Glycine
Ingredient in Productive Sleep

Glycine is a semi-essential amino acid. It is semi-essential because, although it is made in the body, it may not be produced in quantities that are adequate for all the uses of glycine under all conditions. The authors did a detailed assessment of all possible sources of glycine and all its metabolic uses, including collagen synthesis (collagen being the most abundant protein in the human body) and concluded that glycine is a semi-essential amino acid and it should be taken as a nutritional supplement to guarantee a healthy metabolism. They do note that a deficiency of glycine is not life-threatening, even in the worst of cases, but that a chronic shortage may result in detrimental effects on the quality of life, such as a slower turnover of collagen (which also occurs as a result of aging), which would increase the likelihood of collagen becoming modified (such as increased cross-linking that decreases plasticity). It is also interesting to note that Directive 67/548/EEC of the European Union describes glycine as "not hazardous" as it does not become toxic in rats when taken orally until a gigantic dose of 8 g/kg is reached, corresponding to around 600g in a human.

Glycine Improves Sleep Quality

A 2012 paper1 describes glycine as a non-essential amino acid* that has indispensable roles in both excitatory and inhibitory neurotransmission via NMDA (N-methyl-D-aspartate) type glutamate receptors and glycine receptors, respectively. The authors of this paper1 report the results of their trial of the effects of glycine supplementation on the sleep quality of rats and of humans complaining of insomnia problems.

As we explain at the beginning of this article, glycine is probably "semi-essential," rather than non-essential. In paper #1, however, the authors have described it as non-essential. "Non-essential" doesn't mean that it doesn't have an important physiological function, but that, under usual conditions, you don't have to get much of it from your diet because you are able to manufacture most of what you need within your own body. One source of information1 states that, in humans, approximately 45g of endogenous glycine is synthesized by the body per day, while 3-5g is taken up from the diet in a day.

Consistent with the reduced core body temperature that occurs in conjunction with the onset of sleep, glycine supplements in rats were accompanied by a reduction in core body temperature associated with an increase in skin blood flow. In addition, glycine was found to passively diffuse across the blood brain barrier by nonspecific transport. The cortical levels of glycine reached a level 2-fold higher than that attained by the animals received only vehicle. A dose of 2 g/kg of glycine increased plasma glycine concentration to a level 13 fold higher than that of control animals given vehicle alone at 30 minutes.
Did the Rats Have a Good Night's Sleep?

Well, we don't know for sure since the rats didn't say, but the data suggests they did. The data in a previous study by these same authors indicated that oral administration of glycine increased extracellular serotonin release in the rat prefrontal cortex, which would be expected to enhance the sleep process. In the extant study, the effect of glycine on sleep in the rats was assessed by EEG/EMG recordings. Glycine (2 g/kg) significantly increased non-REM (NREM) sleep and reduced wake state in sleep-disturbed rats after 2 h of oral administration. When glycine was bilaterally injected into the SCN (suprachiasmatic nucleus, the center for regulating circadian rhythms), it acted on NDDA receptors in the SCN, resulting in vasodilation (as indicated by increased cutaneous blood flow) and decreased core body temperature. Hence, the sleep-inducing pathway was enhanced in the rats.

The Effects of Glycine on Sleep in Humans

The researchers also investigated the effects of glycine on sleep quality in people with sleep complaints. These subjects were given 3 grams of glycine or a placebo just before bedtime. The study (a randomized double-blind crossover study) included 19 female volunteers 24 to 53 years of age, average 31.1). Their sleep quality was assessed by a standard measure, the Pittsburgh Sleep Quality Index. At scores of 6 or greater, this was said to indicate that the subjects had continuously experienced unsatisfactory sleep. The subjects were also evaluated for their subjective quality of sleep following the glycine (or placebo) treatment using the St. Mary's Hospital (SMH) Sleep Questionnaire and the Space Aeromedicine (SAM) Fatigue Checklist. Glycine was found to significantly reduce the feeling of fatigue the next morning, supporting an improvement in sleep quality by glycine.

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The researchers had also published an earlier study of the improvement by glycine (3 grams just before bedtime) of sleep quality in a randomized, single blinded study of human volunteers. In that study, subjects (11 healthy volunteers, 8 female, 3 male) had improved subjective sleep quality, lessened daytime sleepiness, and improved performance of memory recognition tasks. In the paper published the year before by the same authors, 19 female volunteers complaining...
about poor sleep were subjects in a similar glycine trial (3 grams just before bedtime) that was a randomized, double blinded, cross-over type. The glycine ingestion was reported to significantly improve fatigue, liveliness, peppiness and clear-headedness.

**Possible Mechanisms for Glycine's Effects on Sleep**

Because the sleep studies reported above were all done by the same group or mostly the same group of researchers, it is particularly important to identify plausible mechanisms for an effect of glycine on sleep. We found such data and describe them here.

