A unified survival theory of the functioning of the hypocretinergic system

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Chase MH. A unified survival theory of the functioning of the hypocretinergic system. J Appl Physiol 115: 954–971, 2013. First published May 2, 2013; doi:10.1152/japplphysiol.00700.2012.—This article advances the theory that the hypocretinergic (orexinergic) system initiates, coordinates, and maintains survival behaviors and survival-related processes (i.e., the Unified Survival Theory of the Functioning of the Hypocretinergic System or “Unified Hypocretinergic Survival Theory”). A priori presumptive support for the Unified Hypocretinergic Survival Theory emanates from the fact that neurons that contain hypocretin are located in the key executive central nervous system (CNS) site, the lateral hypothalamus, that for decades has been well-documented to govern core survival behaviors such as fight, flight, and food consumption. In addition, the hypocretinergic system exhibits the requisite morphological and electrophysiological capabilities to control survival behaviors and related processes. Complementary behavioral data demonstrate that all facets of “survival” are coordinated by the hypocretinergic system and that hypocretinergic directives are not promulgated except during survival behaviors. Importantly, it has been shown that survival behaviors are selectively impacted when the hypocretinergic system is impaired or rendered nonfunctional, whereas other behaviors are relatively unaffected. The Unified Hypocretinergic Survival Theory resolves the disparate, perplexing, and often paradoxical-appearing results of previous studies; it also provides a foundation for future hypothesis-driven basic science and clinical explorations of the hypocretinergic system.

hypocretin; orexin; behaviors; survival

THE HYPOCRETINERGIC (also called orexinergic) system, which consists of hypocretinergic neurons and their receptors, has been researched extensively since its discovery in 1998 (43, 141). During this period, numerous processes, mechanisms, and behaviors have been shown to be subjected to hypocretinergic control, including, but not limited to, sleep, wakefulness, stress, motor activity, food consumption, thermogenesis, reproduction, development, aging, locomotion, energy metabolism, and the secretion of hormones (112, 119, 139, 140, 143). Although there have been major findings, no integrative concept of the functioning of the hypocretinergic system has been proposed that accounts for the vast number of responses that occur following activation of this system, many of which appear to be contradictory and/or paradoxical.

This article advances a Unified Survival Theory of the Functioning of the Hypocretinergic System (i.e., the Unified Hypocretinergic Survival Theory) that the principal function of the hypocretinergic system is to orchestrate the coordinated patterns of central nervous system (CNS) and peripheral organ activities that comprise survival behaviors and related processes (Fig. 1). It is the intent to present sufficient data to justify the Unified Hypocretinergic Survival Theory as a credible, formal unifying description of the functioning of the hypocretinergic system. Data are reviewed that reveal that the hypocretinergic system is capable of initiating, coordinating, and maintaining survival behaviors and related processes, and that other behaviors and processes are not directly impacted by its actions (see Control of Survival Behaviors by the Hypocretinergic System). Data are also presented demonstrating that, when hypocretinergic directives are not present, survival behaviors and related processes are selectively compromised (9, 14, 86, 119, 140).

Elements of the Unified Hypocretinergic Survival Theory have been proposed by a number of other investigators, such as those who are quoted in Fig. 2. Although they have concluded that the hypocretinergic system plays a key role in certain aspects of survival behaviors, the data have not been organized in a manner that allows one to examine the comprehensive theory presented in this review that the hypocretinergic system functions primarily to generate survival behaviors and related processes.

To substantiate the executive role of hypocretinergic neurons and their receptors in the control of survival behaviors, it is necessary to demonstrate that survival and related behaviors are not only dependent on the hypocretinergic system for their successful enactment but that they are also independent of the forebrain. In this regard, decades of research have confirmed that neurons in the lateral hypothalamus are capable of controlling all of the critical components of survival behaviors (3, 17, 26, 30, 60, 62, 128). For example, as early as 1951, Anand and Brobeck (5, 6) reported that a group of cells (which were
The Unified Survival Theory of the Functioning of the Hypocretinergic System

The hypocretinergic system controls survival behaviors and survival-related processes.

1) The hypocretinergic system

“The hypocretinergic system” consists of hypocretinergic neurons and hypocretinergic receptors.

Hypocretinergic neurons – A small phenotypically distinct group of neurons, approximately 80,000 in humans and 20,000 in rats (158), that are located exclusively in the lateral hypothalamus, whose axonal projections release the neurotransmitters hypocretin-1 and/or -2.

Hypocretinergic receptors – Receptors for hypocretin-1 and hypocretin-2 that are expressed by neurons in the CNS and by cells of peripheral organs.

2) Controls

“Controls” refers to the “direct” effects or actions of the hypocretinergic system in modulating the activity of particular behaviors, processes, mechanisms, etc.

3) Survival Behaviors

“Survival behaviors” refer to behaviors that occur in response to exteroceptive or interoceptive stimuli or inputs that are essential in maintaining the life of an organism and/or the species. Behavioral responses encompass changes in somatomotor, visceromotor, hormonal and other processes at all levels including subcellular, cellular and systems.

4) Survival-related processes

“Survival-related processes” prevent the death of the organism or strengthen its ability to survive, such as angiogenesis and neurogenesis; they also include numerous cellular directives including those that reduce or prevent neurodegeneration and inflammatory reactions.

Fig. 1.

