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Review Article

Alpha casozepine and L-theanine in ameliorating stress levels in infertile couples: a review

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ABSTRACT

Globally, the fertility rate has decreased significantly in the last two decades. Infertility can lead to psychological and emotional stress, particularly for couples who have been married for a long period. According to the literature, stress can alter the metabolic environment and reduce the likelihood of pregnancy. The fertility treatments involving assisted reproductive technology put additional physical, mental, and financial strain on patients, especially women who are frequently subjected to invasive procedures as part of the process. Stress affects the hypothalamic-pituitary-adrenal (HPA) axis, the concentration of reproductive hormones (FSH, GnRH, and LH), and other biological processes through a variety of mechanisms. Alteration of glucocorticoid hormone levels in the blood was observed because of stress in infertile couples. Moreover, the males also get affected by stress as per the semen parameters and quality analysis. Available evidence strongly suggests that stress reduction should be the first step in a fertility therapy regimen. Further, managing stress can boost ovarian function and semen parameters. The current review focuses on the state-of-the-art research on stress-induced reproductive dysfunction as well as the positive effects of alpha-casozepine, an anxiolytic-like bioactive decapeptide and L-theanine, an amino acid found primarily in green tea on reducing stress levels and improving treatment outcomes in infertile couples.

Keywords: Alpha-casozepine, Stress, Infertility, L-theanine, HPA axis, Hypothalamic-pituitary-gonadal axis

INTRODUCTION

Globally, the fertility rate is steadily decreasing. Millions of people around the world who are of reproductive age struggle with infertility. The term ‘infertility’ refers to a disorder of the male or female reproductive system which is characterized by the inability to conceive after 12 months or more of frequent, unprotected sexual activity.[1] According to recent data, infertility affects between 48 million couples and 186 million people worldwide.[2] However, infertility management in the public health sector is frequently of a low standard or non-existent in many underdeveloped nations. They will have access to a variety of treatments, some of which may be of variable quality and value. The average cost of *in-vitro* fertilization (IVF) for couples is close to $25,000 in the USA.[3] Considering the Indian scenario, around 15% of Indian couples struggle with infertility. The issue is exacerbated by late marriages, stressful lifestyles, high junk food intake, obesity, alcohol, smoking, and drug addiction. Due to infertility, married couples especially those who have been together for a long time without having children, experience psychological and emotional stress.[4]

A general definition of stress is a strong, irregular threat to homeostasis that causes a non-specific reaction, including widespread activation of the HPA axis and sympathomimetic system. Stress and the stress response are the terms used for the stimulus and the body's response, respectively. Stress can be broadly divided into "physical" or "psychological" stress based on the immediate effects on the body, the endocrine system, as well as neural reactions.

Stress levels can change both partners' physiological environment and lessen the chances of pregnancy during fertility treatments.[5] Patients who undergo assisted reproductive technology (ART) procedures have an increased physical, mental, and financial load; in particular, women who routinely undergo uncomfortable procedures as part of infertility treatments are said to experience extremely high levels of stress.[6] The hypothalamic-pituitary-adrenal (HPA) axis, reproductive hormones (FSH, GnRH, and LH), and other biological processes can all be impacted by these elevated stress levels.[7] Stress can alter the levels of the glucocorticoid hormone in the ovarian follicles.[8] and can affect libido, sperm quality, ovulatory function, and implantation.

As more and more infertile couples are seeking treatments using assisted reproductive technology.[9] Stress can cause treatment failures, requiring additional IVF cycles or possibly termination of treatment. Pre-existing anxiety, depression, and a great deal of discomfort can potentially harm the success of treatment.[10]

Interventions for stress reduction may increase the likelihood of a successful pregnancy, according to clinical evidence. interventions like counselling, cognitive behavioural therapy, mind or body-oriented relaxation, education, and psychodynamic therapy have a positive impact on pregnancy rates.[11] A meta-analysis that included 22 research studies indicated that psychotherapy is beneficial for conception. In this meta-analysis, 45% of intervention group participants showed a positive pregnancy rate compared to only 14% of controls.[12]

These findings have led to an increased focus on stress management for couples undergoing reproductive treatments. According to the Australian Assisted Reproductive Treatment Act of 2008, pre-treatment counselling is required and must cover potential stressors and coping mechanisms.[13] Stress management has the potential to significantly boost rates of reproductive success if we can identify the correct strategies that work best for infertile couples.

