CLINICAL REVIEW

Autonomic disturbances in narcolepsy

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SUMMARY

Narcolepsy is a clinical condition characterized mainly by excessive sleepiness and cataplexy. Hypnagogic hallucinations and sleep paralysis complete the narcoleptic tetrad; disrupted night sleep, automatic behaviors and weight gain are also usual complaints.

Different studies focus on autonomic changes or dysfunctions among narcoleptic patients, such as pupillary abnormalities, fainting spells, erectile dysfunction, night sweats, gastric problems, low body temperature, systemic hypotension, dry mouth, heart palpitations, headache and extremities dysthermia. Even if many studies lack sufficient standardization or their results have not been replicated, a non-secondary involvement of the autonomic nervous system in narcolepsy is strongly suggested, mainly by metabolic and cardiovascular findings. Furthermore, the recent discovery of a high risk for overweight and for metabolic syndrome in narcoleptic patients represents an important warning for clinicians in order to monitor and follow them up for their autonomic functions.

We review here studies on autonomic functions and clinical disturbances in narcoleptic patients, trying to shed light on the possible contribute of alterations of the hypocretin system in autonomic pathophysiology.

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Introduction

Narcolepsy is a clinical condition characterized by excessive sleepiness, and in its most typical presentation is associated with cataplexy, i.e., brief sudden lapses of muscle tone triggered by emotions. The classic "narcoleptic tetrad" is completed by sleep paralysis and hypnagogic hallucinations, though it is fairly uncommon to have all four symptoms.[1] Nocturnal sleep disruption and automatic behavior are usual complaints among patients with the disease.[1,2] Weight gain and metabolic dysfunctions are also common in patients with narcolepsy with cataplexy.[3–5]

Narcolepsy with cataplexy in humans is associated to the loss of the hypocretin-producing cells of the lateral and posterior hypothalamus and to the markedly reduced level of cerebrospinal fluid (CSF) hypocretin-1. Animal studies pinpoint an important role for hypocretins in various autonomic functions, such as cardiovascular, metabolic, thermoregulatory, and gastrointestinal regulation.

A variety of autonomic disorders have been described in narcoleptic patients,[6–10] but they have been poorly characterized. Reports on autonomic system involvement in narcoleptic patients are still controversial, mostly because of differences in standardized conditions or in methodological approaches; however, some findings (especially metabolic, hearth rate variability and body temperature alterations) seem to indicate the presence of an autonomic imbalance.

The relatively recent discovery of the key role of hypocretin deficiency in narcolepsy with cataplexy might be the unifying interpretation of the complex symptomatology of this condition. We analyze in this review the different autonomic abnormalities reported and try to discuss, whenever possible, the extent to which they can be related to hypocretin deficiency.

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Abbreviations

BAT	brown adipose tissue	MSNA	muscle sympathetic nerve activity
BMI	body mass index	NPT	nocturnal penile tumescence
BP	blood pressure	NPY	neuropeptide Y
CAP	cyclic alternating pattern	NREM	non-REM sleep
CSF	cerebrospinal fluid	NTS	nucleus of the solitary tract
DMN	dorsal motor nucleus of the vagus	PVN	paraventricular nucleus
DVC	dorsal vagal complex	REM	rapid eye movement
EMG	electromyography	RSA	respiratory sinus arrhythmia
HF	high frequency	RSNA	renal sympathetic nerve activity
HR	heart rate	RVLM	rostral ventrolateral medulla
HRV	heart rate variability	SCN	suprachiasmatic nucleus
i.c.v.	intracerebroventricular	SNA	sympathetic nerve activity
i.v.	intravenous	Tb	body temperature
LF	low-frequency	VMMR	ventromedial medullary raphe
		VMN	ventromedial nucleus
		WAT	white adipose tissue

Clinical aspects

Pupillary abnormalities

Pupil size and stability are affected by the level of sleepiness: ongoing forced wakefulness provokes a significant decrease of pupil size and pupillary low-frequency diameter oscillations increase with the duration of sleep deprivation in normal volunteers.[11] The demonstration that the preganglionic neurons of the ciliary ganglion receive a robust hypocretin-1 input[12] explains how the size of the pupil, its responses to light, and its naturally occurring fluctuations in diameter vary with the degree of alertness[13] and with emotional arousal.[14] The above findings (and the altered hypocretin system of narcoleptic patients) can contribute to better explain the mechanisms underlying the earliest description of hippus in narcoleptic patients, which was formerly ascribed to a poor autonomic balance[15,16] and thought to be mediated by arousal.[8] Fluctuations of arousal influence pupil diameter of narcoleptic patients, provoking periodic diameter cycles, approximating to 90 min, with maximum pupil size coinciding with the highest alert levels, and minimum with the lowest subjective ratings of alertness.[15,17,18] Moreover, contrary to the spontaneous pupillary oscillations that appear in healthy subjects with a presumably intact hypocretin system, narcoleptic patients display blunted and random pupillary oscillations under constant illumination.[19]

Sexual complaints

"Disturbances of libido and/or impotence" were reported in 21% of 347 narcoleptic patients, being more frequent among women (29%) than men (17%).[6] The frequency of sexual disorders among idiopathic and symptomatic narcolepsy did not differ in men, whereas they were twice as frequent in the secondary form in women. Sexual symptoms did not develop until 10–20 years after the disease onset.[6] However, in these reports, the lack of information on comorbidities such as cardiometabolic and psychiatric alterations and drug status is an important bias, considering that a connection between the traditional drugs (i.e., stimulants and antidepressants) used in narcolepsy and development of impotence has been noticed,[7] also by the patients themselves.[20]

Nocturnal penile tumescence (NPT) normally occurs during rapid eye movement (REM) sleep, also in narcoleptic subjects.[20] In a series of 28 narcoleptic patients[7] complaining of erectile dysfunction in the absence of any psychiatric features, none of the 23 medicated patients had complete NPT episodes, and their

duration was reduced. The authors hypothesized a neurogenic or vasculogenic substrate for a greater susceptibility of narcoleptic patients to secondary effects of medications used in their treatment; however, case-control studies are still lacking.

