

DELTA-SLEEP-INDUCING PEPTIDE

by Regina Patrick RPSGT



In 1907, French scientists Rene Legendre and Henri Pieron extracted a factor (they called "hypnotoxin") from the blood of sleep-deprived dogs, injected it into other dogs, and found that the recipients had an overwhelming impulse to sleep. Five years later, they reported that a factor in cerebral spinal fluid (CSF) from sleep-deprived dogs could induce sleep when injected into the brain of another dog. Other researchers had difficulty in repeating Legendre and Pieron's results until the work of Swiss scientist Marcel Monnier during the 1960s and 1970s in which he achieved the same sleep-inducing effect in rabbits. In various experiments, Monnier and associates would first, artificially stimulate a donor rabbit's thalamus to induce sleep; second, withdraw cerebral venous blood from the animal; and third, dialyze the blood and inject the dialysate into recipient rabbits. The recipient rabbits would sleep. EEG recordings showed that the sleep-inducing substance in the dialysate could induce slow wave sleep (i.e., delta sleep) and so the substance was initially called "factor delta." In 1972, Marcel began the process of purifying the factor from blood through the use of various filtration techniques. By 1977, Guido A. Schoenenberger in association with Monnier and other scientists purified factor delta and determined that it was a nonapeptide. The factor was named delta-sleep-inducing peptide (DSIP). Since its discovery, scientists have focused on using DSIP to treat insomnia and other sleep disorders such as narcolepsy and circadian rhythm disorders.

Identifying the site of DSIP synthesis in the brain has eluded scientists since its discovery. For example, scientists have not been

able to identify a DSIP gene or a receptor for the peptide. However, radioimmunoassay (RIA) and other immunochemical techniques reveal that in the brain DSIP is present primarily in the hypothalamus, limbic system and pituitary gland. It is also present in the thalamus, hippocampus, midbrain, and brainstem structures such as the reticular formation, raphe nuclei, and locus ceruleus. Its presence in these structures may explain the effects that DSIP has on sleep architecture: it decreases sleep onset; increases slow wave sleep; and decreases REM sleep duration.

In vitro research suggests that DSIP may decrease sleep onset through its ability to induce the neuronal release of metenkephalin. Metenkephalin is a pentapeptide which binds with opiate receptors thereby bringing on sedation. Hypothalamic, midbrain, hippocampal, and thalamic neurons release metenkephalin in response to DSIP. This effect in turn allows sleep onset to occur more quickly.

The effect of DSIP on slow wave sleep may result from its ability to induce an influx of calcium ions into hypothalamic, midbrain, hippocampal, and thalamic neurons. Since these areas play a role in slow wave sleep, DSIP-induced calcium influx may hasten the onset of slow wave sleep and increase its duration.

The diminishing effect that DSIP has on REM sleep duration may be the consequence of the fact that the molecule contains tryptophan. The nine amino acid sequence for DSIP is TRP-Ala-Gly-Gly-Asp-Ala-Ser-Gly-Glu (TRP stands for tryptophan; Ala, alanine; Gly, glycine; Ser, serine; and Glu, glutamic acid.) Tryptophan is converted to serotonin which stimulates the raphe nuclei located in the midline of the brainstem. Serotonergic stimulation of these cells inhibits the onset of REM sleep. The presence of tryptophan in DSIP may reduce the amount of REM sleep by sustaining serotonergic stimulation of the raphe nuclei.

As scientists continue to learn exactly how DSIP works in the brain, other research has focused on clinically using its sleep-inducing, slow wave sleep-enhancing, or REM-shortening effects. These effects may be beneficial in circadian rhythm disorders, insomnia, and narcolepsy in the following ways.

DSIP and Circadian Rhythm Disorders

Because of its sleep-inducing effect, the level of DSIP should be highest at night and before or during slow wave sleep. Some research, however, suggests that the production of DSIP may be tied to one's circadian rhythmicity rather than to sleep stages.

Researchers Theodore C. Friedman et al. examined the correlation between sleep stages and DSIP. They measured the blood levels of another peptide, DSIP immunoreactive peptide (DIP), to indirectly assess the level of DSIP. (DIP is a large peptide which reacts with DSIP antibodies. High levels of DIP would reflect high levels of DSIP; low levels of DIP would reflect low levels of DSIP.) They measured DIP levels of 12 healthy volunteers every 30 minutes for 24 hours and found that the highest levels of DIP occurred around 3:00 pm and the lowest levels around 1:00 am. This meant that DSIP levels are higher during the day than during the night. They also found that during sleep:

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1) the level of DIP was lower during slow wave sleep than during wake and substantially lower during rapid eye movement (REM) sleep than during wake; and 2) the DIP level did not rise significantly before, during, or after SWS episodes. Surprisingly, they found that there was a positive correlation between DIP levels and body temperature (i.e., both are at their highest during the day and lowest at night). The latter finding lead them to conclude that the production of DSIP as reflected by changes in DIP levels may be associated with body temperature changes rather than sleep stages. They are unsure whether DSIP plays a direct or indirect role in the circadian rhythmicity of body temperature.