HPA AXIS: INFLUENCE OF STRESS

Interoceptive, homeostatic, and systemic physical stressors are those that can immediately compromise tissue integrity and specifically activate the central amygdala, the entire HPA axis, and the sympathomimetic system.[14] Further, stress is characterized by a threat to tissue disturbance, as well as a distinct medial amygdala and caudal A1 and A2 brainstem noradrenergic pattern of neuronal activation.[15]

Both physical and psychological stress activates the sympathetic-adrenal-medullary system, resulting in the release of adrenaline, and noradrenaline, increasing heart rate, blood pressure, respiration, and blood glucose levels. At acute stress, the HPA axis gets activated, and the cells expressing corticotropin-releasing hormone (CRH) and arginine vasopressin in the paraventricular nucleus of the hypothalamus (PVN), get stimulated and release CRH which further stimulates corticotropes from the anterior pituitary gland to release adrenocorticoids within 20-30 minutes.[16,17] Adrenocorticoids (ACTH) stimulate the synthesis and release of glucocorticoids into circulation by acting on melanocortin-2 receptors in the adrenal cortex. Glucocorticoids remain elevated for the next 60-120 minutes and play a role in immunosuppression, glucose uptake, mobilization, and storage of fat. [18] Once the stress is resolved glucocorticoids act on glucocorticoid and mineralocorticoid receptors, primarily in the hippocampus and hypothalamus, inhibiting further paraventricular nucleus (PVN) activation and thus suppressing ongoing HPA axis activation (Figure 1).[19]

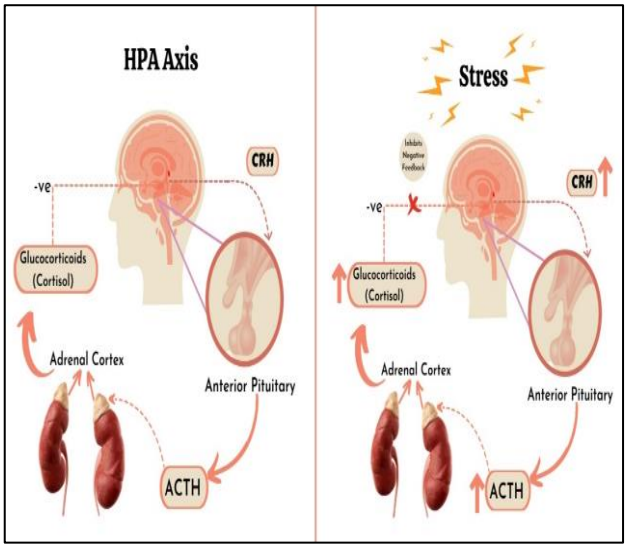

Figure 1: Stress and its impact on HPA axis.

In most cases, the acute stress reaction is a highly adaptive event that enables the person to effectively deal with the stressor and recuperate. Negative effects, however, may result if a stressor persists, as in the case of a protracted sickness or exposure to substantial life obstacles like infertility.[20]

HYPOTHALAMIC-PITUITARY-GONADAL AXIS: INFLUENCE OF STRESS

Reproduction is an essential function governed by a complex regulatory network of neuroendocrine signals generated and integrated by the hypothalamic-pituitary-gonadal (HPG) axis. The HPG hormonal cascade begins in the hypothalamus' medial preoptic area (mPOA) with the release of gonadotropin-releasing hormone (GnRH). The GnRH is released in a synchronized pulsatile manner and serves as the central control mechanism for the reproductive cycle.[21]The GnRH peptide is secreted from the nerve endings into the hypophyseal portal system to stimulate the synthesis and release of the anterior pituitary gonadotropins, luteinizing hormone (LH), and follicle-stimulating hormone (FSH).[22]

