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EDITORIAL

Delta sleep-inducing peptide

Delta sleep-inducing peptide (DSIP) is a naturally occurring substance, which was originally isolated from rabbit brain in 1977 [1]. This curious substance is a nonapeptide that is normally synthesized in the hypothalamus and targets multiple sites including some within the brainstem [2]. As its name suggests DSIP promotes sleep and this has been demonstrated in rabbits, mice, rats, cats and human beings [3–5]. In fact DSIP promotes a particular type of sleep which is characterized by an increase in the delta rhythm of the EEG.

DSIP is normally present in minute amounts in the blood. Brain and plasma DSIP concentrations exhibit a marked diurnal variation [6] and there has been shown to be a correlation between DSIP plasma concentrations and circadian rhythm in human beings. Concentrations are low in the mornings and higher in the afternoons. An elevation of endogenous DSIP concentration has been shown to be associated with suppression of both slow-wave sleep and rapid-eye-movement sleep and interestingly also with body temperature [7]. Plasma concentrations of DSIP are influenced by the initiation of sleep [8]. Patients with Cushing's syndrome suffer from a lack of slow-wave sleep but the diurnal variation in slow-wave and rapid-eye-movement sleep in those patients appears to be similar to that in normal patients [9].

When compared with most other peptides, DSIP is unusual in that it can freely cross the blood–brain barrier and is readily absorbed from the gut without being denatured by enzymes [10,11]. DSIP is present in relatively high concentrations in human milk (10–30 ng mL^{-1}). Any mother who has breast-fed her babies will attest to the ability of a feed to induce sleep. However, a feed of artificial milk may have a similar effect, and it is not known whether DSIP concentrations are related to the sleep–wake cycle in human neonates [12].

DSIP has been synthesized. Administration of the synthetic substance does not induce tolerance [13]. DSIP can be assayed by several techniques including radioimmunoassay (RIA), enzyme immunoassay and high-performance liquid chromatography with RIA [14–16]. DSIP has a half-life in human plasma of between 7 and 8 min [2]. It is degraded in blood, the pathway involving the amino-peptidases [17]. A potential drug interaction might therefore be envisaged between DSIP and drugs which inhibit or are themselves metabolized by peptidases. Captopril is one such agent and patients currently undergoing treatment with any of the angiotensin-converting enzyme inhibitors should probably be excluded from any DSIP treatment protocol until further studies have been undertaken.

DSIP and sleep

The innate controlling mechanisms of sleep have fascinated scientists for generations and many different endogenous compounds have been proposed as controllers of sleep over the years. These include cholecystokinin, prostaglandin I2 and various unknown substances labelled 'sleep-promoting substances'. Indeed, the majority of humoral mediators seem to have some relation to sleep by, for example, affecting circadian rhythms or arousal states. In some cases, however, it is not clear if the humoral mediator is driving the sleep pattern or responding to the sleep pattern.

Since the discovery of DSIP a number of studies have been undertaken to test the hypothesis that DSIP may be the principal endogenous sleep factor. It is reported to increase the 'pressure to sleep' in human subjects who have been injected with small doses and this, together with its ability to induce delta-wave sleep, led to its consideration as a treatment for insomnia. A number of studies have examined this use with varied success [18–21].

DSIP has been described as a sleep-promoting substance rather than a sedative. There is a modulating effect on sleep and wake functions with a greater activity in circumstances where sleep is disturbed. There are minimal effects in healthy subjects who are not suffering from sleep disturbance [22]. DSIP is not a

night sedation drug which needs to be given just before retiring. A dose of DSIP given during the course of the day will promote improved sleep on the next night and for several nights thereafter. Despite these clear short-term benefits, however, doubt has been cast on whether or not DSIP treatment will prove to be of major benefit in long-term management of insomnia.

Studies have been undertaken in patients suffering from the sleep apnoea syndrome and from narcolepsy. Unfortunately, no difference in DSIP concentrations has been found between those patients and normal patients [23]. DSIP may, paradoxically, be of use in the treatment of narcolepsy and it is possible that it exerts its effect by restoring circadian rhythms [24]. When single and multiple injections of DSIP were given in a controlled double-blind study, disturbed sleep was normalized and better performance and increased alertness was seen during awake cycles together with improved stress tolerance and coping behaviour [22].

Non-sleep effects

DSIP has been shown to have an anticonvulsant action in the rat. The threshold to NMDA- and picrotoxin-induced convulsions is increased by DSIP [25,26]. This anticonvulsant effect may undergo a diurnal variation with greater antiepileptic activity seen at night [27]. DSIP is not unique in possessing a diurnal variation in anticonvulsant activity as melatonin, β-endorphin and dexamphetamine all reduce seizure threshold during the day and it is possible that DSIP simply represents one of the endogenous controls of brain excitability [28]. DSIP has an antinociceptive action in mice, an effect which is blocked by naloxone [29].

