnosed with ADHD have a higher disposition in developing a mood disorder or bipolar disorder or MDD<sup>56</sup>

Substance Use Disorders are prevalent amongst individuals who have ADHD. In particular, adolescents are at twice the risk for nicotine dependence than their peers without ADHD<sup>56</sup>. The early exposure of adolescents to cigarette use is known to be a gateway to further alcohol and drug use, and this increased risk is potentiated with adolescents with ADHD<sup>57</sup>, as they pose a stronger chance in developing nicotine dependence than non-ADHD individuals<sup>58</sup>. Furthermore, individuals with ADHD tend to develop a stronger physical and psychological dependence on nicotine and tend to sustain their addictions for a longer period compared to their non-ADHD cohorts<sup>59</sup>. In a sense, individuals with ADHD may be self-medicating their condition to improve cognition and focus, and their dependency on nicotine may be a way of coping with co-morbid mood and anxiety disorders.

## **Biology of ADHD**

### **Genetics**

The prevalence of ADHD worldwide has been estimated at roughly 5%<sup>57</sup>. Family studies show evidence of a strong genetic factor in the etiology of ADHD. Although the

complexity of the development of ADHD is multi-factorial - both from a genetic standpoint as well as an environmental one, much of the empirical evidence shows that having a family history of ADHD increases the risk of the individual in manifesting the disorder<sup>57</sup>. Twin and adoption studies prove a strong correlation of genetic predisposition of ADHD, with a greater similarity for ADHD and its genetic components between monozygotic twins vs dizygotic twins<sup>56,60</sup>. The apparent association of the strong genetic component of ADHD is further validated through 20 extant twin studies which estimate the heritability ( $h^2$ ) of one obtaining ADHD to be 75-91%<sup>60</sup>. Additionally, the estimated risk of parents with the disorder when having children with ADHD is two to eight fold, after controlling for gender and socioeconomic status<sup>61</sup>. Without a doubt, relatives of individuals with ADHD are at a higher risk, and ADHD is thought to be one of the most widely recognized psychiatric disorders with a genetic component<sup>56</sup>.

The polygenetic nature of ADHD is confirmed by studies of the dopaminergic neurotransmission genes related to Dopamine D4 Receptor (DRD4), Dopamine D5 Receptor (DRD5), Dopamine Transporter (DAT1), Dopamine Beta Hydroxylase (DBH), and serotonergic transmission system genes affecting the Serotonin Transporter gene (SERT), Serotonin HTR1B receptor (HTR1B), and systems affecting neuronal plasticity and modulation, the Synaptosomal-Associated Protein 25 (SNAP-25)<sup>60</sup>.

### **Pathophysiology of ADHD: Dopamine Hypothesis**

Like mood disorders, it seems that the imbalance and dysregulation of

catecholamine neurotransmission plays a significant role in the pathophysiology of ADHD<sup>56</sup>. The concept of understanding the neurobiology of ADHD has developed a hypothesis that ADHD is mainly a disorder with deficits in executive function – cognitive abilities related to attentional control, cognitive flexibility, inhibitory control, and working memory<sup>62</sup>. The main part of the brain that seems to be primarily involved in executive function is the frontal lobe<sup>56</sup>.

Neurotransmission of dopamine is implicated in most studies, and also provides the basis of the strong genetic component of ADHD when comparing studies involving dopaminergic transmission, specifically the DRD4, DRD5, DAT, and DBH<sup>6063</sup>. Dopamine pathways originating in the locus coeruleus and ventral tegmental area, which then project to the frontal cortex, are responsible for the modulation of executive function, as well as motivation, voluntary motor function, and the perception of reward<sup>64</sup>.

The basis of the dopamine hypothesis in the pathophysiology of ADHD was provided by the initial observation of psychostimulants in the laboratory<sup>65</sup>. Psychostimulants, which increase extracellular dopamine concentrations in the neuronal synaptic cleft, often had a calming effect, attenuating hyperactive symptoms and inability to focus<sup>66</sup>. This was somewhat of a paradox, as using stimulants to treat hyperactivity lead to a reduction of ADHD symptoms, rather than increasing them. For example, DAT knockout mice, which displayed hyperactive symptoms, responded to acute methylphenidate (MPH) treatment, and alleviated ADHD symptoms<sup>66</sup>. MPH binds and blocks DAT and NE transporters, functioning technically as a NDRI, with a stronger effect on DAT<sup>67</sup>. The enhanced effect of MPH modulating the levels of dopamine in the

synaptic cleft with a corresponding profound alleviation of ADHD symptoms allowed the medical community to obtain greater detail on the dopamine hypothesis and the utility of psychostimulants in the treatment of ADHD<sup>68</sup>.

Removal of DAT has profound implications on neuronal effects and activity. Since DA levels in the synaptic cleft are primarily regulated by the DAT, studies with knockout mice having no DAT showed profound effects in cognition, including hyperactivity and motor dysfunction<sup>69</sup>.