FSH and LH stimulate gonadal gamete production and the release of sex steroids such as estrogen, progesterone, and testosterone.[23] The levels of hormones are influenced by neuroendocrine signals and are regulated by complex positive and negative feedback loops. The HPA and HPG axis are well known to co-regulate each other both centrally and peripherally. The extent of stress (acute versus chronic), sex, and individual differences in resilience all influence stress' ability to influence reproduction (Figure 2).[24]

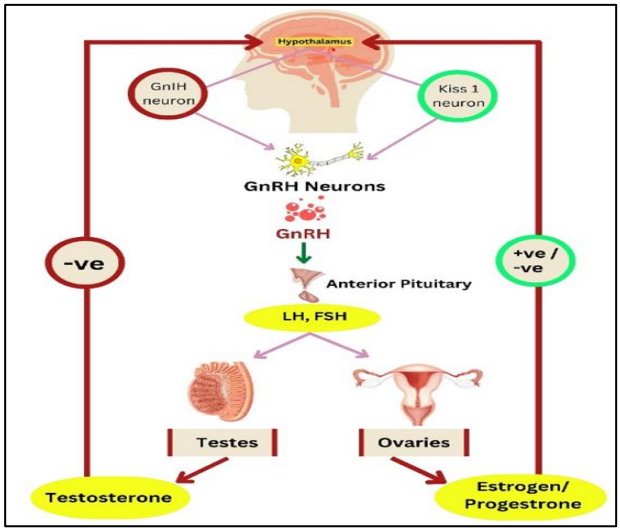

Figure 2: HPG axis.

Stress has an impact on the hypothalamic GnRH pulse generator. Stress decreases pulsatile gonadotropin release, causing amenorrhea and other reproductive dysregulations associated with a loss of pulsatility (Figure 3).

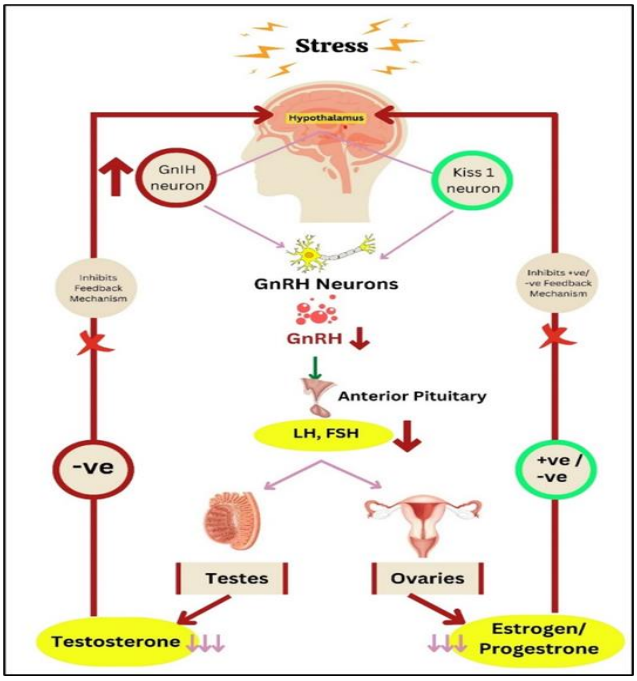

Figure 3: Effects of stress on HPG axis.

