

# Improving Mood, Sleep and Behaviour

## with Tryptophan, Ornithine, Serine, Glycine and Magnesium

Mood and sleep are intrinsically linked whereby biochemical or environmental disturbances can influence a cascade of dysregulation and disease manifestation. The 'monoamine hypothesis' suggests that the development of mood, sleep and behaviour disorders occurs when monoamines, such as the neurotransmitters serotonin and noradrenaline, are at insufficient levels in the synaptic cleft. Therefore, associated symptoms and conditions can be improved by increasing synaptic levels of monoamines (such as by supporting neurotransmitter synthesis, release or breakdown), and subsequent activation of serotonergic and noradrenergic postsynaptic and autoreceptors.<sup>1</sup> Whilst low serotonin can indeed contribute to lower mood, poor sleeping patterns and altered behaviour, this does not occur in isolation. Psychosocial and environmental factors, stress, nutritional status, inflammation and a range of other influences also contribute to the development of sleep and mood dysregulation and should be taken into consideration when implementing a nutritional intervention.

### Synthesising Serotonin with Neurotransmitter Precursors

Serotonin (5-hydroxytryptamine, 5-HT) is a neurotransmitter that exerts its influence via the serotonergic system, a diffuse network within the central nervous system that plays a significant role in the regulation of mood, behaviour, cognition, sleep, learning and memory.<sup>2</sup> The essential amino-acid L-tryptophan (tryptophan), is the sole precursor of peripherally- and centrally-produced serotonin. As a result, deficiency of tryptophan, and consequently serotonin in the brain can lead to dysfunction of the serotonergic system and has been associated not only with depression but a range of other disorders. (see Figure 1)

Tryptophan is also a precursor to melatonin, tryptamine, kynurenine, quinolinate and niacin. Nicotinic acid (vitamin B3) is synthesised from tryptophan through the kynurenine pathway.<sup>3</sup> If nicotinic acid levels are low, tryptophan metabolism may favour this pathway and therefore the rate of serotonin synthesis may decline. (see Figure 2)

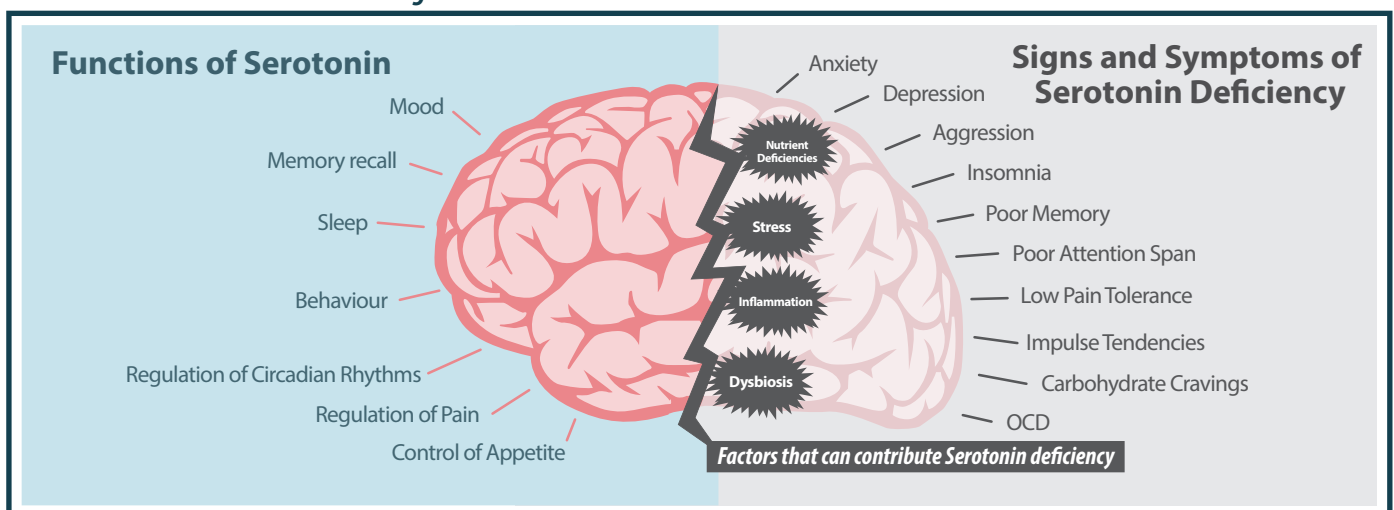
Tryptophan hydroxylase is the essential enzyme required for the conversion of tryptophan to 5-hydroxytryptophan (5-HTP).<sup>3</sup> This enzyme is dependent on certain nutrients such as vitamin B6, zinc, magnesium, vitamin C and folate.