Studies on the pharmacodynamic effects of psychostimulants as a viable treatment for ADHD recognized the utility in increasing dopamine levels in the PFC as a way of attenuating symptomatic behavior of the disorder<sup>68</sup>. Nevertheless, it was still considered a paradox to treat hyperactive patients with stimulants. The basis of the approval and utility as a viable ADHD treatment, as with the discovery of many psychotropic agents, was that by exhibiting a favorable clinical response in treating the symptoms of the disorder, there was clinical justification for the use of psychostimulants in the treatment of child and adult patients with ADHD<sup>69</sup>.

Further research is warranted to delve into the specific mechanisms involving the pharmacodynamic effect of psychostimulants. For many years, the central dogma in understanding the mechanistic effect of stimulants, such as methylphenidate, in the treatment of ADHD was that the increased levels of DA in the synapse as a result of binding to the DAT led to a decrease in hyperactive symptoms and an increase in focus – providing a paradoxical calming effect and alleviating ADHD symptoms.

What is interesting to note is that in DAT knockout mice, where there was an



overwhelming increase in the levels of DA, the administration of methylphenidate would also alleviate such hyperactivity, although mice had already substantially higher amounts of DA in the synaptic cleft prior to administration. This led to the development of another important facet in the theorized pathophysiology of ADHD, involving the neurotransmitter serotonin, 5-HT.

### **Serotonin Modulation: Role in ADHD**

Serotonin, or 5-hydroxytryptamine, (5-HT), is a monoamine NT derived from the amino acid tryptophan. It is mainly found in the gastrointestinal tract of enterochromaffin cells, where it regulates gastrointestinal motility and digestion<sup>70</sup>. It is also found in blood platelets where it regulates clotting with its release<sup>70</sup>. Lastly, it is found in the CNS and, like DA and NE, functions in neurotransmission<sup>70</sup>. It is a known modality in pharmacotherapeutics in the treatment of mood disorders such as MDD and panic disorders such as GAD. Recently, studies have suggested that serotonin may be implicated in modulating dopaminergic neurotransmission as well.

For many years, a large majority of the research into the pathophysiology of ADHD was directed towards understanding more about dopamine and its role in CNS neurotransmission. This could be attributed to the success of methylphenidate in treating the disorder, in which its apparent effects on dopaminergic neurotransmission through the inhibition of DAT was thought to normalize deficient levels of DA leading to a reduction in hyperactivity and improvement of symptomatic behavior associated with ADHD<sup>71</sup>.

Although methylphenidate is classified as a dopamine-norepinephrine reuptake inhibitor (NDRI), the pharmacodynamics of methylphenidate shows a receptor binding profile of the SERT, 5HT<sub>1A</sub>, and 5HT<sub>2B</sub> as well<sup>72</sup>. One of the paradoxical studies that helped contribute to the theory of serotonin modulation in its role in the development of ADHD was the evidence that the use of methylphenidate led to the attenuation of hyperactive symptoms in mice who lacked the DAT transporter, in which methylphenidate did not noticeably change any levels of DA in the knock-out mice<sup>69</sup>. This was not observed in the wild-type mice, despite the similar effect of a non-substantial change in DA levels as the knock-out mice<sup>71</sup>. This study provided insight into the role of serotonin in modulating the development of dopaminergic transmission and thus the development of ADHD<sup>71</sup>.

The serotonergic and dopaminergic systems have been shown to not be mutually exclusive<sup>73</sup>. Administration of the SSRI, citalopram, has shown changes in extracellular striatal dopamine concentrations through the use of positron emission tomography<sup>73</sup>. Additionally, the use of a 5-HT antagonist, altanserin, has shown to modulate DA in freely-moving rats through measurement of in vivo microdialysis<sup>73</sup>. Since it is understood that the intricate overlap of dopaminergic and serotonergic neurotransmission modulate and influence each other in the CNS, the dynamic interaction of both NT's in synaptic transmission infers a validation in the dopamine hypothesis in the biological origin of ADHD, as well as affirming the argument of serotonergic modulation in influencing the pathophysiology of ADHD<sup>71</sup>.

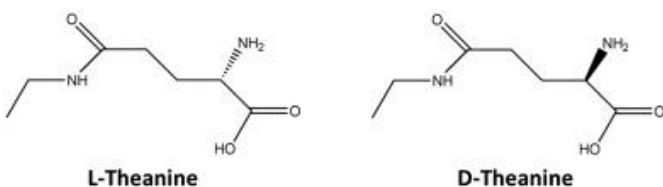
Much evidence exists that the serotonergic system exerts both a phasic and tonic inhibitory control of the mesocorticolimbic dopaminergic system originating from the VTA<sup>74</sup>. The utility of the serotonergic system as a modality in dopaminergic function provides a potential therapeutic option in the treatment of disorders not necessarily only involving 5-HT, but DA as well. Interestingly, the complexity of the intricate overlay and interaction of the dopaminergic and serotonergic systems can be validated by evidence that the 5HT1B receptor functions dually as a presynaptic and postsynaptic autoreceptor<sup>75</sup>. Furthermore, the 5-HT1B receptor functions as a heteroreceptor as well, influencing NT release from non-serotonergic nerve endings<sup>75</sup>.