The inhibition of the GnRH pulse generator by CRH in several animal and human models exhibits that the stress delays the pituitary's release of gonadotropins. The CRH neuropeptide family integrates neuroendocrine stress responses in the brain via two distinct receptor subtypes, CRH receptor type 1 (CRH-R1) and type 2 (CRH-R2), with CRH having a higher binding affinity to CRH-R1.[25] CRH-R1 is abundant in the brain and pituitary glands, but not in peripheral tissues. CRH-R1 is primarily responsible for driving HPA axis activation during stress, and CRH-R2 is responsible for stress-induced suppression of the GnRH pulse generator.[26]

EFFECTS OF STRESS IS MEDIATED BY γ-AMINOBUTYRIC ACID (GABA)

The inhibitory effect of stress on GnRH pulsatility is likely to be mediated by γ -aminobutyric acid (GABA)-ergic signaling. Most studies have reported GABA inhibitory effects on GnRH/LH pulsatility, by inhibitory actions on GnRH neurons. Predominantly, GABA-A receptor activation has been proposed to mediate the inhibitory effects of GABA-ergic signaling. GABA-A and GABA-B receptors in the medial preoptic area (mPOA) of the hypothalamus are involved in different ways in mediating the effects of stress on LH pulsatility, and antagonists of both receptors have been shown to block CRH-induced inhibition of LH release in rats.[27]

FEEDBACK MECHANISM OF GLUCOCORTICOIDS DURING STRESS

The glucocorticoids can directly act on the pituitary gland to inhibit its responsiveness to GnRH and reduce gonadotropin release (FSH, LH) both in vivo and in vitro.[28] Stress is typically associated with decreased gonadal steroid (sex steroids) production associated with stress-induced increases in glucocorticoids.[29,30] Glucocorticoids act directly on leydig cells that express glucocorticoid receptors in the testis and have a direct effect on the ovary.[31] Glucocorticoid receptors are expressed in a variety of ovarian cell types, and their expression is maintained during follicular maturation, ovulation, and pregnancy.[32] 11-β hydroxysteroid dehydrogenase regulates glucocorticoid action in the ovary and reduced 11-β hydroxysteroid dehydrogenase activity mediates cortisol-induced inhibition of ovarian steroidogenesis in cultured human granulosa-lutein cells.[33]

ROLE OF NOVEL ALPHA CASOZEPINE IN REDUCING STRESS

Stress during sorrowful events and wartime experiences have both been linked to lower sperm quality.[34] Studies reported that job loss and unemployment are linked to poor sperm quality and lower testosterone. These findings indicate that increased anxiety and depression are independently linked to poor fertility.[35] Early life stress may influence the impact of stress on testosterone levels in adult males. Stress is treated by pharmacologic

interventions including benzodiazepines (BDZ) and selective serotonin reuptake inhibitors (SSRIs). In clinical practice, benzodiazepines and SSRIs can provide benefits including rapid control of anxiety, or improved control of episodic anxiety that arises in response to stimuli. These advantages must be balanced against the drawbacks of adverse effects, drug misuse, and the possibility of drug dependence. Further, the chances of ectopic pregnancies are associated with benzodiazepines and SSRIs.[36]

To date, a natural supplement of alpha-casozepine is effective at all levels of the HPA axis in not only decreasing glucocorticoid secretion but also rebalancing the pathway. alpha-casozepine is a unique bioactive decapeptide within a milk protein hydrolysate.[37]

Alpha-casozepine has exhibited antistress effects, in addition to blood pressure control, immune modulation, and antithrombosis effects.[38,39] It has two flexible tyrosine aromatic rings with similar structures to the classical benzodiazepine aromatic rings, thus demonstrating anxiolytic effects (Figure 4).[40]

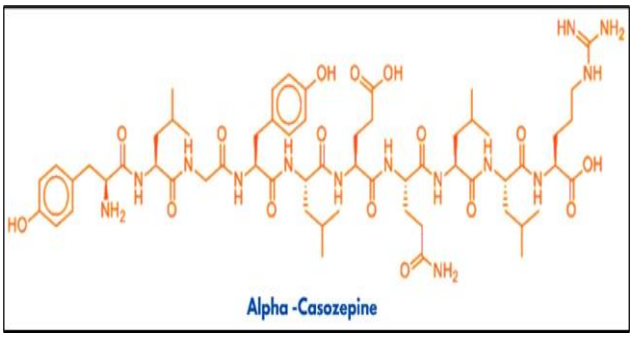

Figure 4: Structure of α-casozepine.