Later identified as hypocretinergic) within the lateral hypothalamus function as a comprehensive “feeding center”; bilateral lesions of these neurons result in the complete cessation of food consumption [see Nishino and Sakurai (119) and Adequate Survival Stimuli Activate the Hypocretinergic System]. There are also a plethora of recent studies, cited in the present text, that confirm that the responsible neurons in the lateral hypothalamus are hypocretinergic (30, 60, 62, 119). Thus, during survival behaviors, there are hypocretinergically induced increases in arterial pressure, heart rate, and ventilation as well as a shift in blood flow from visceral to skeletal muscles in conjunction with cortical arousal; all of these survival-related responses are significantly lacking in preprohypocretin knockout and hypocretin neuron-ablated animals (14, 83). It is also well established that hypocretinergic neurons in the lateral hypothalamus promote not only the individual components of survival behaviors, but that they also coordinate the complex patterns that constitute these behaviors, as discussed in Adequate Survival Stimuli Activate the Hypocretinergic System.

Although the full complement of survival behaviors is dependent upon a functioning hypocretinergic system, other areas of the CNS are capable of influencing, to a limited extent, portions of these behaviors. Consequently, if hypothalamic-lesioned animals, which are initially anorectic, are kept alive by the intragastric intubation of liquid nutrients, eventually they are able to maintain some aspects of food consumption, which occur because other sites are able to promote certain uncoordinated feeding processes (128). Similarly, although integrated survival-related stress responses to external inputs are dependent upon hypocretinergic actions, localized stressors may require only brain stem centers for the generation of a response (128). Accordingly, Furlong et al. (56) found that “Stress responses to inputs coming from lower CNS levels may not require more than brain stem centers (medulla pons and midbrain) to orchestrate the appropriate cardiovascular and behavioral responses,” whereas “Hcrt neurons are preferentially driven by inputs originating high in the nervous system (forebrain) rather than inputs originating from lower levels.” These and related findings led Zhang et al. (196) to conclude that hypocretinergic neurons “in the lateral hypothalamus play a role as a master switch to activate multiple efferent pathways of the defense response.”

It is evident that, although the forebrain (e.g., the cerebral cortex) assists in directing survival behaviors and in assuring that they are appropriate to changes in the external environment, the basic circuitry for these behaviors resides within pools of hypocretinergic neurons in the lateral hypothalamus (37, 67). For example, in the absence of the forebrain, multiple studies, including the seminal work of Hess (67), have shown that flight, flight, and other survival behaviors are “undirected” and can be easily evoked by a variety of stimuli that normally would not induce these kinds of behavioral reactions, as in sham rage. The preceding effects are consistent with extensively documented patterns of brain functioning, wherein be-
Support for the Unified Survival Theory of the Functioning of the Hypocretinergic System

A number of researchers, such as those who are quoted below, have proposed that the hypocretinergic system controls key elements of survival behaviors and processes. However, they have not presented a unified framework that accounts for the totality of the actions of the hypocretinergic system. Their conclusions, which link the hypocretinergic system with survival behaviors, lend credence to the Unified Hypocretinergic Survival Theory, presented in this article, that the function of the hypocretinergic system is to command and coordinate survival and related behaviors and processes.

“The hypocretin system is one of the most critical systems for regulating vigilance, linking fundamental hypothalamic functions required for survival.” Nishino and Sakurai (119)

“Orexin systems are involved in sensing the body’s external and internal environments as well as regulating the states of sleep and wakefulness, which are beneficial for survival.” Tsujino and Sakurai (164)

“In our view, therefore, the LH orexin system is very well placed to orchestrate the diverse subsystems involved in foraging under potentially dangerous circumstances, i.e., finding and ingesting food without oneself becoming a meal for someone else.” Rodgers et al. (137)

“The synaptic organization of the hypocretinergic system provides the foundation for easy arousal (from sleep), an ability that, for most species, is paramount to survival.” De Lecea and Sutcliffe (45)

“This unique wiring and acute stress-induced plasticity of the hypocretin neurons correlates well with their being involved in the control of arousal and alertness that are so vital to survival.” Horvath and Gao (71)

“. . . hypocretin neurons may act as an ‘energy gauge’ in the brain, which integrates nutritional, energetic and behavioral signals critical for the survival of animals.” Liu et al. (94)

“Orexin-mediated maintenance of consolidated wakefulness states” ... is important . . . “because proper maintenance of arousal during food searching and intake is essential for an animal’s survival.” Ohno and Sakurai (122)

Evolutionary and Phylogenetic Analysis of the Hypocretinergic System

The role of the hypocretins in mediating survival behaviors and related processes is supported by the fact that the hypocretin gene arose ~650 million years ago, early in chordate evolution (4, 66, 120). In addition, the hypocretins (hypocretin-1 and hypocretin-2) are extraordinarily well-conserved neu-
Hypocretinergic Neurons and Receptors Constitute a Command System for Survival Behaviors

The term “command neuron,” which was first presented in 1964, was initially used to describe single cells in the crayfish that control “tail flips,” which this species employs to escape predators (125, 170). The key characteristics of these and other command neurons are their receipt of a multitude of sensory inputs and their output to a multifarious group of effector cells (122). Gradually, the concept of a command neuron was expanded to that of a “command system,” which was defined as a small group of integrated neurons that controls specific, naturally occurring behaviors (51, 91).

It is clear that hypocretinergic neurons exhibit unique characteristics that provide them with the capability of serving as the key component of a command system for survival behaviors. Hypocretinergic neurons are few in number and all are located in a discrete region of the lateral hypothalamus (102, 131, 143, 194). Many hypocretinergic somata are small to medium in size (35) and are therefore relatively easy to excite by afferents that emanate from all sensory systems (see Hypocretinergic Actions in Response to Survival Stimuli) and sites throughout the CNS; they are also activated by recurrent collaterals that arise from their own cell bodies. In turn, hypocretinergic neurons have long projecting axons with a multiplicity of bifurcations that allow them to innervate, bilaterally, cells throughout the entire neuraxis (119, 132, 139, 140, 143).