### **L-Theanine: Synthesis and Occurrence**

L-theanine, also known as L- $\gamma$ -glutamylethylamide and *N*<sup>5</sup>-ethyl-L-glutamine, is a non-essential amino acid found naturally in tea plants<sup>76</sup>. It is what is thought to give green tea its delicate, organic flavor, and also activates umami receptors, which are thought to give a tingling and pleasant sensation of the palate, contributing to the flavor<sup>77</sup>. Although it is found in some fungal species, it accounts for up to 50% of the amino acids in green tea, and thus a major determinant of the quality of tea leaves<sup>76</sup>.

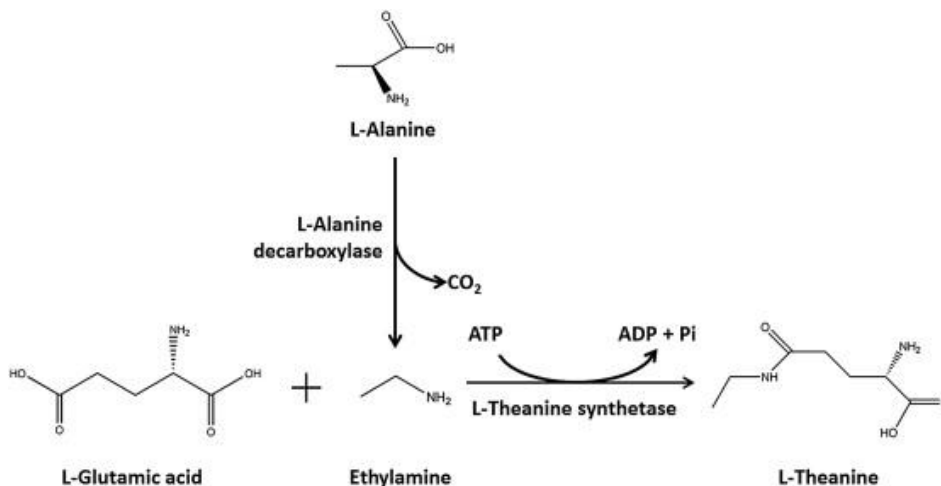
The species of tea plants in which L-theanine exist include the *Camellia sinensis*, known for its leaves in making green tea. Additionally, it has been found in fungal species, including the *Xerocomus badius*<sup>76</sup>. In the species *C. sinensis*, L-theanine is synthesized from L-glutamic acid and ethylamine to produce L-theanine via L-theanine

synthetase. Ethylamine is produced by L-alanine by L-alanine decarboxylase. Like other alpha-amino acids, theanine possesses chirality, and since L-theanine is naturally produced in *C. sinensis* from L-glutamic acid, it is the L-theanine enantiomer that is found readily available in tea plants.



**Figure 2: Structure of L-theanine and D-Theanine**

Mu W, Zhang T, Jiang B. An overview of biological production of L-theanine. *Biotechnol Adv.*



**Figure 3: Biosynthetic pathway of L-theanine proposed in *Camellia sinensis***

Mu W, Zhang T, Jiang B. An overview of biological production of L-theanine. *Biotechnol Adv.*

## **Pharmacokinetic Properties of L-Theanine**

The pharmacodynamic property of L-theanine of crossing the blood - brain barrier was first reported from Terashima et al<sup>78</sup>. The study showed that concentrations of L-theanine increased in serum, liver and brain up to 1 hour after administration, and subsequently after the first hour, dramatically declined in the serum and hepatic circulation, but concentrations in brain tissue steadily remained until 5 hours after administration, when its levels began to decrease<sup>7879</sup>. Terashima et al. proposed the route by which L-theanine was incorporated in the CNS, crossing the blood brain barrier through the leucine-preferring transport system<sup>79</sup>. When L-theanine was administered intraperitoneally, experiments by Kimura and Murata showed that L-theanine was taken up by brain tissue in little as 30 minutes<sup>80</sup>. L-theanine seems to have a significant half life, as concentrations decrease at a gradual rate during a 24 hour period<sup>79</sup>.

Studies have shown that L-theanine is absorbed primarily in the gastrointestinal tract, through the use of Na-coupled active transporters on the brush border membrane in a mechanism similar to glutamine, with a peak absorption of about 0.5-2 hours<sup>8182</sup>. Animal studies have shown the enantiomeric selectivity of L-theanine vs D-theanine in vivo. When measuring plasma theanine concentrations via oral administration, there was a significant decrease in gastrointestinal absorption of D-theanine compared to the psychoactive L-theanine.

L-theanine tended to be preferentially reabsorbed and metabolized by the kidney, whereas D-theanine was actively and preferentially secreted, unmetabolized in the

urine<sup>82</sup>. Not much is known about the specific metabolic effects, as it seems that L-theanine is primarily metabolized by the kidney and mostly excreted, with little change in plasma concentrations of its metabolites. The proposed mechanism is the hydrolysis of L-theanine to ethylamine and glutamic acid in the kidneys by phosphate-independent glutaminase, as the kidney is one of the most effective sites of hydrolysis for its metabolism to glutamic acid and ethylamine<sup>83</sup>.