Alpha-casozepine is effective in decreasing glucocorticoid secretion and influences the HPA pathway.[41] Alpha-casozepine works at three levels of the HPA-axis: 1) It binds specifically to the benzodiazepine (BZD) site of the GABA-A receptor and does NOT bind to the peripheral-type benzodiazepine receptor (PBR) site of the GABA-A receptor which is responsible for the sedating effects seen with benzodiazepines. 2) It increases the sensitivity of the hypothalamus to cortisol, re-establishing receptor sensitivity feedback within the HPA axis. The amount of CRH produced due to stress is decreased. 3) It decreases the amount of cortisol released by the adrenal glands during acute and chronic stress (Figure 5).[41]

Alpha-casozepine is alternatively known as Lactium® (Ingredia nutritional) which has been extensively studied. It is a clinically tested anti-stress ingredient that has been used for over ten years and was patented in Europe, the United States, and Japan. It is currently available in over 120 countries. As mentioned earlier, Lactium binds with the central nervous system's gamma-aminobutyric acid (GABA-A)-A receptors. There are three binding sites on the GABA-A receptor, and at least 19 distinct subunits. These are sites ω1, ω2, and ω3. The preferential binding of Lactium to the ω2 binding site results in anxiety and stress control without having any sedative effects. According to several preclinical and clinical studies, Lactium lowers blood cortisol levels, enhances the efficiency and quality of sleep, and lessens stress-related digestive disorders, anxiety, and overall exhaustion.

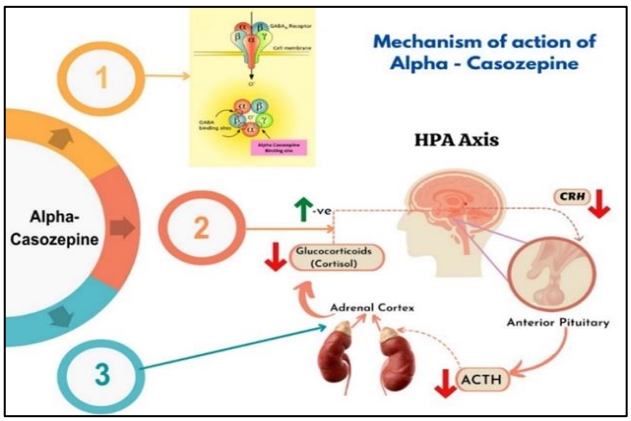

Figure 5: Mechanism of action of alpha-casozepine.

In a study, male Wistar rats used in the conditioned defensive burying (CDB) model showed a substantial anxiolytic- response to intraperitoneally administered alpha-casozepine at 0.4 and 0.6 mg/kg body weight, that was comparable to diazepam at 1.0 mg/kg body weight.