The majority of the synapses on hypocretinergic somata and dendrites are asymmetric with small, round, clear vesicles (type 1) that reflect excitatory neural transmission (193). In fact, hypocretinergic neurons are dominated by excitatory inputs; the ratio of excitatory to inhibitory synaptic contacts is ~10:1, which is unprecedented in the CNS (71). This pattern of synaptic organization, which results in noise assuming the characteristics of signal, allows hypocretinergic neurons to be easily activated, leading to rapid arousal (71). In addition, the terminals of hypocretinergic axons are large dense core vesicles that contain hypocretin as well as other excitatory neuropeptides. Therefore, hypocretinergic neurons are activated not only by excitatory neurotransmitters such as glutamate that are released from other axonal projections but also by the actions of their own recurrent collaterals (71, 72, 194).

The presynaptic control of, and by, hypocretinergic neurons is novel and very extensive. For example, there is a strategic positioning of presynaptic hypocretinergic boutons on postsynaptic targets. The extensive interaction of hypocretinergic presynaptic boutons with other axonal terminals further amplifies the impact of the release of hypocretin from their axon terminals (165). As noted above, hypocretin is also expressed in the presynaptic boutons of recurrent collaterals from hypocretinergic axons that make excitatory synaptic connections with hypocretin-containing neurons in the lateral hypothalamus (165, 191). In addition, there is a superior hierarchical positioning of presynaptic hypocretinergic inputs on the somas and proximal dendrites of the bodies of neurons that they innervate; consequently, hypocretinergic neurons are able to exercise predominate excitatory control of their postsynaptic targets, which is the basis for the robust effects that hypocretinergic directives are able to exert (166, 194).

Another important aspect of the synaptic control of hypocretinergic neurons was discovered by Horvath and Gao (71), who found that the activity of hypocretinergic neurons is governed to a large extent by local excitatory interneurons (132). These data are complemented by the fact that hypocretinergic neurons exhibit infoldings in their nuclear envelopes, which is a characteristic that is typical of high-activity neurons that are responsible for promoting complex behaviors (134).

The synaptic organization of the hypocretinergic system is also unusual in that not all inputs that control the excitability of hypocretinergic neurons are hard-wired; a large number of hypocretinergic neurons contain specialized organelles, called nematosomes or botryosomes, that function to enhance synaptic plasticity (135). These findings led Horvath and Gao to conclude that “this unique wiring and acute stress-induced plasticity of the hypocretin neurons correlates well with their being involved in the control of arousal and alertness that are so vital to survival” (71). Hypocretinergic synapses in adult animals also exhibit immature characteristics, such as incomplete postsynaptic densities, which provide these neurons with the ability to react in an adaptive manner to changing circumstances, such as those that arise in conjunction with the execution of survival behaviors (68). For example, in animals that are fasted, hypocretinergic perikarya, which are already dominated by excitatory inputs, recruit even more excitatory synapses, which enhance their activation, resulting in increased directives to promote food consumption (71).

The preceding patterns of presynaptic and postsynaptic control provide hypocretinergic neurons with the ability to react, rapidly and powerfully, when excited (71, 132, 134, 135). In addition, when activated, long periods of sustained firing occur, which is the requisite response of a system that controls.
and coordinates complicated survival behaviors (71). Thus, hypocretinergic neurons possess the critical synaptic processes and morphological characteristics as well as the necessary afferent inputs and efferent projections (see below) to serve as a command system that is capable of controlling all aspects of survival behaviors.

The following section describes the manner in which the hypocretinergic system produces coherent organized responses of CNS sites and peripheral organs to afferent inputs that comprise “adequate stimuli” for survival behaviors and related processes.

Adequate Survival Stimuli Activate the Hypocretinergic System

Prototypical survival behaviors that are controlled by the lateral hypothalamus, such as fight, flight, and food consumption, are triggered by adequate stimuli, which are defined as a single form of stimulus energy to which they are specifically adapted and are most sensitive. For example, light is the adequate stimulus for rods in the retina, even though pressure may also activate them under abnormal circumstances (Fig. 3).

In the wild, animals exhibit reactionary prey behaviors when hypocretinergic neurons in the lateral hypothalamus of prey animals are activated by adequate exteroceptive inputs (Fig. 3) detailing the presence of a hungry predator. Similarly, an initiating “adequate” interoceptive stimulus for the generation of food consumption is a decrease in blood glucose (Fig. 3), which results in the discharge of glucose-sensing hypocretinergic neurons in the lateral hypothalamus. Interoceptive survival stimuli activate the hypocretinergic system. Approximately fifty years ago, a specialized set of neurons in the lateral hypothalamus was discovered whose discharge rate increased, pari passu, with a decrease in the concentration of blood glucose (5, 6, 93). Fast forward to the discovery of the hypocretins in 1998 (43, 141) and the subsequent revelation that ~20% of hypocretinergic cells use glucose as a signaling molecule to alter their action potential frequency (44, 93). Thus, a decrease in glucose concentration