A neuroprotective effect has been demonstrated in rats subjected to bilateral carotid ligation [30]. A reduced mortality was observed together with a reduction in postischaemia function. DSIP also reduced brain swelling in a model of toxic cerebral oedema in the rat [31].

DSIP attenuates emotional and psychological responses to stress and also reduces the central amine responses to stress in rats [32]. The action of corticotrophin releasing factor on the pituitary gland in the rat is attenuated with a consequential inhibition of pituitary adrenocorticotrophic hormone (ACTH) secretion [33]. The situation is less clear in man as although one study confirmed this finding [34] another reported no inhibitory effect on the adrenocortical axis to both physiological and stressor stimuli [35]. DSIP had no effect on growth hormone or prolactin concentrations when administered to human volunteers [36]. In one study, infusions of 3 or 4 mg (an enormous dose) had no effect on ACTH levels or on cortisol secretion [35] although in another study DSIP 25 nmol kg^{-1} significantly decreased ACTH concentrations [36].

DSIP concentrations change during certain psychiatric disorders. Patients suffering from schizophrenia and depression have lower plasma and cerebrospinal fluid concentrations of DSIP than comparable normal volunteers [37]. Concentrations were also inversely correlated with sleep disturbance in those patients.

As might be expected of any substance which is naturally occurring, side-effects are uncommon. Normally, concentrations would be very low and therefore the injection of large, probably non-physiological doses might be expected to at least produce some unwanted effect. No significant side-effects have so far been reported with DSIP. In some human studies, transient headache, nausea and vertigo have been reported. DSIP actually appears to be incredibly safe as its LD_{50} has never been determined because it has never so far proved possible to kill an animal whatever the dose of DSIP administered.

Clinical uses

Clinical uses for DSIP already exist. The agent has been used for the treatment of alcohol and opioid withdrawal with some success [38]. Clinical symptoms and signs disappear after injection of DSIP although some patients have reported occasional headaches.

DSIP possesses a number of other apparently unrelated properties. In hypertensive rats, 200 μg kg^{-1} day^{-1} of DSIP for 10 days had an antihypertensive effect [39]. DSIP has also been reported to possess antimetastatic activity [40]. It may also reduce amphetamine-induced hyperthermia and may be beneficial in some chronic pain conditions [41].

An interesting study reported in 1986 injected DSIP and several analogues of the peptide directly into the cerebral ventricle of rats. DSIP did not increase sleep and this was thought to be due to its very rapid metabolism. However, two of the analogues did induce sleep but one produced arousal. It would

appear therefore that there might be the potential for not only sleep but sleep reversal within the analogues of DSIP [42].

The molecular sites for the action of anaesthetic agents are being identified. Volatile agents appear to act on specific sites of the GABA-A and glycine receptors, whereas ketamine and xenon act on the NMDA receptors. These sites are reproducible and clearly defined, but what is their natural purpose, as neither volatile anaesthetic agents nor xenon are usually found in physiological systems? It is possible, but has yet to be demonstrated, that DSIP and other neuroactive peptides selectively bind to these regions of GABA-A, glycine and/or NMDA receptors.

Is DSIP of relevance to the anaesthesiologist?

Anaesthesia is physiologically distinct from natural sleep and anaesthetic agents appear to work on receptor mechanisms normally dedicated to the control of brain metabolism. Conventional sleep staging does not indicate the depth of anaesthesia; rapid-eye movements (REM) and other characteristics of natural sleep are not seen during anaesthesia. It is possible, however, that anaesthesia is mimicking a natural phenomenon such as hibernation by copying the action of natural neuroactive peptides such as DSIP.

What is the significance of DSIP to anaesthesia? Could DSIP be the body's natural anaesthetic? Is activation of the DSIP receptors related to the state of anaesthesia? These questions must remain speculative for the present. Whether or not DSIP is the body's natural anaesthetic, or a substance closely involved in this process, it may not prove to be possible to administer it in a way which could be regarded as anaesthesia. Could it therefore be used as the body's natural sedative? No studies have been performed to investigate this possible use although it would theoretically seem to have potential.