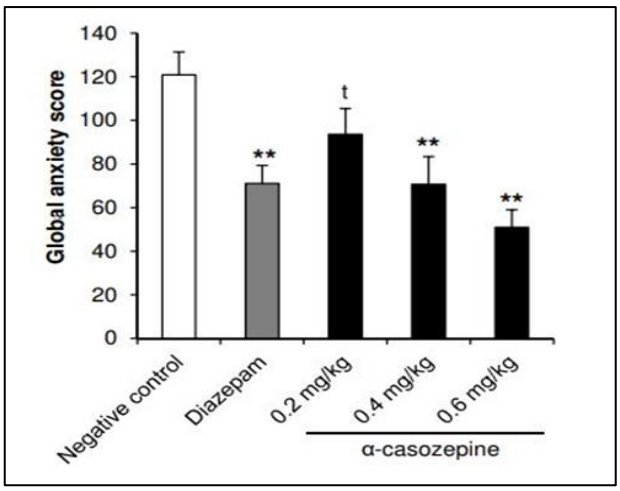

Figure 6: Global anxiety scores for rats were significantly reduced in the CDB test after I. P. administration of alpha-casozepine (0.2, 0.4, and 0.6 mg/kg BW), diazepam (1 mg/kg BW) or the NaCl solution (vehicle as negative control). Data are mean ± SEM. (t p<0.1, **p<0.01).[77]

Boulier et al concluded that the anxiolytic effect of Lactium is related to GABA modulation via the benzodiazepine site of the GABA-A receptor. Messaoudi et al conducted a clinical study to evaluate the protective properties of Lactium against stress by using 3×400 mg of Lactium within 24 hours before a psychological test

(Stroop test of color conflict) followed by a physical test (hand immersion in cold water) by measuring blood pressure and heart rate. Stress can raise blood pressure quickly by increasing the number of heartbeats and cardiac output. Catecholamines, cortisol, vasopressin, endorphins, and aldosterone levels have been observed to rise in response to acute stress, which may help to explain the reason for increasing heart rate and blood pressure. It was observed that both heart rate and blood pressure rose much less during the stressful period in the Lactium-treated group than in the placebo group.[42] Additionally, the Lactium-treated group experienced a significant decrease in plasma cortisol levels following the stress tests, but not the placebo group.[43]

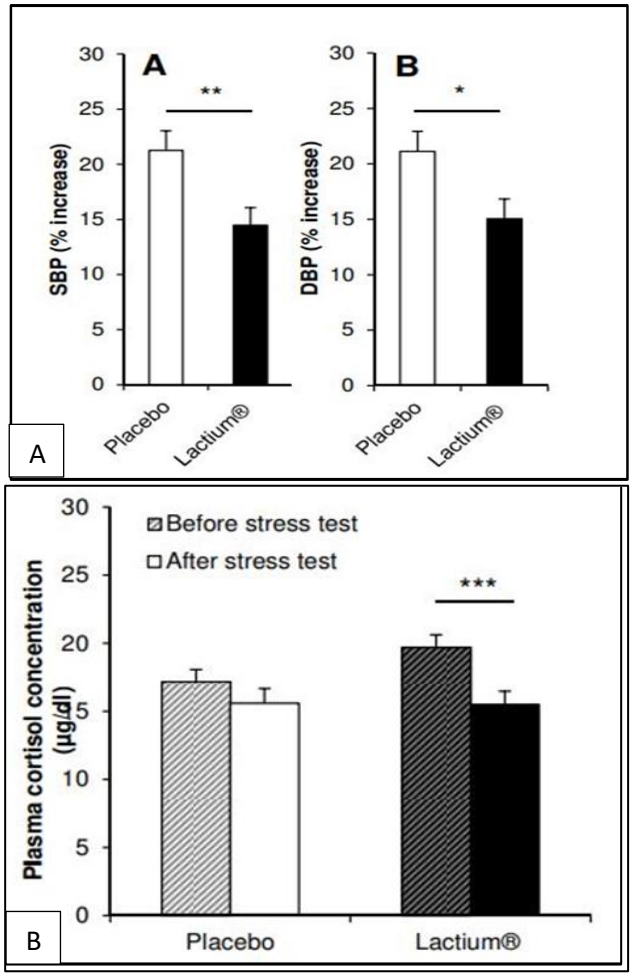

Figure 7 (A and B): Increase of systolic and diastolic blood pressure during the Stroop test.