### Improving Sleep and Stress Resilience with Amino Acids

Stress has been shown to induce a physiological response via the hypothalamic-pituitary-adrenal (HPA) axis, leading to the release of cortisol as well as altering the transmission and synthesis of a variety of neurotransmitters and catecholamines. It has been suggested that inflammation, stress and cortisol can activate the kynurenine pathway of tryptophan metabolism. As a result, there can be decreased availability of tryptophan and subsequent synthesis of serotonin and melatonin, contributing to poor mood and sleep.<sup>3</sup>

Modulating the HPA-axis, down-regulating the stress response and promoting sleep quality requires a comprehensive and holistic approach to decrease allostatic load whilst improving stress resilience and adaptation. The effects of an increased allostatic load, sleep disturbance or deprivation from physical, psychological or environmental stressors on the brain, mind and body includes not only fatigue and depression, but also cognitive inefficiency, mood disruptions, sleepiness, impaired attention and memory deficits leading to impaired quality of life.<sup>3</sup> New research highlights the novel, multi-target mechanisms that the amino acids L-ornithine, L-serine and L-glycine can exert as modulators of the HPA-axis, cortisol, mood and sleep.

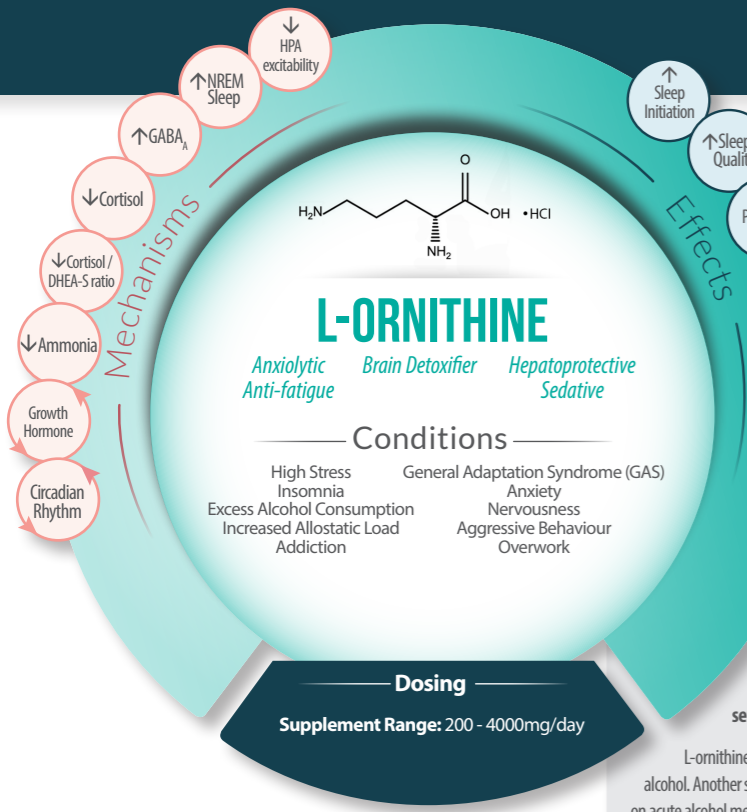
Figure 1: Serotonin's involvement in mood and behaviour



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# Improving Mood, Sleep and Behaviour with Tryptophan, Ornithine, Serine, Glycine and Magnesium



**Stress Less with L-Ornithine:** L-ornithine is a non-protein, non-essential amino acid found only in very small quantities in foods, however L-ornithine plays a very important role in lipid metabolism and detoxification pathways including the urea cycle. It facilitates and enhances the removal of ammonia from the body via the liver. Cerebral ammonia uptake and accumulation promotes the subjective feeling of fatigue, therefore L-ornithine can be used therapeutically as a potential "brain detoxifier".<sup>7</sup>

