

Hypocretin/Orexin and Motor Function

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1. INTRODUCTION

As the literature on hypocretin/orexin has grown, so has the list of functions attributed to this system. Recent papers have routinely listed sleep and arousal control, blood pressure regulation, feeding, motor control, and others as functions for the hypocretin system (1-4). The question I address here is whether such an inclusive listing is an appropriate acknowledgement of the complexity and subtlety of hypocretin's function or whether a simpler relationship may underlie the multiple correlations that have been seen.

Some neuronal cell groups have well-understood functions. Although motor neurons can be fairly described as being correlated with many different behaviors (e.g., food consumption, arousal, blood pressure elevation, and so on), the most accurate formulation is that they cause muscular contraction and that this is utilized in multiple functions. The same sort of argument can be applied to neurons in sensory pathways. However "interneurons" in integrative regions such as the hypocretin neurons of the hypothalamus cannot be so easily understood because their anatomy alone does not explain their function, and the relevant physiological and behavioral parameters are often unknown. In the case of the hypocretin system, the dynamics of its behavioral physiology are just beginning to be understood.

What we now know about the behavioral physiology of hypocretin neurons suggests that they function to support certain kinds of motivated motor activity (5). According to this hypothesis, they facilitate muscle contraction and simultaneously activate brain arousal systems so as to allow appropriate perceptual processing of signals generated by movement. Many of the correlations with other behaviors can be best understood as a consequence of this relationship.

2. HYPOCRETIN RELEASE

We taken advantage of the ease of extracting cerebrospinal fluid (CSF) from the canine cisterna magna to perform a series of studies on hypocretin release. Hypocretin neurons are located in both the lateral and medial hypothalamus. The lateral hypothalamus is well known to have a role in feeding as well as other motivated behaviors. Because early studies administering large amounts of hypocretin to rats icv had suggested that this peptide might mediate feeding behavior, we studied the pattern of release of this peptide under food deprivation and feeding conditions (6). Figure 1 shows the result. The level of feeding inducing peptides such as neuropeptide Y increases with food deprivation. However, hypocretin levels are not elevated across a 48-h period of food deprivation in the normal dog, instead showing a

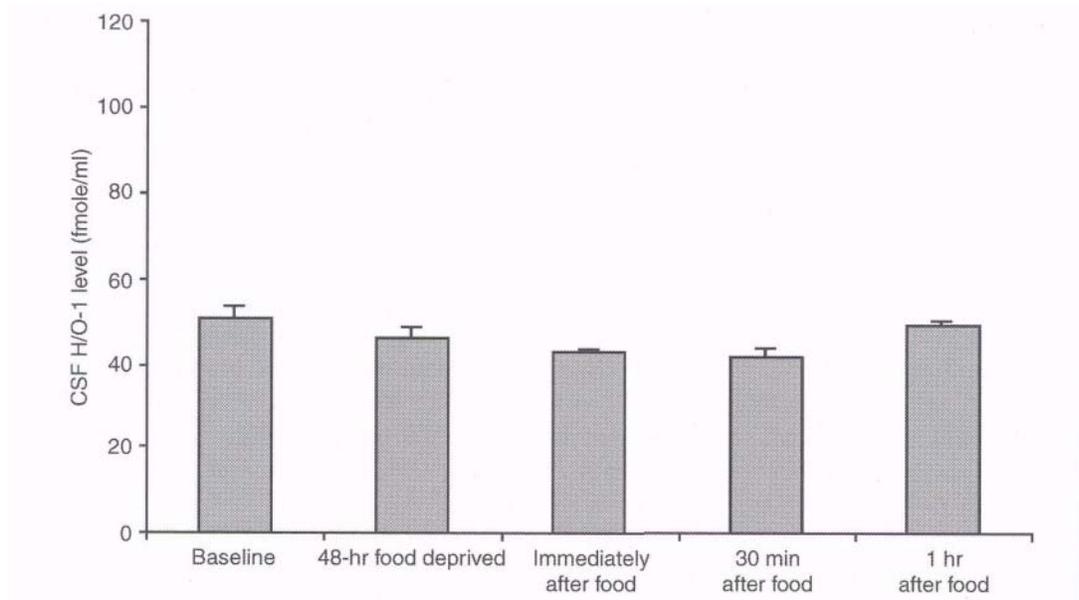


Fig. 1. Food deprivation and refeeding do not substantially alter hypocretin levels in the dog. CSF, cerebrospinal fluid. (From ref. 6.)

nonsignificant decrease. We also sampled hypocretin at various intervals after feeding. We found that this also did not produce a significant change in hypocretin level.