Cardiovascular abnormalities

The first evidence of impaired autonomic control in narcoleptic patients came from the work of Sachs and Kaijser.[21,22] They tested autonomic cardiovascular reflexes [cardiovascular responses to isometric muscular contraction, respiratory sinus arrhythmia (RSA) and heart rate (HR) response to the Valsalva maneuver (Valsalva ratio)] and demonstrated an attenuated reactivity in the vegetative control system of narcoleptic patients (i.e., smaller increase in HR, smaller RSA), compared to control subjects and sleep apnea patients. Interestingly, amphetamine administration did not modify the responses, and cardiovascular reflex abnormalities were not due to chronic use of central stimulant medications.

Increases in blood flow are mediated by sympathetic efferents (beta-adrenergic) whereas increases in HR are the result of vagal inhibition. Several autonomic nervous system responses (e.g., diving reflex produced by increased vagal activity) found to be normal (indicating intact peripheral nerves) in narcoleptic patients, together with evidence of other sympathetic and parasympathetic alterations, pinpoint a central origin of the autonomic imbalance. This is also suggested by the finding that functions depending on central excitatory mechanisms like muscle-induced HR and blood flow increases are attenuated, while peripherally elicited responses such as cardiovascular responses to orthostatic test or HR-slowing mechanisms are essentially normal.[21,22]

Nevertheless these results have not been confirmed by subsequent studies that failed to disclose such abnormalities, reporting normal circadian blood pressure (BP) variations,[23] normal deep breathing, Valsalva and orthostatic tests for HR and BP among unmedicated patients.[24,25]

Ferini-Strambi et al.[26] performed a spectral analysis of HR variability (HRV) in ten drug-naive sex-matched narcoleptic patients during sleep, in order to rule out the possible influence of vigilance state on autonomic balance. They excluded a primary disturbance of the cardiac autonomic nervous system in narcolepsy, finding a higher sympathovagal balance in patients compared to controls during wakefulness before sleep, as a result of an attenuated activation of the parasympathetic activity, probably due to the sleep-wakefulness cycle impairment in narcoleptic patients.

Fronczek et al.,[27] using the Fast Fourier Transform, found higher power in all HRV frequency bands in nine untreated male

narcoleptic with cataplexy patients in supine position, compared to controls, with a normal low-frequency/high frequency (LF/HF) ratio. The authors hypothesized a reduced sympathetic tone in patients, even if mean HR did not differ between the groups.

Conversely, studying HRV in rest supine condition and during head-up tilt test, an enhanced sympathetic activity at rest (increased LF/HF ratio and basal mean HR) with a reduced response to the orthostatic stress has been found in narcoleptic with cataplexy patients.[25] Notably, the different results may be ascribed to methodological differences from the previous work (absolute versus normalized HF and LF values, focus on R–R interval, Fast Fourier Transform and autoregressive analysis) or patient condition (wakefulness versus sleep or pre-sleep-wakefulness, body position).

The variable results of these studies emphasize the insufficiency of single assessments of the autonomic nervous system during wakefulness and probably reflect the insufficient standardization of test conditions.

Metabolic rate and body temperature abnormalities

Narcolepsy is often associated with body weight/body mass index (BMI) increase; weight gain usually occurs around the onset of the disease, and patients may become overweight or even obese.[3,4,28–34] The endeavour to explain the observed body fat accumulation is challenging. In fact, firstly, weight increase seems to be independent of calorie intake, which is paradoxically lower in narcolepsy patients,[5,35] and, moreover, they present a similar amount of motor activity and immobility periods when compared to healthy subjects.[36]

Energy metabolism and basal metabolic rate have also been investigated: in Chabas et al.,[37] rest energy expenditure, measured by means of indirect calorimetry, has been shown to be significantly lower in 13 narcoleptic patients, compared to 9 healthy controls; the groups were not BMI-matched, but this feature seemed to be independent of BMI, therefore intrinsic to the disease per se. Nevertheless, comparing BMI-matched groups (15 narcoleptic hypocretin-deficient patients versus 15 controls), Fronczek and colleagues did not find any significant difference in rest metabolic rate, nor in O_2 consumption, respiratory index, or carbohydrate or fat substrate combustion.[27] Interestingly, they hypothesized a reduced sympathetic tone on the basis of the finding of an increased HRV in narcoleptic patients.[27] Since the autonomic system innervates white (WAT) and brown (BAT) adipose tissue, inducing catabolic processes throughout sympathetic inputs, and anabolic processes, throughout parasympathetic inputs,[38] it is possible that the sympathetic tone reduction explains the increased fat accumulation observed in narcolepsy. The authors concluded that the possible link between basal metabolic rate and sympathetic tone still remains unclear.[27]

Finally, Dahmen et al.,[39] combining the two methodological approaches of the previous papers,[27,37] found a lower energy expenditure and a lower basal metabolic rate in 13 narcoleptic patients compared to 30 controls, although the difference was not significant. Interestingly, these authors found significant differences by comparing narcoleptic patients versus controls, all with BMI <30, showing a lower energy expenditure and a lower basal metabolic rate in non-obese narcoleptics. Dahmen et al. in interpreting this finding, proposed that narcolepsy may lead to a shift of individual BMI set points (i.e., higher).