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References

1 Schoenenberger GA, Monnier M. Characterization of a delta-electroencephalogram (-sleep)-inducing peptide. *Proc Natl Acad Sci USA* 1977; **74**: 1282–1286.
2 Graf MV, Kastin AJ. Delta-sleep-inducing peptide (DSIP): an update. *Peptides* 1986; **7**: 1165–1187.
3 Aliautdin RN, Kalikhevich VN, Churkina VI. [Hypnogenic properties of the delta-sleep peptide and its structural analogs]. *Farmakol Toksikol* 1984; **47**: 26–30.
4 Kimura M, Honda K, Komoda Y, Inoue S. Interacting sleep-modulatory effects of simultaneously administered delta-sleep-inducing peptide, muramyl dipeptide and uridine in unrestrained rats. *Neurosci Res* 1987; **5**: 157–166.
5 Susic V. The effect of subcutaneous administration of delta sleep-inducing peptide (DSIP) on some parameters of sleep in the cat. *Physiol Behav* 1987; **40**: 569–572.
6 Banks WA, Kastin AJ, Selznick JK. Modulation of immunoactive levels of DSIP and blood-brain permeability by lighting and diurnal rhythm. *J Neurosci Res* 1985; **14**: 347–355.
7 Friedman TC, Garcia-Borreguero D, Hardwick D *et al.* Diurnal rhythm of plasma delta-sleep-inducing peptide in humans: evidence for positive correlation with body temperature and negative correlation with rapid eye movement and slow wave sleep. *J Clin Endocrinol Metab* 1994; **78**: 1085–1089.
8 Seifritz E, Muller MJ, Schonenberger GA *et al.* Human plasma DSIP decreases at the initiation of sleep at different circadian times. *Peptides* 1995; **16**: 1475–1481.
9 Friedman TC, Garcia-Borreguero D, Hardwick D *et al.* Decreased delta-sleep and plasma delta-sleep-inducing peptide in patients with Cushing syndrome. *Neuroendocrinology* 1994; **60**: 626–634.
10 Kastin AJ, Banks WA, Castellanos PF, Nissen C, Coy DH. Differential penetration of DSIP peptides into rat brain. *Pharmacol Biochem Behav* 1982; **17**: 1187–1191.
11 Banks WA, Kastin AJ, Coy DH, Angulo E. Entry of DSIP peptides into dog CSF. role of physicochemical and pharmacokinetic parameters. *Brain Res Bull* 1986; **17**: 155–158.
12 Graf MV, Hunter CA, Kastin AJ. Presence of delta-sleep-inducing peptide-like material in human milk. *J Clin Endocrinol Metab* 1984; **59**: 127–132.
13 Ji AX, Li CX, Ye YH *et al.* Synthesis of delta sleep-inducing peptide (DSIP) and its physiological activity. *Sci Sin [B]* 1983; **26**: 174–185.
14 Graf MV, Kastin AJ, Fischman AJDSIP occurs in free form in mammalian plasma, human CSF and urine. *Pharmacol Biochem Behav* 1984; **21**: 761–766.
15 Nagaki S, Kato N. Delta sleep-inducing peptide-like material in rat brain as determined by enzyme immuno-