Because our work and the work of others had implicated hypocretin loss in the pathology of human narcolepsy (7-9), we studied the effect of sleep deprivation under the same CSF sampling and assay conditions as our food deprivation and refeeding studies (6). We found that 24 h of sleep deprivation produced a significant and substantial increase in hypocretin (Fig. 2). However, when we studied the correlation between the amount of hypocretin elevation and sleep loss within our group of animals, we saw no relationship. However, we found that the amount of motor activity during sleep deprivation was strongly correlated with hypocretin elevation. This led us to hypothesize that motor activation or behaviors associated with motor activation, rather than sleep loss, might be the determinant of hypocretin level. Therefore we exercised these dogs for 30 min to 2 h and compared hypocretin levels after exercise with those in the same animals kept awake for the same period. Figure 3 illustrates that this manipulation produced a marked elevation of hypocretin level. This work demonstrates that exercise is sufficient to elevate hypocretin level even in the absence of differences in sleep.

We next studied the same phenomenon in normal cats. Figure 4 shows that we saw an elevation of hypocretin level with exercise (10). We were able to conduct the first microdialysis assay of hypocretin across the sleep cycle. We found that levels were maximal in active waking, reduced in non-REM sleep, and increased again in REM sleep (Fig. 5). This finding fits with the motor activation explanation of hypocretin release, since REM sleep is a state of internal motor activation, blocked at the periphery by motoneuron atonia.

3. DIRECT VERSUS INDIRECT ACTIONS OF HYPOCRETIN

Hypocretin release can activate the motor system through several routes. Torterolo and colleagues (11) have shown that hypocretin neurons directly contact motoneurons. This may

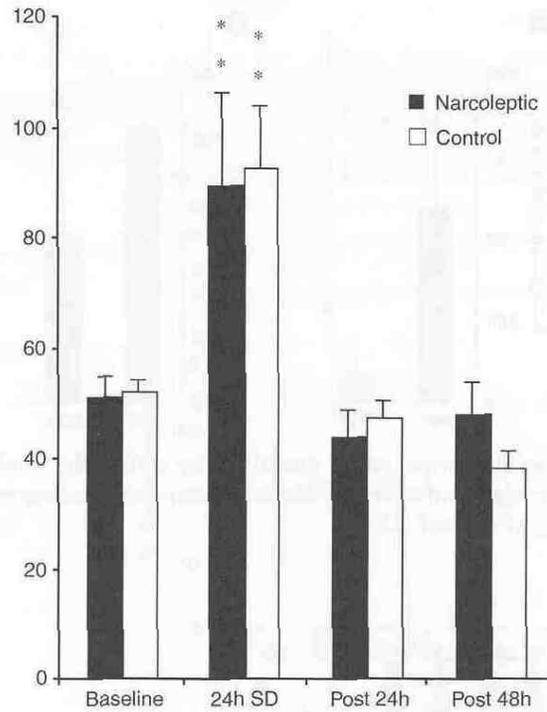


Fig. 2. Sleep deprivation produces a substantial increase in hypocretin levels in both normal and hypocretin receptor-2 mutant dogs. (From ref. 6.)