As a possible player, due to its interaction with sympathetic tone, leptin has been considered with controversial findings. Leptin is a hormone produced by adipocytes that, among other functions, signals satiety. A significant blunt of the late evening physiological peak has been reported in hypocretin-deficient narcoleptic patients,[40] and this was attributed to the concomitant reduction in sympathetic tone.[27] Hypocretin neurons may mediate the influence of the suprachiasmatic nucleus on the circadian distribution of autonomic activity or, alternatively, the altered pattern of sleep-wakefulness in narcolepsy may disrupt the normal sleep-mediated reduction in sympathetic tone and thus affect the nocturnal rise of leptin levels.[40] Plasma leptin is sensitive to phase-shifting of sleep[41] and is considerably reduced upon sleep deprivation in healthy adults.[42] Schuld and colleagues also found a significant decrease of leptin levels in plasma (but not in CSF) of 15 narcoleptic patients BMI-matched with controls, although narcolepsy patients displayed a higher BMI; the loss of leptin could therefore explain the increase in body mass due to the loss of leptin central signaling.[3] Reduction of leptin plasma levels and loss of its circadian rythmicity was reported in hypocretin-deficient narcoleptic patients,[40] but no difference in CSF leptin levels has been found. Conversely, Nishino et al.[43] observed a significantly increased concentration of leptin CSF levels in 38 narcoleptic patients versus controls after BMI adjustment, and hypothesized that increased leptin levels could depend on higher BMI or that the leptin resistance condition may cause obesity. Arnulf and coll. in a large study with 166 narcolepsy patients did not find any significative alteration of leptin concentration neither in plasma nor in CSF of narcolepsy patients, therefore not supporting a possible role of leptin in mediating the increased BMI observed in narcolepsy.[44]

The normal pattern of the circadian core body temperature cycle seems to be preserved in narcoleptic patients,[45] although not all the authors agree, being a decreased core body temperature also reported in narcoleptic patients.[46,47] Fronczek et al. studying skin temperature regulation in unmedicated narcoleptic patients throughout the day reported an elevated distal skin temperature. The same feature appears during night-time, prolonged heat stress or continuous supine posture in normal subjects.[48] Distal skin temperature increased over the day in narcoleptic patients and, as in controls, higher distal-to-proximal gradient of skin temperature – i.e., augmentation in distal temperature – correlated with sleep propensity.[48] Experimentally-induced changes in core body and skin temperature of narcoleptic patients can also modify vigilance and sleepiness.[47] The authors attributed skin temperature alterations to a decreased sympathetic distal vasoconstrictor tone due to the hypocretin deficiency of narcoleptic patients.[48]

Other autonomic symptoms

Intermittent drenching night sweats and abrupt panic attacks with subjective tachycardia were equally present in a cohort of patients with excessive sleepiness among sleep apnea sufferers, narcoleptic patients and non narcoleptic patients with excessive drowsiness[49]; palpitations were noted especially in the patients with narcolepsy. An increase in 24-h urinary and plasma catecholamines was found in the sleep apnea group only; while an increased sensitivity for cardiovascular response triggered by isoproterenol was found in patients with excessive sleepiness.[49] The authors concluded that narcoleptic patients are caught in the paradox of a brain sleepy but hyperresponsive to adrenergic stimulation, a finding in line with clinical observations that many patients with narcolepsy swing between extremes, describing themselves as having two speeds: "off" and "fast".[49] In this regard, neurophysiological investigations have documented brainstem hyperexcitability during cataplexy[50] with exaggerated startle reflex in narcoleptic patients with cataplexy with a trend toward an increased response in patients using stimulants (catecholamine agonists).[51] A dysfunction of hypothalamic–amygdala interaction may, indeed, impair the normal process of stimulus recognition[52] taking-off the "top-down" inhibitory influences[53,54] and releasing pre-programmed subcortically-stored behaviors regarding

reflex actions, posture and movement with their own autonomic correlates.[55]

Dahmen et al. found in two different studies that narcoleptic patients have a greatly increased prevalence of migraine: 23 and 35% in men, 44 and 64% in women, in contrast to 8% and up to 25%, respectively, in the general population; migraine seems to have a characteristic late onset in narcoleptic patients.[56,57] These results have not been confirmed by a case-control study of the German Migraine and Headache Society, who reported an association between narcolepsy and tension-type headache but not between narcolepsy and migraine.[58]

Autonomic system and cataplexy

Cataplexy is characteristically triggered by emotions that are well known to be highly charged by autonomic changes. It is thought that baroreceptor activation may trigger cataplexy[59] in a way similar to REM sleep induced by vago-aortic nerve stimulation.[60] Indeed, symptoms of autonomic activation have been reported during or prior to cataplexy in humans (i.e., light-headedness, flushing or sensation of temperature changes).[61]

Siegel et al.[62] studied cataplexy-related HR and BP changes in a canine model of narcolepsy. Modifications in these variables were recorded during spontaneous cataplectic episodes. No reliable changes were found in BP associated with cataplexy. HR, instead, showed an increase (+18%) in the 10 s preceding the onset of cataplexy, reaching its peak at or shortly after the disappearance of muscle tone, and falling by a mean of 10% in the 10 s after cataplexy onset.