Fig. 3. Hypocretinergic circuitry mediating survival behaviors. The proposed hypocretinergic command and control circuitry that initiates and maintains survival behaviors in response to adequate survival stimuli is presented in this figure. Multiple functions of the hypocretinergic system are combined since it is not known whether the same or different hypocretinergic neurons promote individual or multiple actions, although there appear to be some regional differences in the functions that are subserved by pools of hypocretinergic neurons (171). When an “adequate” exteroceptive survival stimulus (1), such as a highly rewarding foodstuff is presented to a food-deprived animal, or an “adequate” interoceptive stimulus (2) arises, such as a decrease in blood glucose, hypocretinergic neurons begin to discharge at high frequencies (3). The initial response to these stimuli is arousal (4), which occurs due to hypocretinergic activation of arousal-producing systems such as the locus coeruleus and the raphe nuclei. Transmission via sensory pathways that relay information that is specifically survival-related is enhanced (5); however, pain sensations are reduced by hypocretinergic directives, which is essential for the successful enactment of survival behaviors. Simultaneously, projections of hypocretinergic neurons activate, bilaterally, a variety of somatomotor (6), visceromotor (7), and other systems (hormonal, endocrine, etc.) and peripheral organs (8) that provide the basic physiological foundations for survival behaviors. The hypocretinergic system also controls circuitry in the floculonodular lobe of the cerebellum (9), which coordinates survival-related interactions between the visual, vestibular, and somatomotor systems, such as pursuit eye movements, that allow animals to perform successfully in fight and flight situations. Sustained arousal is also assured by virtue of direct monosynaptic hypocretinergic excitatory projections to the nonspecific arousal-producing nuclei in the thalamus (10). In addition, global activation of the cerebral cortex (11) occurs due to the hypocretinergic innervation, selectively, of cortical layer 6b, which produces a general increase in cortical excitability. Reward and stress-related sites are also activated as are other subcortical areas (12), such as the amygdala, basal ganglia, and hippocampus, which receive hypocretinergic projections and provide background support for survival behaviors. As discussed in Hypocretinergic Actions in Response to Survival Stimuli, the preceding circuitry is selectively activated during survival situations, whereas survival-related behaviors are selectively compromised when this circuitry does not function.

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Successful survival behaviors require that animals maintain a homeostatic level of blood glucose, i.e., sufficient energy to encode variations in blood glucose levels reflecting those that occur between normal meals (57).

Hypocretinergic neurons not only function as glucose sensors for the entire brain and body, but they are also capable of initiating and maintaining the survival behavior of food consumption by activating arousal, sensory, somatomotor, visceral, motor, hormonal, and other systems, which results in the restoration of a homeostatic level of blood glucose (17, 142). Physiologically, this makes a great deal of sense. Hypocretinergic neurons first detect a deficit in energy resources, i.e., glucose, which is the primary metabolic “fuel” for neural and nonneural cells; they then promote the survival behavior of food consumption, which eliminates the deficit. These findings led Yamanaka et al. (179) to conclude that the maintenance of a homeostatic level of blood glucose is also important to note that these glucose-sensing hypocretinergic neurons are sufficiently sensitive to encode variations in blood glucose levels reflecting those that occur between normal meals (57).

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Extroceptive survival stimuli activate the hypocretinergic system. Successful survival behaviors require that animals maximize the functioning of their sensory systems to critically evaluate their external environment. Thus, it was not unexpected to find that specific survival-related information from sensory receptors for vision, olfaction, audition, taste, etc., are transmitted via high-priority “fast tracks” directly and indirectly to hypocretinergic neurons (3, 10, 24, 36, 58, 64, 71, 80, 119, 130, 147, 149, 184). There are also direct (i.e., monosynaptic) projections to all sensory systems from hypocretinergic neurons that enhance the receipt of survival-related sensory information (55, 61, 116, 127, 144, 146).

It is clear that the hypocretinergic system functions to maximize sensory inputs that are of paramount importance in promoting survival behaviors. For example, hypocretinergic neurons innervate, selectively, specific receptive areas for high-frequency sounds in the inferior colliculus, which is the key CNS site that processes acoustic information and determines the form in which this information is conveyed to cephalic sites (48, 96, 133, 161, 173). The question then arises: why does the hypocretinergic system selectively enhance the receipt of high-frequency auditory information? The answer is provided by an analysis of the characteristics of high-frequency sounds and the manner in which they are employed during survival behaviors. High-frequency auditory waves, which are capable of being rapidly transmitted over considerable distances, contain a great amount of data but are difficult to localize by predators. Therefore, it was not unexpected to find that most vertebrates respond when threatened by a predator by generating “alarm signals” (after the Old Italian all’arme, i.e., “to arms”), which are high-frequency acoustic waves that encode information about the type of predator, the urgency of the response, etc. For example, specific alarm calls of Vervet monkeys communicate the presence of different predators such as eagles, leopards, and pythons; this information is then employed to generate idiosyncratic behavioral responses that are threat-specific. Wistar rats produce unique alarm calls that inform the colony that a predator is approaching, whereas “shrieking” is a piercing, high-pitched squeak that guinea pigs use as an alarm call (24). Thus, hypocretinergic drives that selectively enhance the transmission of information within high-frequency receptive areas of the inferior colliculus are an essential component of alarm calls that activate survival behaviors. When the acoustic processing of alarm calls is not enhanced by the hypocretinergic system, deficits in survival behaviors in animals arise and, in humans, various pathologies occur (40, 145). For example, individuals with cataplexy who lack a functioning hypocretinergic system exhibit auditory hallucinations, deficits in the cognitive processing of auditory information, etc. (142).