assay: effect of sleep deprivation. *Neurosci Lett* 1984; **51**: 253–257.
16 Fischman AJ, Kastin AJ, Graf MVHPLC shadowing: artifacts in peptide characterization monitored by RIA. *Peptides* 1984; **5**: 1007–1010.
17 Nyberg F, Thornwall M, Hetta J. Aminopeptidase in human CSF which degrades delta-sleep inducing peptide (DSIP). *Biochem Biophys Res Commun* 1990; **167**: 1256–1262.
18 Monti JM, Debellis J, Alterwain P, Pellejero T, Monti D. Study of delta sleep-inducing peptide efficacy in improving sleep on short-term administration to chronic insomniacs. *Int J Clin Pharmacol Res* 1987; **7**: 105–110.
19 Schneider-Helmert D. DSIP in insomnia. *Eur Neurol* 1984; **23**: 358–363.
20 Schneider-Helmert D. Effects of delta-sleep-inducing peptide on 24-hour sleep-wake behaviour in severe chronic insomnia. *Eur Neurol* 1987; **27**: 120–129.
21 Bes F, Hofman W, Van Schuur J, BC. Effects of delta sleep-inducing peptide on sleep of chronic insomniac patients. A double-blind study. *Neuropsychobiology* 1992; **26**: 193–197.
22 Schneider-Helmert D, Schoenenberger GA. Effects of DSIP in man. Multifunctional psychophysiological properties besides induction of natural sleep. *Neuropsychobiology* 1983; **9**: 197–206.
23 Vgontzas AN, Friedman TC, Chrousos GP, Bixler EO, Vela-Bueno A, Kales A. Delta sleep-inducing peptide in normal humans and in patients with sleep apnea and narcolepsy. *Peptides* 1995; **16**: 1153–1156.
24 Schneider-Helmert D. Effects of DSIP on narcolepsy. *Eur Neurol* 1984; **23**: 353–357.
25 Shandra AA, Godlevskii LS, Brusentsov AI, Karlyuga VA. Effects of delta-sleep-inducing peptide on NMDA-induced convulsive activity in rats. *Neuroscibehavphysiol* 1998; **28**: 694–697.
26 Brusentsov AI, Moroz VV, Suprun SA, Pomazanova TN, Shandra AA, Godlevskii LS. [Changes in the blastogenic lumphocyte transformation during kindling induced by picrotoxin in rats]. *Ross Fiziol Zh Im I M Sechenova* 1998; **84**: 233–237.
27 Yehuda S, Mostofsky DI. Circadian effects of beta-endorphin, melatonin, DSIP and amphetamine on pentylenetetrazol-induced seizures. *Peptides* 1993; **14**: 203–205.
28 Shandra AA, Godlevskii LS, Mazarati AM, Oleshko AA, Mikhaleva II. The influence of the delta-sleep-inducing peptide on convulsive activity. *Neurosci Behav Physiol* 1993; **23**: 480–485.
29 Nakamura A, Nakashima M, Sugao T, Kanemoto H, Fukumura Y, Shiomi H. Potent antinociceptive effect of centrally administered delta-sleep-inducing peptide (DSIP). *Eur J Pharmacol* 1988; **155**: 247–253.
30 Shandra AA, Godlevskii LS, Brusentsov AI *et al.* Effects of delta-sleep-inducing peptide in cerebral ischemia in rats. *Neurosci Behav Physiol* 1998; **28**: 443–446.
31 Platonov IA, Iasnetsov VV. [The effect of the delta sleep-inducing peptide on the development of toxic brain edema-swelling]. *Biull Eksp Biol Med* 1992; **114**: 463–464.
32 Sudakov KV, Coghlan JP, Kotov AV, Salieva RM, Polyntsev YV, Koplik EV. Delta-sleep-inducing peptide sequels in the mechanisms of resistance to emotional stress. *Ann N Y Acad Sci USA* 1995; **771**: 240–251.
33 Graf MV, Kastin AJ, Coy DH, Fischman AJ. Delta-sleep-inducing peptide reduces CRF-induced corticosterone release. *Neuroendocrinology* 1985; **41**: 353–356.
34 Chiodera P, Volpi R, Capretti L *et al.* Different effects of delta-sleep-inducing peptide on arginine-vasopressin and ACTH secretion in normal men. *Horm Res* 1994; **42**: 267–272.
35 Spath-Schwalbe E Schafer A, Uthgenannt D, Born J, Fehm HL. Delta-sleep-inducing peptide does not affect CRH and meal-induced ACTH and cortisol secretion. *Psychoneuroendocrinology* 1995; **20**: 231–237.
36 Giusti M, Carraro A, Porcella E *et al.* Delta sleep-inducing peptide administration does not influence growth hormone and prolactin secretion in normal women. *Psychoneuroendocrinology* 1993; **18**: 79–84.
37 Lindstrom LH, Ekman R, Walleus H, Widerlov E. Delta-sleep inducing peptide in cerebrospinal fluid from schizophrenics, depressives and healthy volunteers. *Prog Neuropsychopharmacol Biol Psychiatry* 1985; **9**: 83–90.
38 Dick P, Costa C, Fayolle K, Grandjean ME, Khoshbeen A, Tissot R. DSIP in the treatment of withdrawal syndromes from alcohol and opiates. *Eur Neurol* 1984; **23**: 364–371.
39 Graf MV, Kastin AJ, Schoenenberger GA. Delta sleep-inducing peptide in spontaneously hypertensive rats. *Pharmacol Biochem Behav* 1986; **24**: 1797–1799.
40 Prudchenko IA, Stashevskaia LV, Shepel' EN *et al.* [Synthesis and biological properties of delta-sleep peptide analogs. 2. Antimetastatic effect]. *Bioorg Khim* 1993; **19**: 1177–1190.
41 Larbig W, Gerber WD, Kluck M, Schoenenberger GA. Therapeutic effects of delta-sleep-inducing peptide (DSIP) in patients with chronic, pronounced pain episodes. A clinical pilot study. *Eur Neurol* 1984; **23**: 372–385.
42 Obal FJ, Kovalzon VM, Kalikhevich VN *et al.* Structure-activity relationship in the effects of delta-sleep-inducing peptide (DSIP) on rat sleep. *Pharmacol Biochem Behav* 1986; **24**: 889–894.