Monitoring of HR and intra-arterial BP during cataplexy in humans showed a decrease in HR and an increase in BP with onset of cataplexy (see an example in Fig. 1), but the change in HR was always subsequent to the change in BP.[63] In particular, just before four of six attacks, a small decrease in systolic and diastolic BP (mean systolic change 25 ± 5 mm Hg, mean diastolic change 15 ± 4 mm Hg) was seen, followed by a return to baseline and an overshoot before the reduction in EMG activity. Another decrease in BP was observed at the end of the attack. The initial drop in BP was also followed by a change in HR occurring either at the time of the return to baseline or at overshoot.
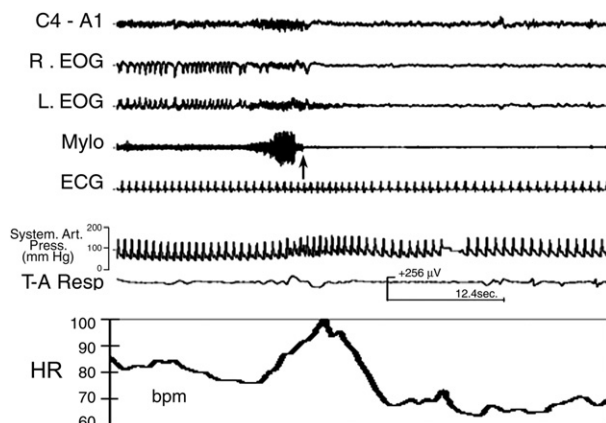
Another study analyzed 11 cataplectic attacks video-polygraphically.[64] Six episodes showed an increase in HR beginning several seconds before and followed by bradycardia starting at the onset of EMG silence that persisted throughout the attack. Heart rate returned to baseline values about 50–70 s after the onset of the episode.

The time course of sympathetic and cardiovascular activities in three patients with hypocretin-deficient narcolepsy was investigated during ten cataplectic episodes by means of microneurographic recordings, monitoring muscle sympathetic nerve activity (MSNA) simultaneously with HR, respiratory movements, arterial finger BP, electroencephalography, electro-oculogram and superficial electromyogram. Results showed no significant autonomic changes before the onset of the cataplectic episodes. Cataplexy was associated with a significant increase in MSNA and systolic BP compared with baseline, whereas HR was markedly decreased (Fig. 2). An irregular breathing pattern mainly characterized by apnea typically occurred during the attacks. The absence of significant changes in autonomic activity prior to cataplexy onset in this study seemed to rule out a triggering role of the autonomic system, whereas the co-activation of sympathetic and parasympathetic autonomic systems (increased MSNA activity concomitant with HR deceleration) during the cataplectic attack is reminiscent of what happens during the vigilance reaction in animals.[65] These data were replicated in another study by Vetrugno et al.[66] and seem to support Sachs and Kajiser's postulates[21] of a central rather than peripheral origin of the paroxysmal autonomic imbalance in narcolepsy with cataplexy, co-activating the sympathetic and parasympathetic central nervous system networks, similarly to what occurs in the diving response, oculo-cardiac reflex and vigilance reaction.

Simple exercise is not a frequent trigger for cataplexy, and cardiovascular activation alone does not seem to be sufficient to induce cataplexy. Activation of the limbic system and amygdala by emotional stimuli could herald cataplexy through secondary activation of pontine structures that regulate muscle tone.[64–66]

As cataplexy is usually triggered by emotions, the psychophysiologic effects of processing visual stimuli with established emotional valences were studied in eight drug-free patients with narcolepsy and in a control group of eight healthy subjects. The effects of exposure to pictures selected from the International Affective Picture System were assessed in muscular, autonomic, cognitive, and subjective systems. The autonomic, muscular, and cognitive systems showed an attenuated reaction to visual stimuli in patients compared to controls, being the lowest responses when
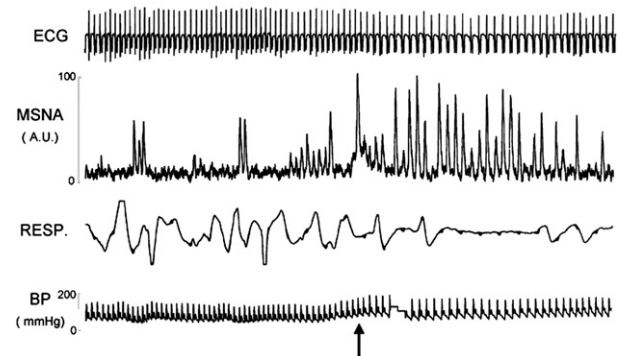

Fig. 1. Polygraphic recording of a global cataplectic attack. Heart rate (HR) changes during a global cataplectic attack ending with the collapse of the patient to the ground. The spectrum of HR waxes just before the complete EMG silence appears on chin muscle (Mylo) (Arrow). During the persistent EMG atonia HR decelerates. With respect to HR variations, systemic arterial pressure remains quite unchanged across the cataplectic episode, except for a transient increase at the beginning of the EMG silence. Note the shallow breathing accompanying the cataplectic attack. EOG: electro-oculogram; Mylo: mylohyoideus; System. Art. Pres.: systemic arterial pressure; T-A Resp: thoraco-abdominal respirogram; HR: heart rate.