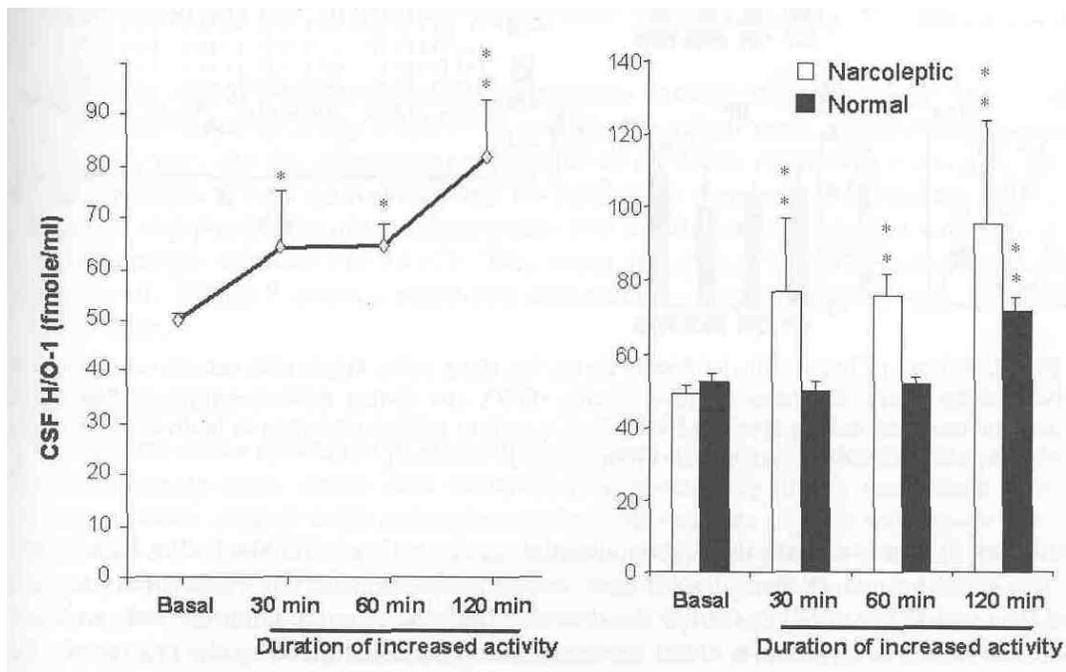


Fig. 3. Increasing duration of motor activity during exercise in a yard produces increasing levels of hypocretin (H/O) relative to the levels seen in the same dogs during equal periods of waking without vigorous movement. CSF, cerebrospinal fluid. (From ref. 6.)

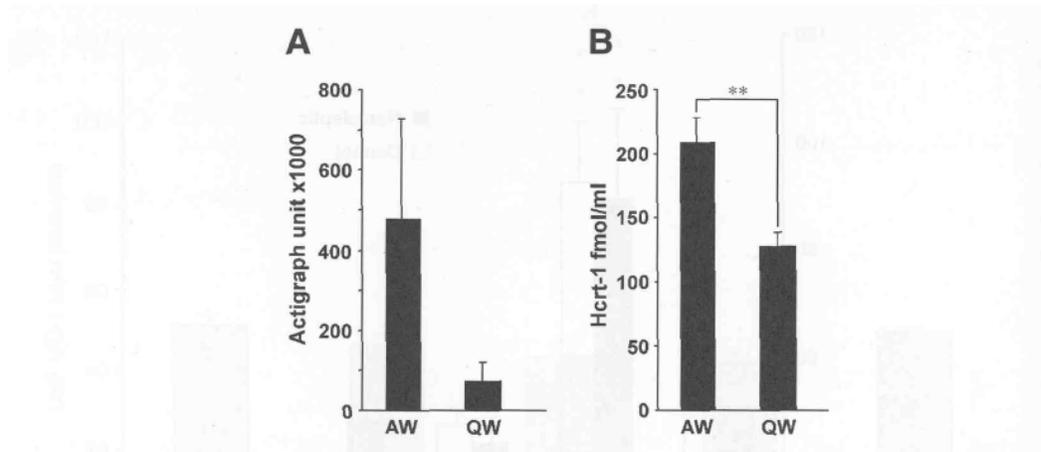


Fig. 4. Motor activity in the normal cat as quantified by actigraphy produces a marked increase in hypocretin (Hcrt) levels relative to equal durations of continuous waking, as in the dog. AW, active waking; QW, quiet waking. (From ref. 23.)