Animal studies suggest that DSIP may directly influence circadian rhythmicity. Markus Graf et al. injected DSIP into rats that had been subjected to a 24 hour light/dark cycles for three days. They noted that the rats had a reduction in their dark phase activity (which would normally be high in these nocturnal animals) and an increase in their light phase activity (which would normally be low). A later Graf study again demonstrated increased activity during the light phase in DSIP-treated rats. This shift occurred although the circadian period in this study consisted of shorter phases (12 hour light/dark phases) rather than 24 hour light/dark phases. Since DSIP caused a shift in circadian phases in these studies, Graf and associates concluded that DSIP plays a role in circadian rhythmicity.

The ability of DSIP to advance sleep/wake phases could potentially be used to treat circadian rhythm disorders. German researchers Dietrich Schneider-Helmert et al. reported the successful use of DSIP in a 47 year old woman whose struggles with chronic insomnia resulted from a delayed sleep-phase. Long usage of a low-dose benzodiazepine (flunitrazepam) had left her

dependent on the drug for sleep. A week of DSIP therapy advanced her sleep phase by five hours and allowed her to quickly withdraw from flunitrazepam. Polysomnographic studies revealed restoration of a normal sleep architecture. Actigraphy monitoring performed some time after initiation of DSIP therapy revealed that the woman maintained a normal sleep schedule with the DSIP therapy. Despite this positive result, not much research has gone into investigating the use of DSIP in treating circadian rhythm disorders.

DSIP and Insomnia

Other studies by Schneider-Helmert as well as studies by other investigators show that DSIP can normalize sleep architecture in insomniacs by increasing total sleep time, reducing arousals, and improving REM sleep. An additional benefit of DSIP treatment is that there is no next day residual sedation.

Some research suggests that the ability of DSIP to relieve insomnia may be initially tempered by the degree of one's insomnia before initiation of treatment. Schneider-Helmert found that sleep more quickly improved in middle-aged insomniacs (29 – 59 years) who were given DSIP treatment than in older insomniacs (60 – 83 years) whose insomnia was more severe. Statistical analysis in his study revealed that severity of insomnia rather than age played a role in the difference in response to DSIP.

DSIP and Narcolepsy

Not many studies have been done investigating the use of DSIP to treat narcolepsy. However, some research suggests that people with narcolepsy have lower than normal levels of DSIP. Adding credence to the possible role of low DSIP levels in people with narcolepsy, Schneider-Helmert reported improvement in symptoms in a 35 year old narcoleptic male after DSIP treatment. Objective tests (e.g., polysomnography, multiple sleep latency test [MSLT], and performance tests) revealed that the subject had enhanced REM sleep; a more consolidated sleep period; a reduction in frequency of sleep attacks; increased activity; increased alertness; and improved daytime performance with DSIP treatment. Schneider-Helmert believe these effects are due to DSIP's ability to enhance circadian and ultradian rhythms.

Research interest in DSIP is broadening from viewing it as simply a hypnogenic substance. There is some scientific hope in using DSIP as an analgesic since it induces a release of met-enkephalin; as an anti-seizure medication since it inhibits neurotransmission in brain structures (e.g., thalamus) involved in seizures; and as an anxiolytic because of its sedative effects and ability to reduce the stress response. DSIP also has antioxidant, neuroendocrine modulatory, and cardiovascular effects. As a result of these effects, scientists have been investigating the ability of DSIP to reduce cancerous tumors, lower hyperglycemia, and lower hypertension.

As interests in the peptide broaden, the original hypnogenic focus of research continues. Currently, scientists have developed several synthetic DSIP analogs which may ultimately open new avenues for treating sleep disorders. Some of the analogs are more potent than the original peptide in inducing sleep. Future studies will reveal to what extent these new peptides are beneficial in treating circadian rhythm disorders, insomnia, narcolepsy, or other sleep disorders. Additionally, scientists continue to try to determine what dosage of DSIP is most effective in humans; how frequently DSIP should be taken; and which route (i.e., intravenous, oral, etc.) will be most effective in humans. Once such answers are known, DSIP treatment may bring relief to people who suffer from insomnia or other sleep disorders.