Fig. 2. Microneurographic recording of a cataplectic episode. Microneurographic recording of a cataplectic episode (the arrow shows the clinical onset) in a narcoleptic patient showing a marked increase in muscle sympathetic nerve activity (MSNA) (both in incidence and amplitude) and in blood pressure (BP) and a decrease in heart rate (HR). An irregular breathing pattern with incoming apnea is also evident. ECG: electrocardiographic activity; MSNA: muscle sympathetic nerve activity; A.U.: arbitrary unit; RESP: respirogram; BP: blood pressure.

unpleasant pictures were presented. The drawback exhibited by narcoleptic patients suggests reduced reactivity of the aversive motivational system responsible for negative or unpleasant emotions.[67]

Autonomic function and sleep microstructure

Cyclic alternating pattern (CAP) is a normal component of NREM sleep. CAP consists of a biphasic pattern characterized by oscillations between greater (A phase) and lower (B phase) degrees of arousal, thought to reflect sleep instability in contrast to non-CAP sleep (stable sleep).[68,69] CAP rate is reduced in narcoleptic adults and children, suggesting an impaired modulation of arousal fluctuation during NREM sleep.[70–72] CAP and autonomic function are interrelated, as demonstrated by HRV studies during normal sleep showing an increase in LF band and LF/HF ratio and a decrease in the HF band during CAP.[73,74] Therefore the fluctuations in sleep microstructure representing CAP are accompanied by modifications of the balance between the sympathetic and vagal components of the autonomic nervous system. Despite the overall vagal predominance during sleep, phases of sustained sympathetic activity occur, and during CAP an increase in baroreflex sensitivity promotes the buffering of such discharges by means of rapid changes in cardiac vagal circuits.[75] However, even if narcoleptic patients present a reduced CAP rate, their overall HRV during nocturnal sleep is similar to that obtained in controls: decreased LF/HF ratio mainly due to a decrease in the LF band component.[26]

Pathophysiological basis

Hypocretins/orexins in autonomic regulation

The role of hypocretins and their receptors in sleep-wakefulness physiology and in narcolepsy is now well established.[76] The production of hypocretins is almost exclusively circumscribed in the lateral and posterior hypothalamus. The relatively few hypocretinergic neurons in these areas have widespread projections in the central nervous system. Both neuroanatomical and neurophysiological data indicate an important role of hypocretins in the regulation of the autonomic system. Hypocretin hypothalamic neurons project to the tractus solitarii (NTS) and to the dorsal motor of the vagus nerve (DMN) nuclei, to the rostral ventrolateral medulla (RVLM), and to the intermediolateral column of the spinal cord.[77–80]

RVLM neurons, which are known to be a relay station for cardiovascular reflexes and major determinants of efferent sympathetic activity,[81] are also involved in the regulation of cutaneous vasomotion.[82] Hypocretin hypothalamic neurons also project strong efference to the ventromedial medullary raphe (VMMR).[80,83] VMMR contains pre-sympathetic neurons projecting to organs involved in thermoregulation, such as BAT, tail (rat) and ear (rabbit) vasculature,[84–88] and is involved in the autonomic cold-defense response.[89] In the rat, VMMR activation induced thermogenic responses, i.e., increase in BAT sympathetic nerve activity (BAT-SNA)[85] and in HR,[90] and a reduction in tail blood flow.[87] Although the evidence of a direct action of hypocretin neurons on VMMR sympathetic pre-motor neurons is still missing, VMMR neurons have been shown to mediate autonomic thermoregulatory effects evoked by activation of lateral hypothalamus neurons.[91]

Other hypocretin projections reach hypothalamic arcuate and paraventricular (PVN) nuclei, and the anterior part of the ventromedial (VMN) nucleus,[92–94] the former being involved mainly in the integration of the autonomic nervous and neuroendocrine systems,[95] and the latter in the homeostatic regulation of body metabolism through the sympathetic nerves. In addition, through a direct action on the locus coeruleus, PVN and NTS may also influence vascular tone by modulating systemic epinephrine release at the level of the adrenal medulla.[96]

Cardiovascular autonomic effects of hypocretins

Emerging evidence indicates that hypocretins have an important role in the central cardiovascular regulation. Central application of hypocretins enhances sympathetic outflow and plasma catecholamine release not only in conscious unrestrained rats, but also in anesthetized animals; therefore, pressor and tachycardic responses are not likely to be a consequence of increased locomotor activity.[95,97] Moreover, in conscious rabbits, pharmacological blockade of ganglion activity abolishes BP and renal sympathetic nerve activity (RSNA) response to intracerebroventricular (i.c.v.) hypocretin administration, suggesting that the cardiovascular effects of hypocretin are due to an activation of the sympathetic outflow.[98] I.c.v. administration of hypocretin-1 produces a significant dose related increase in BP, HR, RSNA, and plasma norepinephrine in conscious, unrestrained, rats.[99,100] All sympathetic effects elicited by hypocretins present larger and longer responses with hypocretin-1.[95,100] In anesthetized rats, intracisternal[97] or intrathecal injection[101] of hypocretin-1 and -2 produces a dose related increase in BP and HR. The results of intrathecal injection suggest that hypocretin may augment spinal sympathetic outflow also by acting directly on sympathetic motor neurons. Hypocretin-1 microinjection in the RVLM of anesthetized[97] or conscious[102] rats produces dose-dependent increases in BP and HR. The small and long-lasting effect of hypocretin-1 on BP observed in awake rats has been interpreted by the authors as indicating a neuromodulatory role for hypocretin on sympathoexcitatory neurons of the RVLM. Hypocretin microinjection in RVLM also activates neuronal circuits that control vagal and sympathetic activity to the heart.[103]