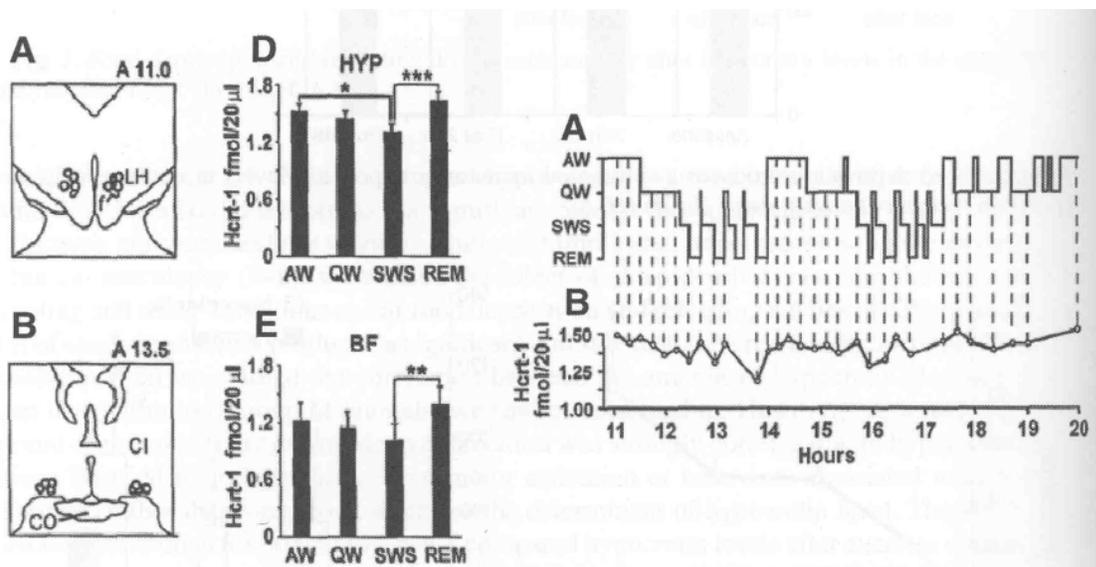


Fig. 5. Release of hypocretin-1 (Hcrt-1) across the sleep cycle. Hypocretin release is maximal in active waking (AW), decreases in quiet waking (QW), and further decreases in non-REM sleep. Release increases to waking levels in REM sleep, a state of intense activation of brain motor systems and hyperpolarization of motoneurons. (From ref. 23.)

contribute to motor activity in waking, although motor activation is blocked in REM sleep by the simultaneous release of inhibitory neurotransmitters such as γ -aminobutyric acid (GABA) and glycine (12) as well as the decreased release of norepinephrine and serotonin (13). The action of hypocretin at the motoneuronal level is mediated by the release of glutamate. Figure 6 shows that intravenous administration of hypocretin causes calcium-dependent (vesicular) release of glutamate in hypocretin-innervated regions. Blockade of glutamate receptors prevents the motoneuronal activation produced by hypocretin (14) (Fig. 7).