Other sensory systems exhibit similar survival-centric patterns of hypocretinergic control. For example, the entire olfactory pathway is intensively innervated by hypocretinergic neurons, and its activity is modulated by the hypocretins in a specific manner that supports a variety of survival behaviors (7, 64). In hungry animals there is an increased release of hypocretin in the olfactory bulb, resulting in a decrease in the threshold for the detection of olfactory information (64, 80). On the other hand, the complete elimination of olfactory sensations following destruction of the olfactory bulbs leads to profound disruptions in sexual and territorial activities, including a dramatic decrease in predatory behaviors (3). Cataplectic individuals also exhibit numerous olfactory-related pathologies that occur because of the absence of hypocretinergic directives (10).

Unique survival processes that involve the transmission of visual information, which begins in the retina and extends to the central processing of visual data, are also dependent on the functioning of the hypocretinergic system (146). For example, the guidance of body movements toward visually detected objects is promoted by hypocretinergic directives (149). In the natural environment, when a prey animal suddenly changes its direction of movement in response to a predator’s actions, hypocretinergic neurons in the predator activate “smooth eye pursuit mechanisms” that control eye movements so that the image of the moving target on the fovea is continuously maintained (149). There are other intimate relationships between the visual system and somatomotor processes during survival behaviors, especially those that involve visual-somatic interactions that are controlled by the cerebellum (which are described in the following section) that depend on hypocretinergic patterns of control.

The hypocretinergic system’s ability to enhance the transmission of a variety of auditory, olfactory, visual, and other sensory information is crucial since it enables animals to respond in an efficacious manner during survival situations. In this regard, it is instructive to recognize the contributions of Fred Merkel with respect to our understanding of the functioning of the hypocretinergic system. Fred Merkel, in 1875, described a unique type of sensory mechanoreceptor (that later bore his name) that is present throughout the entire epidermis; these receptors are also located in hair follicles as well as in the oral mucosa (13). Merkel mechanoreceptors are activated during survival behaviors when animals (such as the rat) sweep their whiskers across objects, at rates approaching 1,500 Hz, before making a behavioral decision (13, 101). In 2004, Merkel...
cells were discovered to contain hypocretin as well as receptors for hypocretin. When these hypocretinergic receptors are activated, they increase the sensitivity and lower the threshold for the discharge of Merkel mechanoreceptors (13). Because touch sensations of the nature conveyed by Merkel cells play an essential role in behaviors such as fight, flight, feeding, and reproduction, the expression of hypocretin receptors by Merkel cells provides unique justification for the Unified Hypocretinergic Survival Theory. In addition, it would be difficult to integrate or rationalize the control of Merkel cells by the hypocretins within other concepts of the integrated functioning of the hypocretinergic system.

Although there are hypocretinergically mediated increases in the transmission of a vast amount of diverse sensory information that is specifically important in initiating and controlling survival behaviors, could the suppression of certain sensory inputs also enhance these behaviors? It was, at first, rather surprising to discover that the hypocretinergic system functions to reduce the transmission of painful (nociceptive) neural impulses, which is opposite to its effects on other sensory modalities. The antinociceptive effects of the hypocretins are exceedingly potent since they involve both presynaptic and postsynaptic processes at all levels of the neuraxis (19, 36, 165). Hypocretinergic reductions in pain also occur at the same time that transmission in other sensory pathways is enhanced and arousal mechanisms are activated by hypocretinergic directives (19).

The preceding unique patterns of sensory control occur because it is essential to be relatively “pain free,” highly alert, but also acutely aware of the environment (both internal and external) during survival situations. It would be counterproductive for animals or humans to be incapacitated by pain when fighting for their lives or procuring food. Soldiers in battle, professional football and basketball players, as well as individuals with grievous injuries are nevertheless able to continue to function and are pain free while engaged in survival-type activities that take place during aroused wakefulness (see following section). Most other systems or drugs that consistently reduce or eliminate pain do not produce arousal, but instead promote sedation, such as the opioids and similar antinociceptive substances. Thus, hypocretinergically mandated reductions in pain that are accompanied by the generation of arousal and heightened sensory “awareness” makes perfect sense based on the clear need to promote these processes and behaviors, concurrently, during survival situations.

**Hypocretinergic Actions in Response to Survival Stimuli**

**Hypocretinergic generation of arousal.** Survival behaviors such as food consumption, reproduction, as well as fight and flight take place during periods of arousal, i.e., heightened alertness. In this regard, the hypocretins have been shown to function as critical regulators of arousal. For example, Horvath and Gao (71) concluded that “it is essential to an animal’s survival that it possesses the ability to adequately respond during aroused wakefulness to threats such as a predator or other life-threatening circumstances (i.e., food deprivation).” Therefore, to mediate survival behaviors, hypocretinergic directives must first produce a highly aroused animal, which it does by directing potent executive monosynaptic excitatory drives to neurons in practically all of the major sites and systems involved in the induction of arousal, such as the locus coeruleus, the raphe nuclei, and the laterodorsal tegmental and pedunculopontine tegmental nuclei, among others (132, 165). During periods of arousal, hypocretin neurons discharge at high frequencies; they are relatively inactive during quiet wakefulness (104, 139). The administration of hypocretin promotes arousal; when there is a deficiency in hypocretin, there is a corresponding decrease in wakefulness and the ability of animals to respond to alerting stimuli (118, 132). Importantly, it has been shown that hypocretinergic neurons are selectively activated during arousal that is associated with the enactment of survival behaviors; however, arousal that occurs in the absence of such behaviors is not correlated with an increase in the discharge of hypocretinergic neurons (160, 163).