The results of hypocretin microinjections into the NTS, the principal terminal site of baroreceptor afferents in the medulla, are controversial. De Oliveira et al. reported a dose-dependent decrease in BP and HR in anesthetized rats suggesting that hypocretin-1 in this site can activate neuronal circuits that increase vagal activity to the heart, inhibit sympathetic activity to the heart and vasculature, and modulate the excitability of NTS neuronal circuits that automatically control the circulation.[104] On the contrary, Smith et al. described an increase in BP and HR.[105] More recent studies demonstrated that microinjection of hypocretin in NTS produces a bi-directional dose-dependent cardiovascular response: at a lower dose (5 pmol), hypocretin decreases BP, HR, and sympathetic neurogenic vasomotor tone, while at higher doses (>20 pmol), cardiovascular excitatory responses are obtained. These bi-directional cardiovascular effects are abolished by hypocretin receptor antagonists.[106] Accordingly, results obtained by Tanida et al. in anesthetized rats support the hypothesis that cardiovascular response to hypocretin administration is dose-dependent: intravenous or i.c.v injection of hypocretin-1 at low doses suppresses or reduces BP and RNSA, whereas at higher doses it increases them.[107] The hypothalamic suprachiasmatic nucleus (SCN) could be involved in these dose-dependent effects of hypocretin-1, because bilateral lesion of SCN abolishes them.[107] SCN participates in the control of BP not only as a master circadian oscillator, but also through direct neural projections to sympathetic and parasympathetic neurons modulating BP.[107]

A recapitulatory description of the physiologic responses to exogenous hypocretin administration can be seen in Table 1.

Through their projections to the NTS, the RVLM, the VMMR, the DMN, and the intermediolateral column of the spinal cord, hypocretin neurons may modulate cardiovascular adjustments to different motivated behaviors. Accordingly, a role of hypocretins in

different features of the defense response has been suggested.[108] The increases in BP, HR, respiratory frequency, and resistance in visceral vascular beds, and the decreases in resistance in the airways and the skeletal muscle vascular bed elicited by stimulation of the perifornical area are significantly attenuated in mouse models of hypocretin deficiency[108]: these animals also show reduced increases in BP, HR and locomotor activity in response to emotional stressors.

Thermoregulation, metabolism and feeding

Hypocretins are expressed in mammals and have also been found in some reptiles. These peptides seem to confer an evolutionary advantage for periods of nutritional depletion, when augmented wakefulness in the proper circadian phase provides increased feeding opportunities.[93] Body temperature cycle is one of the strongest circadian rhythms in humans, and is sufficiently dominant to influence other behavioral and physiological parameters such as feeding and motor behaviors, sleep, enzyme activities, hormone concentrations, cardiovascular function, etc. In turn, arousal status tonically influences circadian changes in body temperature (changing with sleep/rest and wakefulness), and both functions have been shown to be regulated by hypocretins in coordination between them.[109] Hypocretin-1 exerts an anabolic effect that is not a mere modification of food intake or temperature regulation, but may be accompanied by hypothermia and a concomitant decrease in metabolic rate; by contrast, hypocretin-2 leads to hyperthermia without associated metabolism changes.[110] Increases in body temperature mediated by hypocretins may be due to a direct effect of the sympathetic outflow to BAT.

Effects of hypocretin administration on thermoregulation and metabolism

Hypocretin-1 can increase peripheral and core temperature. This increase is independent of locomotor activity, suggesting a pivotal role of BAT in non-shivering thermogenesis (thermogenesis unrelated to muscle activity), at least in animal models.[111] Physiologically, BAT plays a major role in increased heat production under conditions of cold exposure or overeating.[84] I.c.v. administration of hypocretin increases body temperature (Tb) in awake rats,[80,109,112] and BAT-SNA activity and Tb, in anesthetized rats.[111,113] The thermogenic effect of hypocretin-1 seems to have a biphasic pattern as it seems to happen on BP and RNSA: high doses induce hyperthermia,[112] while low doses lead to hypothermia through vasodilation.[110,114] Other authors[111] found a dose-effect curve in sympathetic and BAT thermogenic activity after i.c.v. hypocretin-1 administration. Nevertheless, adrenergic pathways are not sufficient to preserve such responses[115]: intact dopaminergic pathways are necessary to complete the thermogenic effect mediated by hypocretin-1.

Hypocretin may also modulate sympathetic nerve activity innervating WAT.[116] Autonomic nerves play an important role in the regulation of lipid metabolism and WAT response to centrally administered hypocretin-1 also displays a biphasic pattern: low doses lead to a decrease in sympathetic activity and in plasma free fatty acid levels, and the opposite effect with higher doses.[116] The same authors also showed that low doses of hypocretin-1 decreased RSNA, while high doses increased it.[107] This finding suggests that higher doses of hypocretin-1 may regulate the lipolytic processes in adipose tissue through facilitation of the sympathetic nervous system, while lower doses may inhibit lipolysis by suppressing sympathetic nerve activity.[116] This could indicate that narcolepsy with cataplexy is associated with more lipogenesis than lipolysis, in good accordance with the overweight or obesity present in most patients.