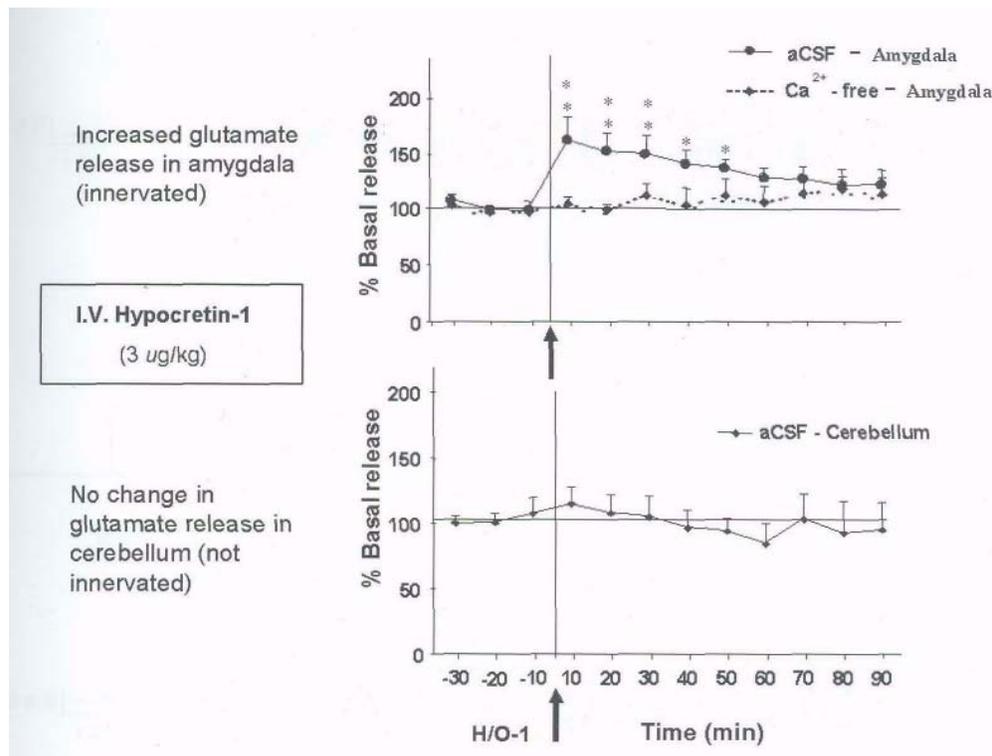


Fig. 6. Intravenous administration of hypocretin-1 to rats causes a calcium-dependent release of glutamate in the amygdala, hypocretin-innervated region, but not in the cerebellum, a region not innervated by hypocretin. a CSF, artificial cerebrospinal fluid. (From ref. 22.)

Indirect routes of hypocretin activation of motor neurons include a major link through the monoaminergic systems. Hypocretin neurons have their most potent extrahypothalamic projection onto the noradrenergic neurons of the locus coeruleus. Excitation of the locus coeruleus (15) (Fig. 8) and other noradrenergic neurons (16) produces increased release of norepinephrine onto motoneurons (13). Similar effects are seen with activation of serotonergic neurons (13,16,17). This route is blocked in REM sleep by GABA release (10). Figure 9 shows a simplified outline of the hypocretin pathways facilitating muscle tone.

4. DISCUSSION

Clearly the motor facilitation produced by hypocretin neurons is not tonic. Narcoleptics are not continuously weak, rather, their weakness is apparent only during the sudden onset of strong emotions, such as those accompanying laughter or anger. Normal individuals can also experience a less severe form of weakness at these times, with people "doubling over" with laughter or needing to sit down when strong emotions are triggered. One can postulate that in normals these episodes of weakness are kept in check by actions of the hypocretin system. However, in narcoleptics the loss of hypocretin neurons leaves this weakness unopposed, causing cataplexy. Loss of the hypocretin-mediated facilitation of forebrain arousal systems results in interruptions of waking arousal, producing the characteristic sleepiness of narcolepsy.

The motor relation of hypocretin cells can most parsimoniously explain the involvement of hypocretin in food intake. Stimulation of the lateral hypothalamus has long been