L-ornithine ameliorates the activity of the hypothalamic-pituitary-adrenal (HPA) axis to reduce the stress reaction and has been identified to act as a sedative and anxiolytic, as well as having mood- and behaviour-altering properties. This unique amino acid also has anti-fatigue properties that may play a direct role in the central nervous system to relieve stress, modulate cortisol, improve sleep and subjective feelings of fatigue and fatigue-related sleep quality.<sup>7</sup>

Researchers have suggested that the anti-fatigue effect of L-ornithine is due to its ability to reduce HPA axis activity, increase the efficiency of energy consumption, and promote the excretion and detoxification of ammonia.

In a randomised, double-blind and placebo controlled trial, healthy individuals were supplemented with 500mg of L-ornithine monohydrochloride (equiv. 400mg of L-ornithine) before bed for eight weeks. L-ornithine was demonstrated to have a favourable effect on the cortisol response, improved sleep quality and perceived mood, and reduced fatigue derived from stress.<sup>7</sup>

L-ornithine was shown to have a significant positive effect on the mood and behaviour of stressed individuals, reducing anger and hostility after supplementation. Additionally, L-ornithine's sedative and anti-stress properties were demonstrated with the improvement of sleep quality, initiation and maintenance, as well as potentiating a reduction of serum cortisol level and cortisol/DHEA-S ratio.<sup>7</sup>

L-ornithine may be a potential dietary supplement for attenuating the "morning after" adverse psychological and physiological effects of alcohol. Another study evaluated the effects of L-ornithine on subjective feelings and salivary markers the morning after alcohol consumption and on acute alcohol metabolism.<sup>8</sup> It was found that supplementation with 500mg of L-ornithine monohydrochloride (equiv. 400mg L-ornithine) after alcohol consumption improved various negative feelings (aggression, hostility, lassitude, fatigue, confusion) and decreased the salivary stress marker cortisol the next morning.<sup>8</sup>

**Tryptophan, The Serotonin Building Block:** L-tryptophan, an essential amino acid, is the precursor to 5-hydroxytryptophan (5-HTP) and the neurotransmitter serotonin. It is also a substrate for other important metabolites in the body including melatonin, tryptamine, kynurenine, quinolinic acid and niacin.<sup>11</sup> A method known as acute tryptophan depletion has been used in numerous studies to determine the effect of tryptophan deficiency, demonstrating tryptophan's potential as an anti-depressant, anxiolytic, sedative and hypnotic.

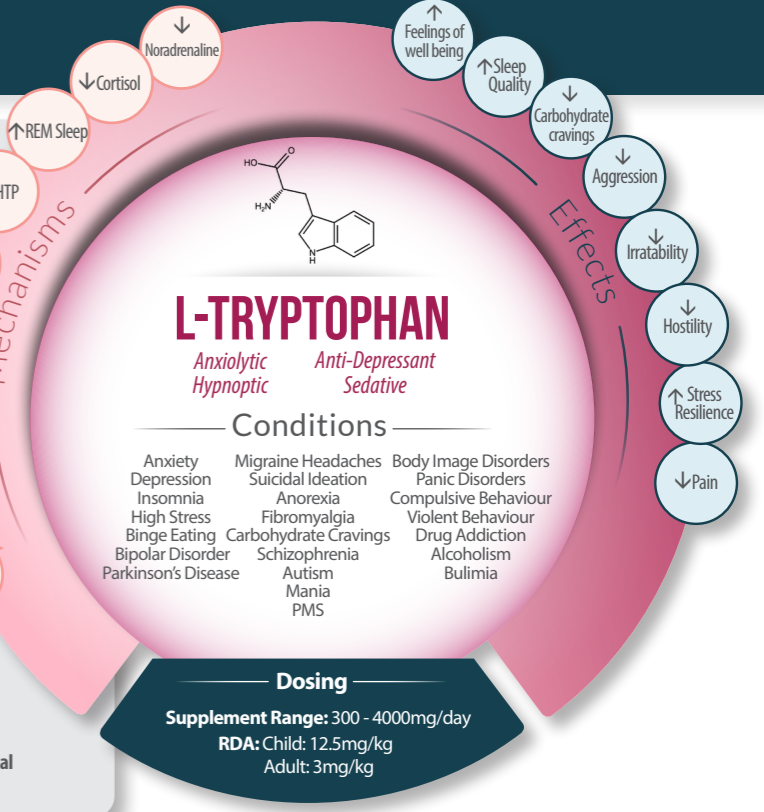
The therapeutic possibilities of tryptophan are numerous including: raising mood; reducing depression and anxiety; eating disorders; improving learning and memory; seasonal affective disorder; premenstrual dysphoric disorder; reducing sleep onset time; and assistance with overcoming addiction.