The maintenance of consolidated periods of alert wakefulness or arousal is an essential aspect of survival behaviors such as food searching and consumption. When faced with reduced food availability, animals adapt with longer periods of arousal, even at the expense of normal circadian patterns of activity (140). Thus, the arousal imperatives of hypocretinergic origin trump circadian directives! The importance of hypocretin-mediated arousal as a prerequisite for food consumption and other survival behaviors is highlighted by the fact that, when hypocretinergic neurons are ablated, animals fail to respond to a low level of blood glucose with increased wakefulness, motor activation, or food consumption (36, 122, 139). Complementary data also reveal that hypocretinergic neurons play a critical role in the maintenance of arousal during fasting (119, 136). However, it is important to note that these actions of the hypocretinergic system are not directed simply to sustain or promote arousal, per se. For example, Torterolo et al. (160, 163) found that hypocretinergic neurons are activated during arousal that is associated with different survival behaviors, including food consumption; in contrast, there is minimal hypocretinergic activation in the absence of these survival behaviors, even though the animals are equivalently aroused (160). In addition, hypocretinergic neurons project selectively to cortical layer 6b and layer 2/3 of the prefrontal cortex, which results in the activation of widespread areas of the cerebral cortex, and arousal (12, 183). Direct monosynaptic hypocretinergic excitatory projections to the nonspecific arousal-producing nuclei in the thalamus as well as various subcortical sites, including the amygdala, basal ganglia, and hippocampus, also provide background support for survival behaviors (12, 45, 176).

Although the hypocretinergic system initiates arousal specifically in conjunction with the execution of survival behaviors, it does not receive synaptic feedback from arousal systems (152, 184). De Lecea and Sutcliffe (45) suggest that this pattern of synaptic control allows animals to rapidly awaken from sleep, which is a critical ability that is necessary for survival. Similarly, Berthoud et al. (18) suggest that hypocretinergic directives evolved as a mechanism to stay alert while foraging, which is one of the prime components of the presence of a potential predator.
survival behaviors. Thus, for hypocretinergic neurons, arousal is the necessary initial response to adequate survival stimuli.

To promote “survival” behaviors that occur during waking states, hypocretinergic neurons interact with diverse functional components of the CNS, one of the most important being the noradrenergic arousal-promoting system (15, 16). A key noradrenergic structure, the locus coeruleus, receives extraordinarily dense projections from hypocretinergic neurons (72, 132) and “serves as a necessary downstream effector for Hcrt function in promoting arousal” (30). It has also been proposed that the actions of the hypocretinergic system and the locus coeruleus that result in arousal are promulgated selectively in conjunction with “stimulus-elicited primitive and goal-directed behaviors” and “that the distinguishing feature of arousal with Hcrt involvement is a high level of vigilance and attention to the surrounding environment” (21, 56). In addition, Rodgers et al. (137) point out “that arousal cannot be an end in itself but, rather, is the means whereby animals engage in certain adaptive behaviors—such as foraging while simultaneously maintaining the level of vigilance necessary to avoid becoming a meal for someone else.” Consequently, hypocretinergic-noradrenergic interactions that initiate and maintain arousal are not only complex, but are also strongly state- and behavior-dependent.

In addition to arousal, the noradrenergic system, under specific conditions, may promote antinociception as well as prociception (130). Although peripheral norepinephrine has little effect on pain in healthy tissue, following injury or inflammation, the central and peripheral noradrenergic systems exert antinociceptive actions that are subject to a number of variables such as the type of receptor excited, the duration of pain, the pathophysiological condition, etc. (130). In contrast, arousal following activation of the hypocretinergic system is consistently associated with antinociception (see Control of Survival Behaviors by the Hypocretinergic System). An analysis of these complicated issues is beyond the scope of the present article; however, they are addressed in Refs. 15, 30, 68, 79, 130, and 139.

The hypocretinergic system also plays an important role in stabilizing transitions between sleep and wakefulness (15, 30, 68, 79, 119, 130, 139, 140). Thus, Sakurai and coworkers have suggested that the hypocretinergic system regulates the states of sleep and wakefulness in relation to its control of survival-type behaviors that include reward and energy homeostasis (139, 140, 142). They also propose that reciprocal feedback loops exist between the hypocretinergic and monoaminergic systems that act to stabilize wakefulness (142). Other researchers have also supported the concept that the hypocretinergic system promotes and stabilizes wakefulness as well as controlling motor processes during waking states, specifically during survival-type situations (30, 119, 142). The consequences that arise, e.g., cataplexy, when there are deficient hypocretinergic actions have also been examined (30, 136, 148). An exploration of the basic mechanisms that result in the abnormal control of motoneurons during cataplexy are beyond the scope of the present discussion. However, it is important to note that the adequate stimuli for the induction of cataplectic attacks during wakefulness are the same as those that initiate survival behaviors, such as the presentation of food during food deprivation (see Refs. 32 and 122). As discussed above, not only is there a homology of stimuli that initiate survival behaviors and cataplexy, but those behavioral and other responses that occur in both conditions can be accounted for by the Unified Hypocretinergic Survival Theory of the role of the hypocretinergic system in promoting survival behaviors.