### **Toxicity**

Studies on the toxicity of L-theanine have shown little or no adverse effects on rats which were administered daily dietary doses of 1500-4000mg/kg/day for at least 13 weeks<sup>84</sup>. Clinical pathology on microscopic and macroscopic levels found L-theanine not to adversely affect male and female rats, even at such profoundly high dosages<sup>84</sup>. Borzelleca et al. concluded that dose-dependent treatment of L-theanine did not produce any adverse toxic effects on parameters measured, including a 78-week chronic toxicity/carcinogenicity study and a negative Ames test<sup>84</sup>. It was concluded through his study that no adverse effects were related to the chronic administration of L-theanine up to 4000mg/kg/bw/day<sup>84</sup>.

### **Effects of L-Theanine on Neurotransmission**

Since L-theanine is derived from the excitatory NT glutamate, the overlap of pharmacologic effects of L-theanine in dopaminergic neurotransmission seems plausible.

Studies have reported the effects of L-theanine on neurotransmission in which, after only 30 minutes of administration, L-theanine could modulate the release and functionality of NTs<sup>81</sup>. A dose-dependent increase of nigrostriatal dopamine release in rats after oral administration and direct injection of L-theanine has been shown, in which the mechanism proposed in dopaminergic modulation is from Ca<sup>++</sup> release from L-theanine stimulation of NMDA receptors<sup>81</sup>.

Studies from Yokogoshi et al. showed that NE neurotransmission may not be affected to the same extent that dopaminergic and serotonergic transmission is influenced<sup>85</sup>. Their study hypothesized that L-theanine may exhibit selective modulation on dopaminergic and serotonergic neurons, as there were substantial increases in both 5-HT and DA in the hippocampus, hypothalamus, and nigrostriatal regions, with little change in the levels of NE<sup>85</sup>.

Furthermore, L-theanine exhibited, in a dose-dependent manner, increases of dopaminergic neurotransmission when administered directly to the nigrostriatal region via microinjection<sup>85</sup>. Interestingly, the use of an antagonist of the NMDA glutamate receptor, (+/-)-2-amino-5-phosphonopentanoic acid (AP-5), dramatically inhibited DA release after L-theanine administration, possibly alluding that a significant modality in which L-theanine influences dopaminergic transmission may be through the action of the NMDA glutamate receptor<sup>85</sup>.

Another study by Yokogoshi et al. provided insight into the modulation of L-theanine on serotonergic neurotransmission. In rats, intragastric administration of L-

theanine was shown to substantially increase the concentrations of the 5-HT precursor, tryptophan, in the brain<sup>86</sup>. Paradoxically, L-theanine had the effect of attenuating 5-HT concentrations, although it would increase tryptophan levels<sup>86</sup>. Although elucidating the significance of these findings proved to be difficult, there was a steady dose-dependent relationship of L-theanine and an increase in the precursor amino acid tryptophan and decrease in 5-HT<sup>86</sup>. Yokogoshi et al. also pointed that there was interesting evidence that tryptophan influenced 5-HT concentrations in the CNS by a mechanism called precursor-mediated control of NT, further validating the intricate nature of overlay between feedback-inhibition and overlap of serotonergic and dopaminergic neurotransmission<sup>86</sup>. It is also thought that L-theanine modulates glutamate reuptake through inhibition and potentiates the effects of GABA, which may contribute to the anxiolytic effects of L-theanine<sup>87</sup>.

### **Anxiolytic Effects on Patients**

Anxiolytic effects of L-theanine have been a recent topic of interest. One study using Sprague-Dawley rats by Heese et al. examined the effects of L-theanine on alleviating anxiety and how it relates to the GABA<sub>A</sub> receptor<sup>88</sup>. Through experiments with a BZD and a GABA<sub>A</sub>receptor antagonist, flumazenil, the behavioral component of anxiety was analyzed<sup>88</sup>. Heese et al. concluded that the anxiolytic effect of L-theanine does not occur through potentiation of the GABA<sub>A</sub> receptor, rather, it was shown that an *additive effect* of anxiolysis was promoted through concurrent administration of the BZD midazolam with L-theanine, including fine motor movements, providing further evidence



of the anxiolytic effects of L-theanine<sup>88</sup>.

Another study evaluating the effects of L-theanine on PTSD studied the changes in gene expression implicated in PTSD individuals through evaluation of the amygdala and hippocampus of Spague-Dawley rats<sup>89</sup>. Using one-way ANOVA, 88 genes were studied, in which 17 had a significant effect size  $>0.138$ <sup>89</sup>. 3 genes in the hippocampal region and amygdala were considered statistically significant with a  $P < 0.05$ <sup>89</sup>. Using reverse transcriptase polymerase chain reaction (RT-PCR), Ceremuga et al. was able to ascertain substantial changes between groups implicated in a variety of anxiety and mood disorders, including DRD2 and DRD1A<sup>89</sup>. Although the mechanisms related to the anxiolytic effects of L-theanine aren't fully understood, it is speculated that the potentiation of GABA is the main biochemical mechanism responsible for the decrease in anxiety related symptoms<sup>87</sup>.