Data are mean ± SEM. Unpaired t-test (2 tail.): **p<0.01 *p<0.05 (Lactium vs placebo). Change in plasma cortisol concentration before and after the stress tests. Data are mean ± SEM. Paired t test: *** p<0.005 (before vs after stress test)

In clinical studies, 300 mg Lactium was used resulting in reducing stress, without side effects. Kim et al study results showed a significant decrease in plasma cortisol throughout the combined stress tests and stable heart rate in the treatment group with Lactium but not in the placebo group. Another study by Kim et al proved that after 30 days of supplementation of Lactium, there is a reduction in stress-related issues including digestive, cardiovascular, intellectual, emotional, and social issues.[44]

A study has been conducted at Necker-Enfants Malades hospital and Biofortis demonstrated the efficacy of Lactium used in higher doses (200 and 300 mg, respectively) in acute stress management and Lactium can be used in managing stress-inducing life events as a non-sedative, non-addictive anxiolytic. Lactium helps to reduce disease-associated anxiety by potentiating the effect of GABA by binding to the GABA-A subtype of receptors, causing an influx of chloride ions, which hyperpolarizes the neurons and decreases the transmission of stress signals.[45]

The association between sleep and infertility is well established, insomnia may -influence HPA and HPG axis resulting in fertility-related issues. Sleep dysregulation (sleep fragmentation, sleep continuity disturbance, short or long sleep duration) may independently alter successful conception through the suppression or augmentation of reproductive hormones; and sleep loss may also affect conception via weakened immunity. Although a list of pharmacological treatment options such as benzodiazepines (e.g., estazolam, temazepam, and triazolam), nonbenzodiazepine hypnotic agents (e.g., eszopiclone, zaleplon, and zolpidem) and orexin receptor antagonists (e.g., suvorexant) are readily available for the treatment of insomnia they do have numerous side effects, such as dizziness, drowsiness, memory damage, cognitive impairment, dependence, tolerance, and could not be used in patients undergoing infertility treatment including ART.

The role of lactium in sleep is worth mentioning. There are many clinical studies evaluating the role of Lactium in sleep. In a study by Buysse et al participants took either 150 mg of Lactium or placebo daily for a total of 4 weeks, and the Pittsburgh Sleep Quality Index (PSQI) was used to evaluate sleep, together with the Epworth Sleepiness Scale (ESS). The questionnaires were administered at baseline (before starting therapy, D0), after two weeks (D14), after four weeks (D28), and after one-week follow-up (D35). It was found that participants got much better sleep after taking Lactium 150 mg a day as compared to a placebo. Given Lactium ‘s anti-stress abilities, it would appear a plausible link between the observed enhancement of sleep to anti-stress characteristics following the administration of lactium.[46,47] According to a study by Dela et al Lactium possesses sedative-free sleep-inducing effects in an animal model.[48] Further to assess the safety profile of Lactium, numerous additional toxicity tests, such as acute oral toxicity, mutagenicity, and teratogenicity studies, were also carried out. In rats treated with Lactium, no treatment-related mortality was noticed. There were no toxicologically significant treatment-related changes in body weight, food, and water intake, organ weight, urinalysis, hematological, serum biochemistry, necropsy, or histopathology.[49]

There is a significant role of Lactium in reducing stress conditions especially beneficial in couples suffering from infertility. Further to add, it reduces the cortisol level which is a stress hormone, and modulation of other gonadal hormones by acting through the HPA and HPG axis. Moreover, the preclinical and clinical studies also suggested that there is no adverse outcome in the treatment group. Lactium will be completely safe and can be used to reduce stress in infertile couples and resulting in higher treatment outcomes.

ROLE OF L-THEANINE IN REDUCING STRESS LEVEL

Apart from alpha-casozepine, another natural component that has a significant effect in reducing stress is L theanine. It is an amino acid that is mostly present in green tea.