Hypocretinergic neurons not only generate aroused wakefulness as a prime component of their control of survival behaviors, they also discharge, in bursts, during the phasic periods of rapid eye movement (REM) sleep (52, 92, 102, 162, 163). However, the effects of hypocretinergic actions during REM sleep are quite different from those produced during wakefulness. For example, whereas somatomotor activation occurs when hypocretinergic neurons discharge during wakefulness (see Control of Survival Behaviors by the Hypocretinergic System), motor inhibition takes place when the hypocretinergic system is activated during REM sleep (Fig. 4) (180, 181). Thus, the hypocretinergic system functions during REM sleep in a manner similar to that of other systems that initiate arousal and somatomotor activity in accordance with the phenomenon of Reticular Response-Reversal (Fig. 4) (33, 34, 85, 180–182). This phenomenon is one wherein motor excitatory drives that occur during wakefulness are transformed to motor inhibitory directives when they arise during REM sleep. In addition to other functions that the hypocretinergic system may express during REM sleep, it also acts to preserve the integrity of REM sleep by preventing the expression of motor activity at a time when the organism is incapable of responding to external threats, which is a pattern of motor control that has a high survival value (23). The hypocretinergic system not only acts to maintain and enhance the occurrence of REM sleep but, conversely, also promotes rapid arousal at the termination of this state when animals awaken (169, 177). Consequently, the Unified Hypocretinergic Survival Theory accounts not only for the totality of hypocretinergic directives that take place during wakefulness, but also during sleep, and provides a rational explanation for the consequences of the discharge of hypocretinergic neurons during sleep as well as waking states.

Hypocretinergic activation of the somatomotor and visceromotor systems. Coordinated patterns of striated (somatomotor) and smooth (visceromotor) muscle activity constitute the foundation for the expression of survival behaviors. Therefore, support for the Unified Hypocretinergic Survival Theory must include data demonstrating that the hypocretinergic system is capable not only of directly controlling somatomotor and visceromotor processes but that this control is bound exclusively to situations related to survival.

There are a wealth of reports that demonstrate that the hypocretinergic system is capable, via direct monosynaptic projections, of coordinating and maintaining somatomotor activity. Excitatory monosynaptic projections from hypocretinergic neurons initiate the discharge of motoneurons at all levels of the neuraxis (Fig. 4); they also activate motor-coordinating sites such as the locomotor center in the brain stem (43, 112, 129, 140, 165, 180–182, 188). In addition, the direct application of hypocretin on intracellularly recorded motoneurons results in depolarization of their membrane potential, a decrease in input resistance, and sustained periods of action potential generation (165, 181, 182). Unit recordings of hypocretinergic neurons also highlight the positive relationship between their discharge and motor activity (104). Moreover, when hypocretin is microinjected intraventricularly, there is an increase in locomotor and muscle activity (63, 73, 112, 129).
The hypocretinergic system not only is capable of directly activating final common pathway motoneurons and somatotonic systems, but it also exercises this control exclusively during survival behaviors. For example, hypocretinergic neurons are activated in conjunction with locomotor activity that occurs when animals are pursuing a food reward. However, when a food reward is not present, even though the same level of motor output is maintained, hypocretinergic neurons are relatively silent (160, 163).

The control of sensorimotor activities that form the foundation for survival behaviors is dependent to a significant extent on functions that are controlled by the cerebellum. Therefore, there initially appeared to be a significant problem vis-à-vis the Unified Hypocretinergic Survival Theory, since early studies reported that, although almost all areas of the CNS were innervated by hypocretinergic axons, there was a major exception, which was the cerebellum (132, 139). However, close inspection of these data and subsequent reports revealed that one area of the cerebellum, the flocculonodular lobe, not only receives projections from hypocretinergic neurons, but that its constituent neurons also contain hypocretinergic receptors (97). The flocculonodular lobe, which constitutes the phylogenetically “ancient” archicerebellum, participates in the execution of critical survival functions (53). In this regard, hypocretinergic neurons have been shown to activate pursuit-related cells in the flocculonodular lobe, which initiate short-latency eye movements that allow animals to track the trajectory of a predator or prey, during walking or running, even if they momentarily disappear behind an object (97, 186). It is also important to note that pursuit-related cerebellar (flocculonodular) neurons are activated by hypocretinergic inputs when external forces, such as prey movements, are the basis for image instability (53, 97). The hypocretinergic system also participates in motor control by modulating the activity of the interpositus nucleus, which is one of the final outputs of the cerebellum (186). Yu et al. (186) have shown that hypocretinergic inputs from the hypothalamus to the nucleus interpositus modulate cerebellar motor functions. Thus, hypocretinergic/cerebellar systems integrate and coordinate...
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The role of the hypocretinergic system in controlling survival behaviors is supported by data involving its pattern of innervation of the cerebellum and the functioning of the floculonodular lobe and interpositus nucleus, as well as by its lack of innervation of cerebellar sites that are not directly involved with the execution of survival behaviors. In this regard, Zhang et al. (190) concluded that, “Our results demonstrate that endogenous orexin is critical for motor control for animals facing a major motor challenge. Therefore, the modulation of the central orexinergic system on motor control may be more readily noticeable when internal and external environments are relatively stable, as during rest or routine movements.” Clearly, any credible theory regarding the functions of the hypocretinergic system must place its activities in context and account for all of its many and varied actions in a state-dependent fashion.