Metabolic changes in hypocretin-deficient mice

There is evidence for hypocretin involvement in metabolic changes and obesity, and animal models have shed interesting insights on this topic. A murine model of narcolepsy, the orexin/ataxin-3 transgenic mouse, characterized by a progressive loss of orexinergic neurons almost complete at 15 weeks of age, displays late-onset obesity and hypophagia.[117,118]

Hara et al. demonstrated that the obesity developed is not only critically dependent on genetic background, but also linked to the complete loss of hypocretinergic neurons: in fact, orexin/ataxin-3 transgenic mice show more severe metabolic consequences than those displayed by prepro-hypocretin knockout mice that have normal growth rather than obesity, being also hypophagic.[117,119] The difference in body weight gain between the two mice models under the same genetic background implicates a role of other neuropeptides physiologically co-localized with hypocretin.[118]

Hypocretins are considered weak-to-moderate appetite stimulators, but they also interact with other neuropeptides to modulate feeding behavior: hypocretinergic neurons activate neuropeptide Y (NPY) neurons located in the arcuate nucleus.[120] Central administration of NPY increases food intake, and also inhibits the thyroid axis, and decreases sympathetic nervous system outflow to brown adipose tissue, thus lowering energy expenditure.

The activity of hypocretinergic neurons is modulated by different peripheral metabolic cues: hypoglycemia activates hypocretinergic neurons, while glucose directly inhibits them. Moreover, both hypocretinergic and NPY neurons are inhibited by leptin[120] that not only inhibits feeding (signaling for satiety and/or acting as a measure of nutritional status), but also regulates energy expenditure, as measured by oxygen consumption and body temperature.[120]

Through their projections to autonomic structures, hypocretin neurons play a role in the phenomenon of hypoglycemia awareness, in which low glucose levels trigger autonomic and behavioral activation and peripheral cathecolamines release, as well as behavioral responses, inducing, for example, awakening from sleep. Accordingly, during fasting, narcoleptic mice with genetic ablation of hypocretin neurons do not exhibit the expected increase in exploratory activity and spend less time awake than wild-type mice.[121] It is worth noticing that in humans the activation of the autonomic system produced by hypoglycemia is significantly reduced during sleep,[122] when hypocretin neurons are less active, and it is even more compromised during sleep in subjects with type 1 diabetes.[123] These patients show a sleep-related hypoglycemia-associated autonomic failure, probably because of their reduced sympathoadrenal responses, and are also significantly less awakened by hypoglycemia.

Gastrointestinal function regulation

The lateral hypothalamus plays a vital role in acid secretion, especially under hunger sensation, as demonstrated by electrical stimulation and lesion models. Central but not peripheral hypocretin-1 administration increases vagal-dependent gastric acid secretion in a dose-dependent fashion, at the same or smaller doses that stimulate food consumption. The vagal system is involved in the stimulation of acid secretion by hypocretin-1 because atropine or surgical vagotomy completely blocks acid stimulation by intracisternal infusion, therefore hypocretin-1 has been proposed as a candidate mediator of the cephalic secretory response phase to feeding.[124] The vagus nerve combines afferents and efferents (gastrointestinal sensory feedback and gut motility and secretory stimulation, respectively) that are integrated at the level of the dorsal vagal complex (DVC), composed of the NTS (where primary visceral afferents terminate) and the DMN

Table 1
Physiological responses to exogenous administered hypocretins in animals.

Vigilance state	Peptide	Administration site	Dose[a] (nmol)	Physiological response	Ref.
C (rats)	Hcrt-1	I4th V	1.0	↑ in food and water intake, HR, core body temperature and locomotion	80
		Within NTS	0.2	No change in food and water intake	
A (rats)	Hcrt-1	IC	0.0056	↑ HR but not BP	97
			0.028–7.0	Dose related ↑ HR and ↑ BP	
	Hcrt-1 and -2	IV	11/Kg	No effect on HR or BP	
	Hcrt-2	IC	0.028–0.28	↑ BP and ↑ HR	
	Hcrt-1	Within RVLM	0.014	↑ BP and ↑ HR	
C (rabbits)	Hcrt-1	ICV	0.1	Dose related ↑ BP, RSNA, E ↑ plasma glucose and insulin ↑ vasopressin	98
		IV	0.1	No effect	
C (rats)	Hcrt-1	ICV	1.0	↑ BP	99
			5.0	↑↑ BP	
	Hcrt-2		1.0	↑ BP	
			5.0	↑ BP	
C (rats)	Hcrt-1	ICV	0.3	↑ BP, RSNA, but not HR	100
			3.0	↑ BP, RSNA, HR, E, NE	
	Hcrt-2		0.3	↑ BP	
			3.0	↑ BP, HR, NE, not RSNA or E	
A (rats)	Hcrt-1	Within magnocellular reticular nucleus (RVMM)	0.0005–0.0025	Dose-dependent ↑ HR, little or no change on BP	103
			0.001–0.0025	Baroreflex attenuation	
A (rats)	Hcrt-1	Within caudal dorsolateral and medial NTS	0.0005–0.0025	Dose related ↓ BP and HR	104
			0.005	no further decrease	
			0.001	Baroreflex potentiation	
		Within commisural NTS	0.0025–0.005	↑ BP with or without an associated HR response	
A (rats)	Hcrt-1	Within NTS	0.01–10.0	Dose related ↑ BP and HR	105
	Hcrt-2		1.0	Dose related ↑ BP	
A (rats)	Hcrt-1	IV	0.0003–0.03	↓ BP and RSNA	107
			0.003	↓ BP and RSNA (maximum response)	
			0.3	↑ BP and RSNA	
		ICV	0.000003	↓ BP and RSNA	
			0.003	↑ BP and RSNA	
C and A (rats)	Hcrt-1	I3rd V	0.6–15.0	Dose related ↑ in body temperature	109
			15.0	↑ plasma glucose and insulin	
C (rats)	Hcrt-1	ICV	3.0–6.0	Dose related ↑ in food intake and ↑ of post-fasting hyperphagia	110
			0.6	Hypothermia followed by hyperthermia	
	Hcrt-2		0.6–6	Dose related hyperthermia	
A (rats)	Hcrt-1	ICV	0.15–15	Dose related ↑ in body temperature	111
C (rats)	Hcrt-1	ICV	1.5	Hypophagia and ↑ in BATSA with hyperthermia, ↑ HR	112
C (rats)	Hcrt-1	ICV	0.6	Hypothermia, no changes in metabolic rate	114
A (rats)	Hcrt-1	ICV	0.003	↓ in WATSA	116
			0.3	↑ in WATSA	
C (rats)	Hcrt-1	IC	0.18, 0.72, 2.88	Dose related ↑ gastric acid secretion	124
	Hcrt-2		2.88	No effect on gastric secretion	
	Hcrt-1	IP	2.88	No effect on gastric secretion	
A (rats)	Hcrt-1	Area postrema (within DMN)	0.001–0.1	↑ in gastric pressure and motility	125
	Hcrt-2		0.01	↑ in gastric pressure and motility	