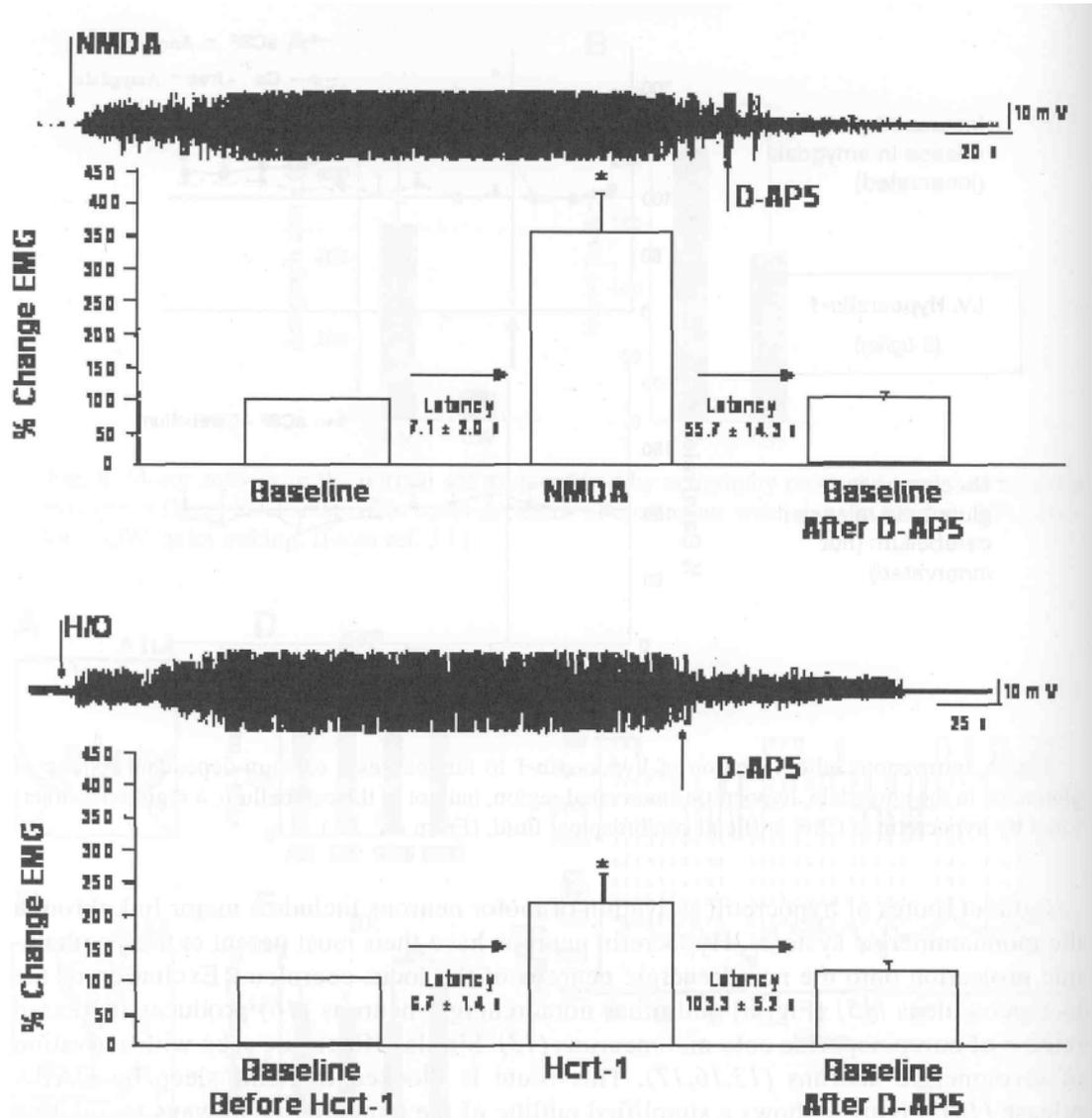


Fig. 7. The increased muscle tone produced by hypocretin-1 (Hcrt-1) microinjection into masseter motoneuron pool is blocked by DAP-5, a non-NMDA glutamate antagonist, indicating that the hypocretin effect is mediated by glutamatergic mechanisms. (From ref. 14.)

known to produce activation and food consumption if food is presented. However, food consumption was not found to be a consistent response, since drinking would occur if water was presented, gnawing if a wood block was presented and sexual behavior if a receptive female was presented. The constant was motivated motor activation (18,19). Studies of the effects of hypocretin administration on feeding have also produced variable responses, with some increase in eating in certain studies, increased grooming and head shake responses in some studies, and no overall change in others (20). Hypocretin knockout rats do not eat less, and ataxin knockout animals actually gain weight relative to controls (reviewed in ref. 6). Narcoleptics are not underweight despite the loss of hypocretin,

