

When your day draws to an end*

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How long can you stay awake? In 1988, Robert McDonald from California managed to trick his sleep for 18 days, 21 hours and 40 minutes. But what exactly was he tricking? Two thousand years ago, it was believed that drowsiness was due to stomach vapours - themselves the result of digestion - which rose to the brain, condensed there and blocked the pores. The head was thus cut off from the rest of the body and sleep ensued. This mechanical concept of sleep survived for almost two millennia. It was only in the second half of the 19th century that a more subtle approach was made, separately, by Kuniomi Ishimori in Japan and Henri Piéron in France. What if sleep were the result of “fatigue substances” that are accumulated during the period of wakefulness and dissipated while sleeping? The hypothesis had its ups and downs. However, in the 1960s, Marcel Monnier and his associates in Switzerland discovered the existence of a very small peptide that seemed to have sleep-inducing effects: the Delta Sleep-Inducing Peptide or DSIP.



'Girl in a green chair', Sharon Hudson

Courtesy of the artist

DSIP was first extracted from the blood of a torpid rabbit. When administered intravenously to a number of animals, it launched them into a deep sleep within an hour. What is more, DSIP improved the animals' delta sleep – hence its name. Delta sleep is a phase we all go through and named so because the electroencephalograph (EEG) shows delta waves. However, over the years, it became apparent that the action of DSIP was not so straightforward. Since it is such a small peptide – only nine amino acids long – it was not such a difficult task to produce synthetic DSIP. And once it became commercially available, extended biochemical and physiological studies were carried out on humans. The results seemed promising.

In humans, experiments showed that DSIP enhances REM sleep. REM sleep is characterised by a rapid eye movement (REM), and, in humans, a number of essential functions are attributed to REM sleep and its organisation, i.e. the synchronisation of chronobiological functions, information processing, memory storage, and a variety of functions that are thought to have a role in our psychic equilibrium by means of dreaming. And if DSIP can help in any one of these respects, it is more than welcome!

DSIP was given to a number of insomniac neurotic patients. The molecule not only offered them better sleep but also a release from inner tension during the day and a greater tolerance to psychic stress. As a result, the patients had a greater ability to cope with problems and emotions. One advantage of DSIP is that it induces sleep “naturally”; it does not extend sleep beyond the normal duration nor does it impair the normal sleep architecture. Unlike synthetic hypnotic substances that tend to alter quite dramatically what should be a normal sleeping pattern.

Insomniacs were not the only patients who benefited from DSIP. DSIP was also reported to have helped patients suffering from drug withdrawal. Some of these patients had serious sleeping disorders, which were restored after a few days thanks to DSIP. In fact, in time, it was found that DSIP helped any kind of sleep disorder, be it insomnia or narcolepsy, and even

patients suffering from chronic, pronounced pain episodes. It was further suggested that increased levels of DSIP in the plasma could be related to chronic insomnia, Alzheimer's disease and perhaps even alcoholism...

Besides coping with sleeping disorders and showing up in the context of diseases, the use of DSIP has been discussed as a pharmacological intervention to fight fatigue and sleep loss in military interventions. Tests showed higher alertness and better performance while the individuals were awake. And if DSIP could enhance military performance, could it not also enhance athletic achievement?

How does DSIP work? No one really knows. Under natural conditions, it probably folds up into a pseudo-cyclic conformation. A cyclic analogue of DSIP was synthesized and actually proved to be more potent than DSIP itself. A major part of the peptide may well bind to other molecules, where the cyclic conformation does not meet. There may even be a DSIP receptor; evidence for an interaction of DSIP with adrenergic receptors in rats was indeed found.

*“The theory of the origin of sleep which has gained the widest credence is the one that attributes it to anaemia of the brain... The idea behind this supposition has been that, as the day draws to an end, the circulatory mechanism becomes fatigued, the vasomotor center exhausted, the tone of the blood vessels deficient, and the energy of the heart diminished, and thus is the circulation to the cerebral arteries lessened.” NATURE, May 5th, 1898.

So, did Robert McDonald trick the level of DSIP? It is very difficult to say. The notion of a sleep factor has never really been accepted. Sleep is made up of so many different stages and is influenced by so many factors - many of which are still unknown - that almost any biologically active compound may be related to some stage or other in sleep.

And because of this, though DSIP sounded promising, it did not meet with international recognition. Since the early 1980s very little has moved. “The reason for this” says Professor Alexander Borbély of the University of Zürich, “is that DSIP turned out to be a flop as a sleep substance and any interest was lost. The results were negative or ambiguous. It may be that the peptide has other biological actions but not a sleep-inducing one.” Professor Guido Schoenenberger of the University of Basel – one of the key scientists to have worked on DSIP in the 1980s – does not agree. According to him, tests were conclusive. It was the lack of money that killed research on DSIP.

Cross-references to Swiss-Prot

Delta sleep-inducing peptide, *Oryctolagus cuniculus* (European rabbit) : P01158

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