A number of studies have found that tryptophan and 5-HTP improve depressive symptoms.<sup>12</sup> Tryptophan may not only be beneficial for depressed patients however, with a recent study finding tryptophan to improve stress resilience in healthy individuals.<sup>13</sup>

Another of tryptophan's well-known therapeutic functions is the treatment of insomnia and sleep difficulties due to its essential role in melatonin synthesis.<sup>14</sup>

A recent review on the topic noted that a range of older studies have found tryptophan to improve sleep latency, that is, the time it takes to get to sleep.<sup>15</sup> A recent study in elderly individuals found that tryptophan-enriched supplementation significantly improved a number of markers of sleep quality including time spent asleep, nocturnal activity and their sleep fragmentation index.<sup>16</sup>

In another study, a group of healthy young adults with both high and low cognitive reactivity were given a drink containing either enriched tryptophan protein, or standard protein, followed by participation in a social stress test. The study found that those subjects who received the tryptophan-enriched drink had a better mood and lower serum cortisol levels following the social stress test compared to those who received the control drink.<sup>13</sup>

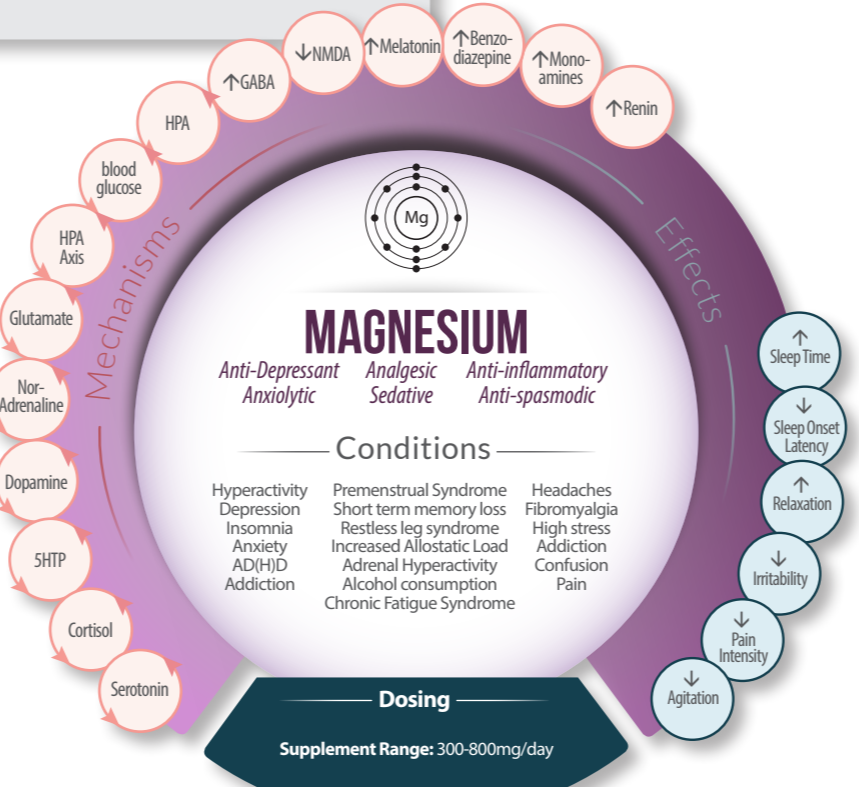
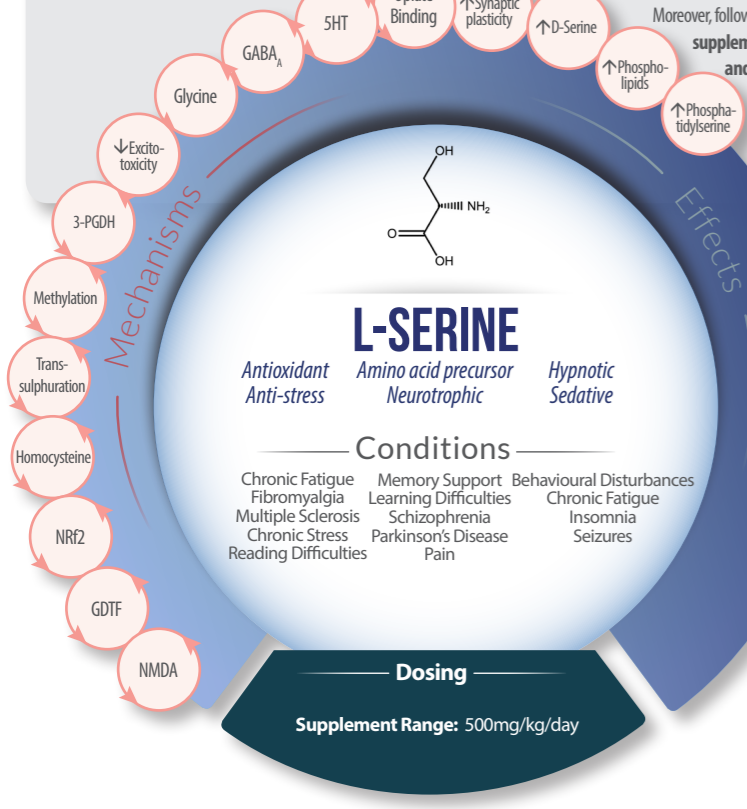