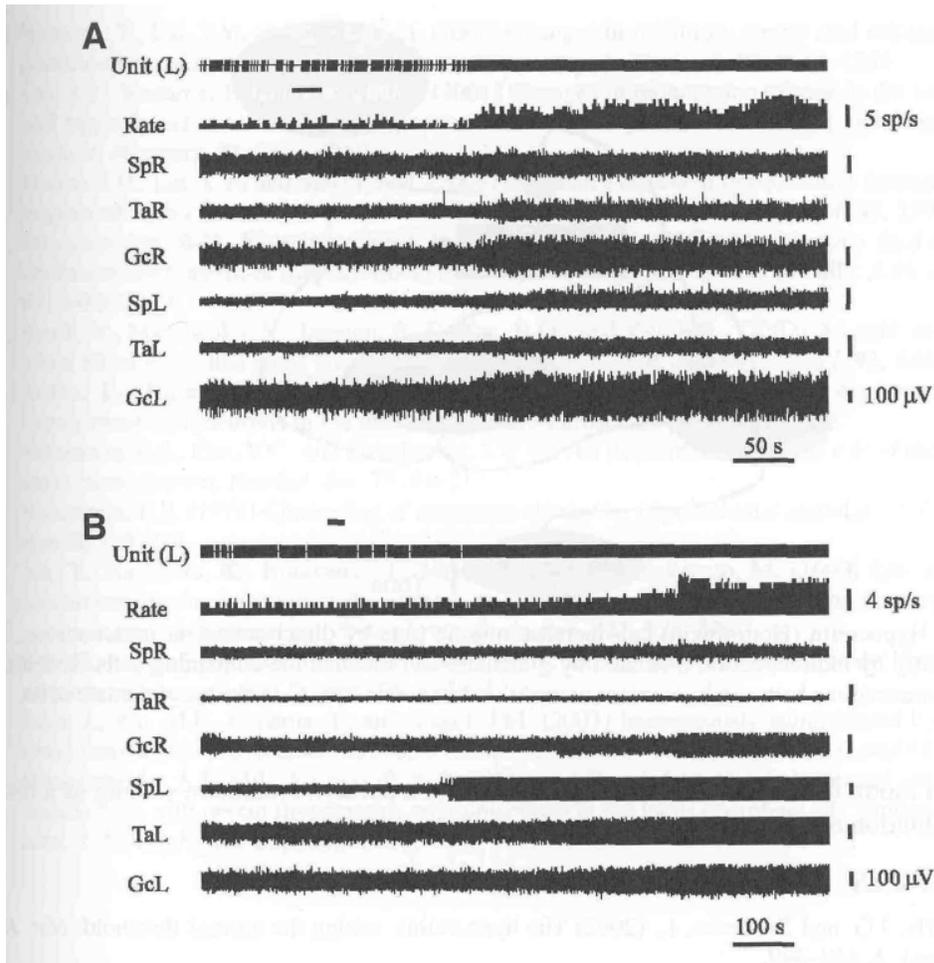


Fig. 8. Microinjection of hypocretin into the locus coeruleus increases muscle tone via adrenergic input to motoneurons SpR, and SpL (splenius, right and left); TaR, and TaL (tibialis anterior, right and left); and GcR, and GcL (gastrocnemius, right and left). (From ref. 23.)

but rather have a tendency toward obesity (27). All these findings can be explained by hypocretin mediation of motor activation, with reduced motor activity producing weight gain even in the absence of increased food intake. Correlations among blood pressure, arousal, and circadian rhythms of hypocretin can be explained by the modulation of motor activity over the 24-h cycle. Although we have tested some aspects of this hypothesis, others remain to be studied.

5. CONCLUSIONS

Hypocretin has a major role in the activation of motor systems. As we have proposed before, the ascending projections of the hypocretin system, particularly those to the histamine and ascending cholinergic system, may be seen as coordinating motor activation with sensory processing and the activation of thalamocortical motor systems. The loss of the hypocretin system causes not only episodic loss of muscle tone (cataplexy) and reduction in the total

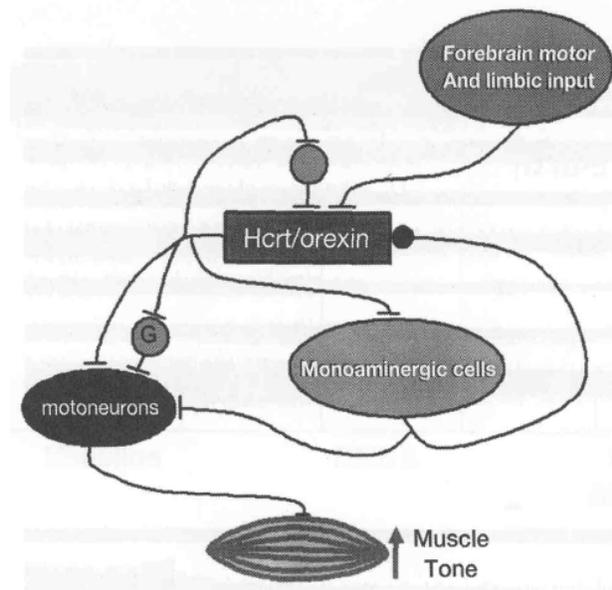


Fig. 9. Hypocretin (Hcrt/orexin) can increase muscle tone by direct action on motoneurons, but more potently by indirect action mediated by glutamate- and monoamine-containing cells. Simplified model of connections between hypocretin neurons and motoneurons. G indicates glutamate cells.

amount of motor activity, but also an impairment of the ability to maintain waking as a result of disfacilitation of these ascending systems.

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