### **Anxiety and Schizophrenia**

An interesting correlate to psychiatric medicine is that there are many studies showing the significant anxiety of patients with schizophrenia<sup>90</sup>. Often times, schizophrenic patients are administered antipsychotic medications which have negative side effects, with anxiety being one of the most common complaints among patients<sup>90</sup>. Additionally, anxiety is often a co-morbidity with schizophrenia, thus exacerbating the devastating effects anxiety can have on the patient, in which suicidal ideation and attempts are often significant risks posed to schizophrenic patients<sup>90</sup>. As a result, recent

studies have shown the substantial attenuation of anxiety that L-theanine may provide, without the long-term consequences or negative side effects associated with conventional treatment modalities of BZDs.

Many of the medications in which schizophrenic patients take often have unwanted side effects, including negative symptoms of blunted affect, alogia and anhedonia, often referred to as SANS. One study by Kardashev et al. suggested that augmenting treatment with L-theanine could drastically attenuate such negative symptoms. Utilizing pregnenolone with L-theanine was shown to offer a dramatic reduction in negative SANS symptoms, compared to placebo<sup>91</sup>. Interestingly, the use of pregnenolone and L-theanine was associated with a decrease in anxiety as related to symptoms of anxious mood and tension<sup>91</sup>.

### **L-Theanine Effects on Mood and Cognition**

One study by Tamano et al. focused on the impact L-theanine may have on recognition memory in young rats<sup>92</sup>. Using 0.3% theanine solution after weaning young rats, object recognition memory was shown to be maintained in the theanine administered rats, compared to the control group<sup>92</sup>. Levels of brain derived neurotrophic factor and nerve growth factor, both constituents of brain development, were shown to be substantially elevated in the hippocampus in the theanine administered group vs control group<sup>92</sup>. Their study implied the beneficial impact theanine administration had on the young rats, possibly improving development of the hippocampus<sup>92</sup>.

## **Studies on Measuring Cognitive Effects In Combination with Caffeine**

Caffeine, one of the most commonly used stimulants in the world, affects the adenosine A1 and A2a receptors and has been implicated in increasing Ach and DA neurotransmission, NT's which are associated with cognition and arousal. L-theanine through its proposed mechanisms of glutamate reuptake inhibition as well as the potentiation on the NT GABA, DA, and 5-HT, may have a modulatory effect of caffeine on its ability to enhance cognition<sup>87</sup>.

The combination of caffeine and L-theanine, as present naturally in green tea, has been shown to increase accuracy in cognition<sup>87</sup>. This was most profound during the first hour post administration<sup>87</sup>. Increases in attention task-switching was most noticeable during the first hour, with a slightly smaller effect in the second hour<sup>87</sup>. The meta-analysis of L-theanine in conjunction with caffeine also showed improvement on unisensory auditory attention, with significant improvement during the second hour<sup>87</sup>. One study by Einother et al. showed how the concomitant dosing of caffeine and L-theanine with a relatively high dose of L-theanine (97mg) with a smaller dose of caffeine (40mg) showed a greater significance in improvement in reaction time the first hour<sup>93</sup>. Nevertheless, the administration of caffeine and L-theanine was shown to significantly improve attention on a switch task in comparison to a placebo, demonstrating that concomitant administration has a positive effect in improving attention<sup>93</sup>.

The meta-analysis by Camfield et al. concluded that the combination of L-theanine and caffeine increased attention switching accuracy for both the first and second hours,

and an improvement of unisensory visual attention accuracy was found following concomitant administration for the first hour postdose<sup>87</sup>. Furthermore, an incremental enhancement of unisensory auditory attention accuracy was found following in the second hour post dose<sup>87</sup>. Although pharmacological study of L-theanine in relation to its improvement on cognition with or without caffeine is a relatively new area of research, more research data would be helpful in validating the claims of current studies, as there is still limited amount of empirical data.

### **Molecular Effects of Caffeine and L-Theanine: Attenuation of L-Theanine on Overstimulation**

L-theanine, being structurally similar to glutamic acid, has been associated with an increase in release of DA, an inhibition of the reuptake of glutamate, and antagonist of hippocampal glutamate receptors, and increase in GABA concentrations, and an increase release of 5-HT in the hippocampus, hypothalamus, and striatum<sup>94</sup>. Interestingly, L-theanine is thought to interact with caffeine by decreasing serotonin levels that have been elevated from caffeine intake<sup>94</sup>. Additionally, L-theanine tends to attenuate potential overstimulation caused by caffeine, as shown by its ability to lower blood pressure changes in response to stress<sup>94</sup>. Thus, it is implicated that the overall moiety of L-theanine on a variety of neurotransmitters, and its overlay of interaction of the molecular transduction of caffeine, is thought to tone-down overstimulation by caffeine. This could

perhaps be the biological mechanism leading to a synergistic effect of caffeine and L-theanine, as the effects on the CNS by L-theanine work in combination with caffeine to enhance cognition and alertness due to increases in the monoamines, as well as providing neuroprotective effects by L-theanine due to its modulation on the glutamate receptors<sup>94</sup>.