**Sleeping Sound with L-Serine:** L-serine is considered a non-essential amino acid and is a precursor of glycine, L-cysteine and D-serine as well as playing an extensive role intracellular metabolism, protein synthesis and the production of cell membrane lipids such as phospholipids and sphingolipids.<sup>17</sup> L-serine's sedative, hypnotic, neurotrophic, anti-stress and anxiolytic properties may represent a good option for individuals who suffer from difficulty sleeping particularly those who are under stress.

A randomised double-blinded crossover study found that supplementation with 3 grams of L-serine 30 minutes before going to bed improved sleep initiation and night time awakenings, resulting in improved feelings of having slept well on waking in the morning.<sup>17</sup>

When taking sleep-improving drugs, resistance after long-term administration or rebound insomnia after discontinuation are frequently problematic as well as experiencing next-day drowsiness. Even after supplementation of 3 grams of L-serine on consecutive days for one month, the improvement in sleep quality persisted even one month after.<sup>17</sup>

Moreover, follow-up one month after discontinuing L-serine supplementation showed no "next day drowsiness" and no worsening of sleep quality compared to before administration. Although the effects were diminished compared to during L-serine intake, improved sleep status tended to be maintained.<sup>17</sup>



**Modulating Mood with Magnesium:** Magnesium is one of the most essential minerals in the human body, connected with brain biochemistry and the fluidity of neuronal membranes. Magnesium has demonstrated in in-vivo and clinical trials to have anti-depressant, anxiolytic and sedative activity.<sup>18</sup>

Several clinical findings indicate the involvement of magnesium in the pathophysiology and treatment of depression, anxiety and insomnia. Although the effect of magnesium on neural function, mood and behaviour is not fully understood, magnesium has an essential role in ion channel conductivity, such as N-Methyl-D-aspartic acid (NMDA) receptor, and unilateral entrance of potassium channels. In addition, magnesium is essential for the connection of monoamines to their receptors.<sup>18</sup>

Several studies have also acknowledged the role of magnesium in the regulation of central nervous system excitability. Magnesium, as a natural antagonist of NMDA and agonist of GABA, seems to play a critical role in sleep regulation.<sup>18</sup>