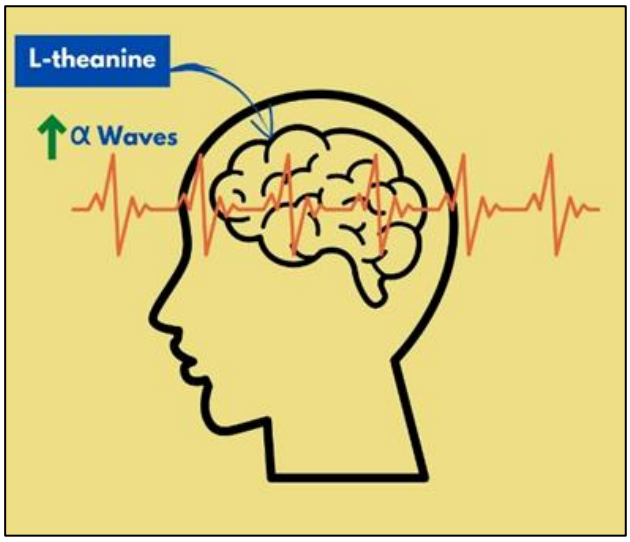

Figure 8: Mechanism of action of L-theanine.

L-theanine can initiate an alpha wave pattern in the EEG of the brain implying a relaxed physical and mental state without drowsiness or impaired motor skills. Many research studies have been conducted to evaluate the role of l-theanine in reducing stress levels. L-theanine consumption has been demonstrated to lower heart rate and serum Immunoglobulin A levels in healthy individuals, which decreases sympathetic nerve activation by preventing the binding of glutamic acid to the appropriate receptors in the brain.[50] Further, Kimura et al demonstrated that consuming l-theanine reduced the heart rate (HR) due to an acute stress task. The decrease in HR was also likely by a lowered sympathetic nerve activity, according to assessments of heart rate variability. The oral intake of L-Theanine could cause anti-stress effects via inhibition of cortical neuron excitation.[51] Additionally, the effect of L-theanine administration on stress-related symptoms and cognitive functioning was evaluated in healthy volunteers in a randomized, placebo-controlled, crossover, and double-blind study. L-theanine (200 mg/day) or placebo pills were randomly and blindly distributed for four weeks of treatment among the 30 participants. L-theanine treatment resulted in lower self-rating depression scale, state-trait anxiety inventory-trait, and Pittsburgh sleep quality index (PSQI) scores (p=0.019, 0.006, and 0.013, respectively). L-theanine treatment was beneficial in the PSQI subscale scores for sleep latency, sleep disruption, and decreased usage of sleep medicine as compared to placebo. The verbal fluency and executive function scores for cognitive processes increased following L-theanine treatment (p=0.001 and 0.031, respectively).[52] The above data demonstrates the potential role of l theanine in reducing stress conditions and improving sleep regulation.

L-theanine has proven efficacy in reducing stress, improving alpha brain waves, and increasing sleep quality. Further clinical evidence also suggests that l theanine significantly improves the cognitive outcome by reducing stress levels and maintaining heart rate and blood pressure. L theanine will be another good option for decreasing stress levels, to improve infertility treatment outcomes and successful pregnancy outcomes.

CONCLUSION

As elucidated above, stress and anxiety are strongly correlated to infertility. Additionally, infertility treatment protocols, invasive procedures or investigations, and frequent visits to infertility clinics have a substantial contribution to stress and anxiety.

The role of Lactium is well-established in reducing stress levels. Lactium is a protein moiety rather than a medication, it does not induce the adverse effects as that of benzodiazepines. Moreover, the effect of Lactium on decreasing cortisol levels is also well-established from numerous clinical studies.

Further L theanine also has a significant impact on improving the sleep cycle and reducing stress without any adverse side effect profile. Both Lactium and l-theanine can be used in infertile couples for reducing stress, and anxiety, improving treatment outcomes with favourable safety profiles. In summary, although there has been extensive research ongoing to explore an effective strategy to reduce stress and improve the outcomes of ART, the use of Lactium and l-theanine shows a promising approach. The authors recommend randomized controlled studies especially in infertile couples to better understand the benefits of Lactium and L-theanine.

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