### **Effects of L-Theanine on Alpha-Wave and Brain Function**

A limited number of studies have shown that L-theanine, an herbal supplement known to help induce relaxation, increases alpha-wave brain activity through studies involving electroencephalography (EEG), indicative of a wakeful, relaxed state<sup>94</sup>. Alpha-wave brain activity is also associated with enhanced performance under stress, increased creativity, improved learning and concentration, as well as decreased anxiety<sup>94</sup>. Thus, the apparent effect of increasing alpha-wave brain activity through measurement of EEG by L-theanine may be what causes the favorable psychologic outcomes of increased cognition, focus, and relaxation<sup>94</sup>.

### **L-Theanine as a Treatment for Sleep Disorders in Patients Co-Morbid with Anxiety Disorders**

Sleep deprivation is associated with an increased risk of various diseases, also causing a poor quality of life and socioeconomic consequences<sup>95</sup>. Anxiolysis is a requisite in the induction of high-quality sleep, and the anxiolytic effects of L-theanine in its potential use as a natural sleep aid was studied by Rao et al<sup>95</sup>.

Anxiolytic effects of L-theanine, as evidenced by an increase in alpha – brain wave activity, have promoted the utility of L-theanine as a natural anxiolytic without the negative side effects of conventional pharmacological modalities. Furthermore, utilizing a small dose of L-theanine, 200mg, Rao et al. provided evidence that the anxiolytic properties of L-theanine may improve sleep quality in patients not because of the sedative effects, but due to its anxiolytic properties associated with increased alpha-wave brain activity<sup>95</sup>. The unique property of L-theanine in promoting relaxation without sedation suggests that it can promote sleep induction and improve the quality of sleep, without the groggy effects often produced by current over-the-counter and prescription treatments<sup>95</sup>. The paradoxical effect of L-theanine promoting relaxation through the stimulation of alpha waves, but without the sedating effects provides substantial evidence of the potential use of L-theanine as a safe and natural sleep aid<sup>95</sup>.

One study by Barrett et al. investigated the current treatment modalities in children with ADHD who were comorbid with insomnia<sup>96</sup>. It showed that although zolpidem and L-theanine exhibited poor response in reducing sleep latency and increasing total sleep time, L-theanine produced an increase in sleep efficiency<sup>96</sup>. This could prove to be beneficial with the pediatric patient population who are administered stimulant medications to treat ADHD, as zolpidem is shown to have high levels of side effects and its compliance is lower in children and adolescents<sup>96</sup>. Thus, it is recommended that further research be pursued on the pharmacologic modalities for individual who have ADHD-related sleep disorders, as well as additional studies on the potential of supplementing L-theanine to help improve sleep quality among ADHD patients.

## **Neuroprotective Effects of L-Theanine**

### **Ischemia**

L-theanine has been implicated in providing neuroprotective effects, with possibly providing neuroprotection from ischemia<sup>97</sup>. Zukhurova et al. investigated on the effects of postischemic administration of L-theanine (1 and 4mg/kg) administered at 3, 12, and 24 hours post reperfusion, as well as the effects of L-theanine on brain injury induced by exogenous administration of NMDA receptor agonists during reperfusion<sup>97</sup>.

After subjecting rats to 30 minutes of middle cerebral artery occlusion followed by 48 hour reperfusion, neurological deficits and infarct size were determined. At 3 and 12 hours after reperfusion, L-theanine was shown to substantially reduce the size of brain infarction<sup>97</sup>. Furthermore, neurological status was improved with postischemic administration of L-theanine at 3, 12, and 24 hours after reperfusion<sup>97</sup>. Additionally, intrastriatal injections of L-theanine (total dose of 800µg/kg) prevented brain injury caused by NMDA receptor agonists, further providing evidence on the neuroprotective effect of L-theanine induced by ischemia or by exogenous administration of glutamate receptor agonists<sup>97</sup>.

### **Parkinson's Disease**

Not only is L-theanine implicated in neuroprotection resulting from ischemic effects and exogenous induction of glutamate receptor agonists, but Cho et al.

investigated the protective effect of L-theanine on nigrostriatal dopaminergic neurons in Parkinson's disease<sup>98</sup>. Using L-theanine as a protective agent in neurotoxicity induced from rotenone and dieldrin, known PD-related neurotoxicants, the study revealed doses of 500 microM reduced both rotenone and dieldrin-induced DNA fragmentation and apoptotic death in the cultured human dopaminergic cell line SH-SY5Y cells<sup>98</sup>.