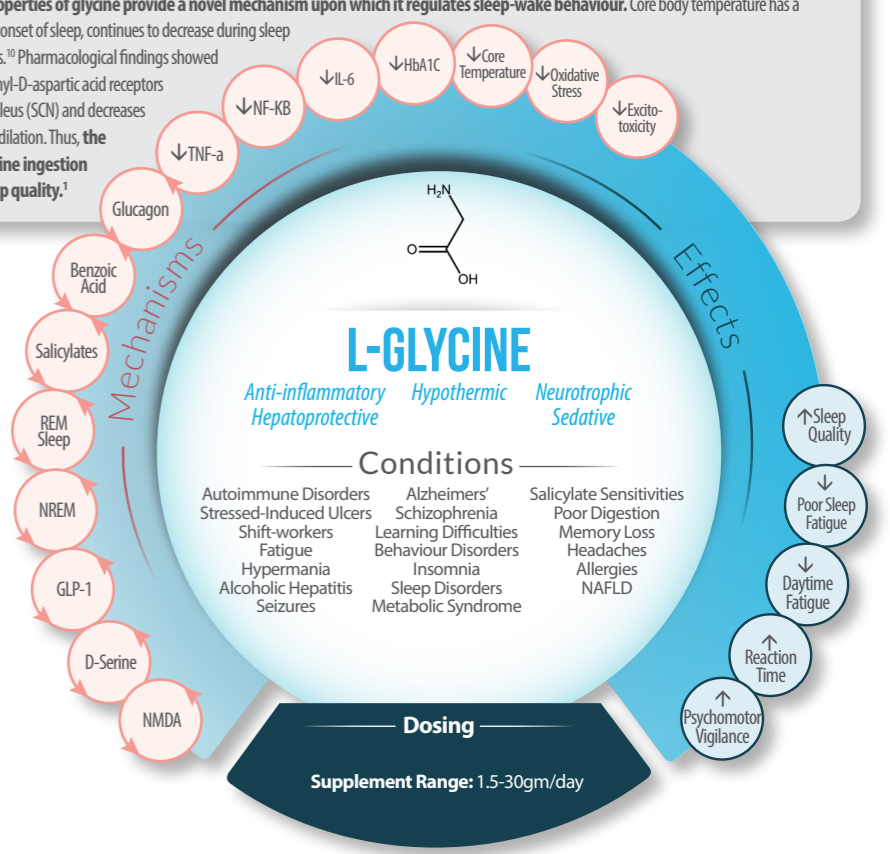
In a double-blind randomised clinical trial, subjects suffering from insomnia were supplemented with the equivalent of 250mg of elemental magnesium over eight weeks. Supplementation of magnesium improved subjective measures of insomnia such as Insomnia Severity Index (ISI) score, sleep efficiency, sleep time and sleep onset latency, early morning awakening, and likewise, objective measures of insomnia such as concentration of serum renin, melatonin, and cortisol.<sup>18</sup>

**Keeping your Cool with L-Glycine:** Glycine plays an essential role by acting as an inhibitory neurotransmitter via glycine receptors in the peripheral and central nervous systems and has demonstrated an ability to promote objective and subjective improvements in sleep quality and leads to natural sleep patterns.<sup>9</sup> Glycine has sedative, neurotrophic, anti-inflammatory and hypothermic properties and plays a particular role as a therapeutic agent in improving sleep initiation and quality, and reducing daytime fatigue. Typically, hypnotics have a sedative effect or cause drowsiness when supplemented either during the day or at night, however, glycine does not have this effect.

In a randomised crossover trial, supplementation of 3 grams of glycine before bedtime significantly shortened the latency to sleep onset and to slow wave sleep emergence, and improved sleep qualities such as satisfaction with sleep, a shortened latency to falling asleep, and sleep efficacy.<sup>9</sup>