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**Evidence That Glycine Mediates the Inhibition of Muscular Activity During Active Sleep**

A 1989 paper describes researchers' findings that there is a non-REM period during active sleep in which muscular movement controlled by spinal cord motoneurons is inhibited (atonia) principally by glycine or a glycinergic substance. (The cholinergic nervous system is involved in atonia during REM sleep.) This study used 5 normally respiring intact cats as subjects. The administration of strychnine (an antagonist of glycine) to the motoneurons of the cats prevented the atonia. Antagonists of GABA, the other major inhibitory neurotransmitter did not affect the muscular atonia of sleep. Glycine is an inhibitory neurotransmitter. What happens if glycine neurotransmission is blocked? The excitatory poison strychnine blocks the glycine receptors, causing abnormal neurological excitation in the brain and, at higher doses, death by convulsions.

**Glycine Increases Extracellular Serotonin But Not Dopamine in the Prefrontal Cortex of Rats**

Researchers who were studying the beneficial effects of glycine in reducing negative symptoms of schizophrenia became interested in glycine because of its improvement of sleep quality. Exploring possible mechanisms to explain glycine’s effects on sleep, they discovered that oral administration of glycine in rats significantly increased extracellular serotonin levels in the rat prefrontal cortex for 10 minutes in the animals receiving 1 g/kg glycine, whereas there was no change in dopamine levels.
(D-Serine, another amino acid tested in this model, also increased extracellular serotonin, although L-serine did not. D-Serine is the unnatural form of serine and is not present in one's diet or one's body.) The animals receiving 2 g/kg of glycine had serotonin levels significantly higher for 20 to 30 minutes after administration. For D-serine, post hoc analysis showed a significant increase of serotonin at 0 to 10, 60 to 70, and 100 to 110 minutes after administration. As before, L-serine did not induce significant changes. The authors hypothesize that the effects of glycine on sleep disorders and negative symptoms of schizophrenia may be associated with an increase of serotonin in the PFC [prefrontal cortex]."

We believe that glycine is a preferred means for obtaining a short-term serotonin increase, such as would be appropriate for a nap.

The researchers note that the increase in serotonin they observed was very short compared to that of a selective serotonin reuptake inhibitor, such as citalopram or venlafaxine, which they say increase brain serotonin for more than 180 minutes in the rat frontal cortex. They suggest that further research is needed to clarify the results they found. We believe that glycine is a preferred means for obtaining a short-term serotonin increase, such as would be appropriate for a nap.

“Glycine may potentially be useful in the treatment or prevention of lung inflammation due to inhaled particles.”

The Interaction Between Glycinergic Neurons and Orexin Neurons

A different group of researchers studying the effects of glycine in sleep reported that glycine had a direct effect on orexin neurons in cell culture, causing the latter to cease firing. This was interesting
to the authors because orexin neurons are involved in the regulation of sleep; disruption of orexin signaling is the cause of narcolepsy, in which people can fall asleep without warning at any time. As a result of the experiments done as part of this study, the authors concluded that their observations indicated that the glycine receptor is expressed in glycinergic synapses in orexin neurons. We recently found that specific pharmacogenetic inhibition of orexin neurons during the active period decreased wakefulness time and increased NREM sleep time in the dark period. For example, extracellular serotonin levels are reported to be increased after oral administration of glycine. Since we found serotonin directly inhibits orexin neurons, glycine administration might partly inhibit orexin neurons through serotonin. The researchers suggest further research to reveal additional details of the complex regulation of sleep.

Glycine Blunts Increases in Inflammatory Cytokines in Alveolar Macrophages

"Because alveolar macrophages are critically involved in the pathogenesis of many pulmonary diseases caused by inhaled particles and endotoxins [such as lipopolysaccharides, LPS, released by bacteria], studies were designed to test the hypothesis that alveolar macrophages could be inactivated by glycine via a glycine-gated chloride channel. The authors explained that the inhalation of organic or cotton dusts, which they report to be highly contaminated with bacterial endotoxin (LPS), result in the overproduction and release of free radicals (such as superoxide) and the inflammatory cytokine TNF-alpha largely from alveolar macrophages as a result of increases in [Ca2+]. Their study reported that glycine at 100 M or more blocked the increased [Ca2+] and LPS-induced production of superoxide in alveolar macrophages. Moreover, the authors explain, the superoxide from macrophages is largely generated from molecular O2 through NADPH oxidase, an enzyme complex activated by phosphorylation by calcium-dependent protein kinases. By blunting the increase in [Ca2+] with glycine, the production of superoxide is reduced most likely by inhibiting calcium-dependent signaling required to activate NADPH oxidase. The authors suggest that glycine may potentially be useful in the treatment or prevention of lung inflammation due to inhaled particles. In a different paper, glycine was reported to protect against endotoxin shock (sepsis) in the rat by inhibiting TNF-alpha (tumor necrosis factor alpha) production and increasing expression of IL-10, an anti-inflammatory cytokine.
References