Additionally, down-regulation of extracellular signal-regulated kinase (ERK 1/2) phosphorylation was substantially blocked with L-theanine administration. Lastly, the attenuation of L-theanine on the down-regulation of BDNF and glial cell line-derived neurotrophic factor (GDNF) provides even more evidence of L-theanine in providing neuroprotection against PD-related toxicants, warranting further research into the investigation of L-theanine as a prophylactic agent to reduce further damage in Parkinson's disease patients with intention to improve the prognosis as well as possibly providing symptomatic relief from Parkinson's disease-related symptoms.

### **Alzheimer's Disease**

There has been recent evidence for the possibly neuroprotective effects of L-theanine on patients with Alzheimer's disease. Much pathologic evidence points to the Amyloid  $\beta$  ( $A\beta$ ) Protein in mediating neurotoxicity and cell death in patients with Alzheimer's disease<sup>99</sup>. The  $A\beta$  Protein accumulates abnormally in the cortex and hippocampus in the brain of AD patients –leading to the direct induction of protein-



mediated neuronal cell death<sup>99</sup>. The overactivation of the mitogen-activated protein kinase pathway (MAPK) and the nuclear factor  $\kappa$ B (NF- $\kappa$ B) pathways are strongly implicated as central pathways in promoting neuronal cell apoptosis<sup>100,101</sup>. Research validating that the inhibition of these pathways is currently limited and could be tremendously useful in the treatment of neurodegenerative diseases using L-theanine<sup>102,103</sup>.

A study by Kim et al. investigated the effects of reactive oxygen species generated by A $\beta$  and the neuroprotective effects of L-theanine through the attenuation of oxidative damage by A $\beta$ <sup>104</sup>. The study showed that oral administration of L-theanine for 5 weeks, followed by injection of A $\beta_{1-42}$ , dramatically reduced memory impairment caused by A $\beta_{1-42}$  in mice<sup>104</sup>. Kim et al. hypothesized that the reduction in memory impairment may have been due to the significant reduction in A $\beta_1$  levels and the concomitant A $\beta_{1-42}$ -induced neuronal cell death, both in the hippocampal region and the cortex of the brain<sup>104</sup>. Furthermore, L-theanine inhibited extracellular signal-related kinase (ERK) and NF- $\kappa$ B, while also promoting a significant attenuation on oxidative protein and lipid damage and elevated glutathione levels in the brain<sup>104</sup>. Such evidence of the reduction on oxidative damage, as well as attenuating pathways associated with neuronal cell apoptosis, warrants continued investigation on the potential use of L-theanine for treatment in Alzheimer's disease.

## **L-Theanine: Anxiolytic effects Which Could Benefit Other Medical Conditions**

### **Diabetes**

There is some evidence that L-theanine may be effective against diabetes mellitus induced neurodegeneration. The CNS is quite susceptible to subtle changes in glucose, and glucose fluctuations related to hyperglycemia can amplify oxidative stress on the brain<sup>105</sup>. Much research has been performed on the increased risk of the development of neurodegenerative diseases among individuals with diabetes<sup>105</sup>. As already demonstrated with the Kim et al. study, L-theanine tends to promote the reduction in oxidative damage related to the CNS, and regular intake of L-theanine through the regular consumption of green tea has been implicated in not only improving DM-related complications, but also providing neuroprotective effects and antioxidant potential to improve cognition in DM patients<sup>105</sup>. The neuroprotective effect caused by a variety of conditions warrants more research into the profound benefits of L-theanine administration among individuals with DM or other neurodegenerative conditions.

### **Hypertension**

A study by Yoto et al has shown not only the benefits of L-theanine on attenuation of anxiety, but also reducing blood pressure increases in high stress-response adults after performing mental tasks compared to placebo. This evidence was consistent with the blood pressure reducing effect of L-theanine in another study by Rogers et al., in which L-theanine attenuated blood pressure increases resulting from caffeine intake<sup>106</sup>. Although stress may not be directly correlated with the development of hypertension, it is known that repeated elevations of blood pressure as a response to stress, can eventually lead to hypertension<sup>107</sup>. In a sense, if L-theanine helps attenuate blood pressure responses

from stressful events or tasks, it could possibly be a therapeutic route to help prevent the development of hypertension<sup>108</sup>.

Thus, it is apparent that additional research on the relationship between anxiety, blood pressure changes, and the administration of L-theanine would be recommended to investigate the potential use of L-theanine in not only treating anxiety, but also as a potential dietary supplement or even a pharmacological modality used to treat hypertension.

## **DISCUSSION**

Negative physiological responses, such as changes in blood pressure in response to anxiety, provide ample evidence of the utility in L-theanine as a potential therapeutic agent in psychiatric conditions of anxiety, mood disorders, a natural sleep aid, as well as providing neuroprotective effects in individuals with neurological disorders of Alzheimer's Disease, Parkinson's disease, and dementia with implications of helping other pathologic conditions of diabetes and hypertension in patients who are co-morbid with such common medical conditions.