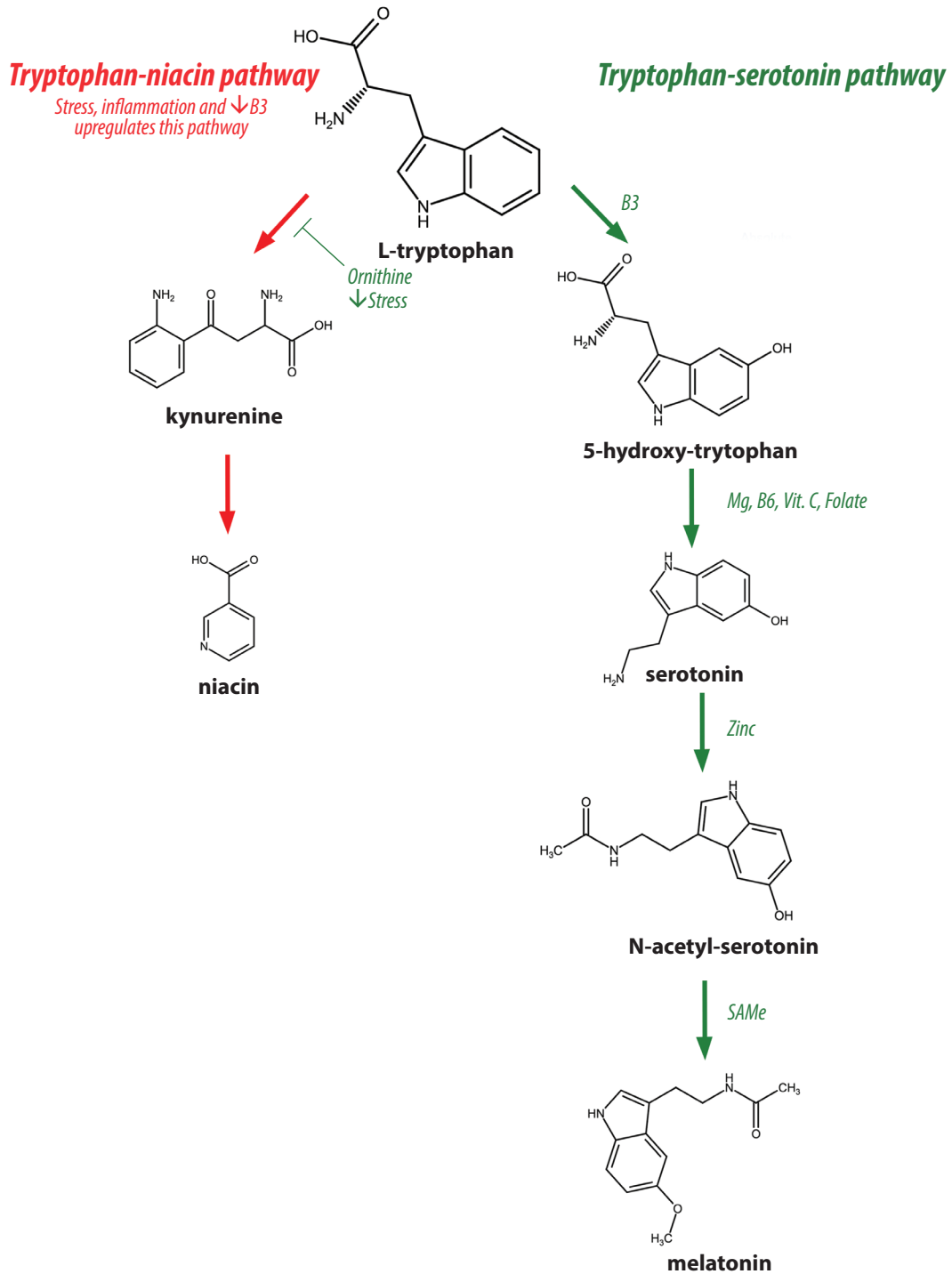
Another trial demonstrated that supplementation with 3 grams of glycine before bed significantly improved feelings of fatigue compared with placebo and showed a tendency to reduce sleepiness and significantly improve performance, particularly in individuals suffering from sleep restrictions.<sup>10</sup>

The hypothermic or "cooling" properties of glycine provide a novel mechanism upon which it regulates sleep-wake behaviour. Core body temperature has a circadian oscillation and drops at the onset of sleep, continues to decrease during sleep and gradually rises as a person wakes.<sup>10</sup> Pharmacological findings showed that glycine primarily acts on N-Methyl-D-aspartic acid receptors (NMDAR) in the suprachiasmatic nucleus (SCN) and decreases the body's core temperature via vasodilation. Thus, the heat dissipation induced by glycine ingestion leads to an improvement in sleep quality.<sup>1</sup>



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**Figure 2: The fate of Tryptophan**



References available upon request.  
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