A: anesthetized; BATSA: brown adipose tissue sympathetic activity; BP: blood pressure; C: conscious; DMN: dorsal motor nucleus of the vagus; E: plasmatic epinephrine; Hcrt-1: hypocretin-1 (3562 Da), Hcrt-2: hypocretin-2 (2937 Da); HR: heart rate; I3rd V: intra-third ventricle; I4th V: intra-fourth ventricle; IC: intracisternal; ICV: intra-cerebroventricular; IP: intraperitoneal; IV intravenous; NE: plasmatic norepinephrine. NTS: nucleus of the solitary tract; Ref.: reference; RSNA: renal sympathetic nerve activity; RVLM: rostral ventral lateral medulla; RVMM: rostral ventral medial medulla; WATSA: white adipose tissue sympathetic activity.
   [a] All dosages have been expressed in nmol for easier comparison, where 1 μg = 0.3 nmol.

(containing the preganglionic neurons for gastrointestinal tract).[125] Fifteen percent of hypocretin-1 neurons on the lateral hypothalamus project to the DVC.[126] Hypocretin action on gastric function has been suggested to be mediated at the DMN level, where a regulation of cardiovascular function is less likely to occur, based on patch-clamp studies disclosing that hypocretin depolarizes only about 30% of DMN neurons, in contrast to a 80–90% of depolarization at the level of PVN or NTS.[94,95] In addition, direct microinjection of hypocretin in the DMN greatly stimulates gastric motor function (contractility and gastric emptying).[91] In opposition to previous reports, recent data seem to exclude the presence of hypocretin-producing cells in enteric nervous tissue, at least in mice and human subjects.[127]

Summary and conclusions

Many symptoms attributed to autonomic dysfunction were initially described in narcoleptic patients, but have been poorly characterized. Most symptoms can be attributed to fluctuation of the arousal level or are unspecific, due to sleep fragmentation (e.g., other sleep disorder comorbidity) or pharmacological therapy. Initial studies lack adequate standardization and therefore their results have not been fully replicated and cannot be considered conclusive. Recent neurophysiological tests and in-depth metabolic biochemical and functional studies seem, however, to demonstrate the existence of an imbalance on autonomic functions in narcoleptic patients, especially in those deputated to control heart rate, body

temperature and metabolism, but unfortunately with still non-univocal results. Moreover, recent studies have shown specific autonomic changes during cataplexy, disclosing a sui-generis autonomic imbalance intrinsic to hypocretin-deficient narcolepsy.

Most early clinical research in the field yielded only subclinical findings, and in our clinical experience autonomic complaints are not common in unmedicated patients with narcolepsy. Nevertheless, one symptom, weight gain, that is not considered an autonomic symptom per se, is increasingly encountered among narcoleptic patients. This symptom can be a clinical manifestation of an underlying autonomic dysfunction of the disease. The discovery of hypocretins sheds new insights into the pathophysiology of narcolepsy, and may explain many of the recent findings in relation to autonomic dysfunction. Hypocretins are unique in that they can control both vagal para-sympathetic and sympathetic outflows: concomitant involvement of the two autonomic nervous system components along with evidence of preserved efferent pathways and effectors confirmed that the essential imbalance occurs at a central level. The loss of hypocretin neurons may lead to weight gain because they play an important role in regulating energy homeostasis not only directly but also through their interaction with leptin and the production of co-localized factors. Lack of hypocretins may lead to fat storage by a direct effect on adipocytes and by a decreased sympathetic tone, leading to metabolic changes in white adipose tissue.

Hypocretins influence a wide variety of autonomic functions. Future experimental and clinical studies will shed light on complex and not fully understood mechanisms and pathways.

Practice points

1. Many studies on autonomic function of narcoleptic patients lack sufficient standardization or their findings have not been subsequently replicated.
2. Neurophysiological tests can demonstrate subclinical autonomic dysfunctions in narcolepsy.
3. Metabolic alterations are common among narcoleptic patients, and particular attention should be taken for their management.
4. Questions on sexual functions should be routinely incorporated into the assessment of narcoleptic patients, ideally before therapy is started.

Research agenda

Studies are needed to:

1. evaluate the role of autonomic and metabolic impact on medical history and life expectancy of narcoleptic patients,
2. outline cases of sexual disturbances independent of medical therapy,
3. monitor blood pressure and cardiac function of narco-leptic patients, and the possible impact of their alter-ations in clinical trials,
4. in-deep studies of body temperature alterations and their role on narcolepsy's pathophysiology,
5. evaluate the effect of drug therapy for narcolepsy on the autonomic function during wakefulness and during sleep.

Acknowledgements

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