The initial studies found on L-theanine to be a natural anxiolytic with potential implications in its use for psychiatric conditions where co-morbidities often exist, show positive results with great therapeutic potential. The widespread utility of L-theanine, a rather non-toxic, non-essential amino acid found mainly in the *C. sinensis* green tea leaves, provides much support in its ability to attenuate anxiety in schizophrenic patients, and

improving cognition in patients, with or without co-morbidities of ADHD, depression, and PTSD.

The relaxation-promoting effects through the stimulation of alpha-wave brain activity provides opportunity for a multitude of uses, from as a natural sleep aid, to an increase in cognition in individuals who have ADHD and/or are co-morbid for anxiety disorders. Additionally, individuals looking for a natural way to induce alpha-wave activity for relaxation and improvement of cognition could use L-theanine as a natural supplement.

Current pharmacologic modalities which are considered gold-standard in treatment of anxiety, such as BZDs, have known long-term negative effects, including effects on cognition, as well as the potential for abuse and physical and psychological dependency. Thus, BZDs should be prescribed with caution, as the apparent long-term use associated with them are apparent. Without a doubt, such pharmacologic agents are known to have negative effects on cognitive function, especially in the elderly, with not a promise of such individuals returning to baseline function. Furthermore, such agents have a tendency to be potentially abused among patient populations, and if it were possible to treat such anxiety disorders with a relatively non-toxic, non-addictive amino acid, it seems that research in comparing the utility of L-theanine and BZDs holds credibility with potential to have a greatly positive impact on patient populations in the medical community.

Since the number of studies available on the pharmacodynamic effects of L-theanine are very limited, it is recommended that further elucidation of the molecular

mechanisms which cause the favorable clinical effects known thus far of L-theanine would be recommended. If we are able to hone and ascertain more about the biology of specific psychiatric conditions of anxiety and mood disorders in their relation to L-theanine, the potential for L-theanine not only as a natural sleep aid or herbal supplement with relaxative and focusing properties would not only be validated, but warrant the true potential as a legitimate psychotropic modality in the field of not only psychiatry, but other fields as well in which the concomitant use of BZDs is pertinent, such as the elderly population who may be seen regularly by a primary care physician.

The specificity in the need of a non-toxic, non-addictive anxiolytic with little effect on the cognitive function of patients proves to be of great utility. Furthermore, understanding the neuroprotective effects of L-theanine promotes another realm of scientific research which has great implications for improving the betterment of the patient populations involving Alzheimer's disease, dementia, and Parkinson's disease.

An overwhelming majority of the patient population affected by dementia and Alzheimer's disease tends to be within the elderly, giving a dual benefit in individuals suffering from both neurologic conditions as well as anxiety disorders. Thus, it seems with exigence that further research into understanding the biologic origins and effects of L-theanine on this patient demographic proves to be extremely useful and worthwhile.

It should be noted that the potential utility of L-theanine in treating neurologic and psychiatric conditions warrants further research and investigation. Additionally, the widespread effects of L-theanine have yet to be determined, and initial studies have shown the potential for L-theanine to be used as an adjunct treatment in modulating

chemotherapy and hyperlipidemia. The wide potential uses of L-theanine not only apply to the realm of neurologic and psychiatric medicine, but also for a plethora of other medical conditions.

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**EDUCATION**

**Boston University School of Medicine – Boston, MA**

Master of Science in Medical Sciences, 2016 (anticipated)

**University of Tennessee Health Science Center – Memphis, TN**

Master of Science in Pharmacology, May 2012

**Pennsylvania State University –University Park, PA**

Bachelor of Science in Biochemistry and Molecular Biology, May 2006

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**PROFESSIONAL EXPERIENCE**

**Elite Medical Scribes**

*Medical Scribe February 2016 - current*

- Provide real-time charting for physicians by shadowing them throughout their shifts and performing a variety of tasks, including recording patients' histories and chief complaints, transcribing physical exams, ordering x-rays, recording diagnostic test results, and preparing plans for follow-up care
- Each shift I was assigned to a physician and work alongside with them as they see patients, documenting directly from the conversation between the provider and patient

**Walgreen's Pharmacy, Inc**

*Research Technician, January 2010- March 2011*

- Entered, filled, and checked out prescriptions to patients
  - Answered phone calls of patients regarding refills
-

## **VOLUNTEER WORK**

### **Boston Medical Center**

*Volunteer Ambassador, January 2015 - June 2015*

- Escorted patients and their families to their appointment on the Boston Medical Center campus
- Comforted and established rapport with a wide variety of demographics

### **Outreach Van Project**

*Outreach Volunteer, January 2015 - June 2015*

- Helped distribute clothing and food to the indigent population of East Boston

### **Christian and Missionary Alliance**

*Teen Camp Counselor, May 2013-2016*

- Camp counselor to adolescents ranging from 11-18 years of age
- Oversaw campsite of 12-15 teenagers

### **Free Medical Clinic of America**

*Clinic Volunteer, August 2009 – December 2009*

- Welcomed and checked in patients of a wide range of demographics
  - Answered phone calls and scheduled appointments
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## **SKILLS**

- **Computers-** Microsoft Word, Excel, Powerpoint, Typing speed 70+ WPM