The hypocretinergic system also activates visceromotor processes and coordinates the output of the autonomic nervous system with respect to the control of heart rate, blood pressure, hormonal secretions, etc., in a manner that enhances survival behaviors (84). It is suggested that this pattern of hypocretinergic signaling is unique and that it evolved to assure that foraging behavior in a potentially dangerous environment is accompanied by appropriate activation of visceromotor processes (84). For example, there are numerous reports that demonstrate that the hypocretins are capable of controlling cardiovascular functions and that this control is expressed selectively during survival situations. In this regard, the following question was posed by Samson et al. (144): “Is the action of orexin needed for an appropriate cardiovascular response to stress?” It was answered in the affirmative by Kayaba et al. (82) who found, under survival-related conditions, that cardiovascular responses to a resident-intruder stress were compromised in hypocretin knockout mice, but not in intact animals. Complementary data were obtained by Nattie and Li (114), who concluded that the hypocretins play a critical role in the defense response from the perspective of its control of central chemoreception; thus, the control of chemoreceptive processes by the hypocretins is not exercised indiscriminately during sleep or even waking states. Luong and Carrive (95) also highlight a hypocretin-raphe relay that contributes to cardiovascular changes evoked by arousal and survival-related stressors. In addition, Silvani et al. (154) report that the hypocretinergic system plays a subtle role in maintaining alterations in heart rate during certain spontaneous survival-type behaviors but that it is not necessary for the occurrence of physiological sleep-dependent changes in systolic blood pressure variability. Hypocretin deficiency in humans, together with altered blood pressure regulation, also increases cardiovascular risk, according to Grimaldì et al. (61). However, the data are somewhat inconsistent, since there is evidence that hypocretin deficiency in animals and humans may not always be associated with reduced sympathetic tone, but may also occur in conjunction with sympathetic activation (47, 60, 61, 95, 152, 196). Additional cardiorespiratory effects elicited by the hypocretins during normal and pathological states are reviewed in Shahid et al. (152).

There are other unique aspects of the control of the visceromotor system by the hypocretins. For example, although the hypocretins are capable of modulating visceromotor receptor activity, this control appears to be dependent upon the animal’s behavioral state and/or condition (82, 89, 171, 185). During survival situations, the hypocretinergic system exercises adaptive control of respiration, as evidenced by the fact that it suppresses or resets the baroreceptor reflex to a higher pressure range to provide for an increase in arterial blood pressure in the brain (82, 89). During nonsurvival conditions, such as nonrapid eye movement sleep, hypocretinergic control of central chemoreception is absent (113, 115). Studies of the influence of the hypocretinergic system on central chemoreception also indicate that the hypocretins participate in the “wakefulness drive” of breathing (113, 114). In contrast, basal ventilation is similar in hypocretin knockout and wild-type mice, irrespective of whether the animals are awake or asleep (82, 89, 171). In addition, in hypocretin knockout animals, the loss of hypocretin neurons does not affect the circadian or sleep/wake regulation of core body or tail temperature, heart rate, or pulse pressure, even though blood pressure is significantly lower during all states of sleep and wakefulness in these animals (150). These conflicting data may be resolved by studies that examine the effects of the hypocretins during sleep and waking states in conjunction with specific survival-related behaviors.

Hypocretinergic neurons are also capable of enhancing other peripheral organ and related visceromotor functions that are critical for survival, such as stress-induced increases in body temperature and energy balance (151). Therefore, it was not surprising to find that neurons that contain hypocretin in the lateral hypothalamus, a site traditionally associated with the promotion of feeding, are also involved in the control of brown fat thermogenesis, which contributes to cold defense (151). These and related data led Oldfield et al. (124) to suggest that “single command neurons in the lateral hypothalamus project to sites responsible for the initiation of feeding behaviors,” thus providing a “substrate whereby information relating to both thermogenesis and food intake may be locally integrated.”

It has been well documented that, when the hypocretinergic system is activated, a panoply of coordinated peripheral organ and hormonal responses arise that provide foundational support for survival behaviors. In this regard, it is of significance to note that almost all peripheral organs contain receptors for hypocretin (77, 78), even though axons of hypocretinergic neurons do not exit the CNS (142). Therefore, peripheral hypocretinergic receptors, most of which are expressed by nonneural cells, must be activated by nonsynaptic mechanisms. For example, circulating hypocretin activates adenocortical cells without any direct axonal input from the CNS (77, 78, 100). Hypocretin receptor expression is strongly upregulated in the ovaries during proestrus; these data, together with the effects of hypocretin in the testes, indicate an important role for hypocretin in the reproductive process that is mediated by nonsynaptic mechanisms (78). The activity of peripheral organs and their visceromotor functions during survival behaviors are also enhanced by hypocretinergic control of the sympathetic and parasympathetic divisions of the autonomic nervous system (82, 89).

In addition to the indirect modulation of the activity of peripheral organs by hypocretinergic activation of CNS sites, there are substantive data that reveal that peripheral hypocretinergic receptors are excited by hypocretin that originates from neurons in the lateral hypothalamus, which is subsequently released into the CSF, and hence into the circulatory system by the hypocretins. For example, although the hypocretins are reviewed in Shahid et al. (152).
system. For example, the concentration of hypocretin in the cerebrospinal fluid (CSF) and blood varies in conjunction with ongoing normal and pathological states and processes (22, 103, 107). Intracerebroventricular injections of hypocretin induce not only central, but also peripheral, effects (65, 121). Therefore, CNS-derived hypocretin is capable, nonsynaptically, of activating hypocretinergic receptors that are expressed by peripheral organs. This conclusion has been supported by studies using supraparamagnetic particles of iron oxide (MNPs) (1, 2), which are conjugated with molecules of hypocretin and then injected into the lateral ventricles (195). With histological and magnetic resonance imaging (MRI) techniques, one can track the location of identified molecules of hypocretin from the CNS to peripheral organs, where they activate their cognizant receptors in a time-dependent manner. Using this novel technology, it was first determined that MNP-“tagged” molecules of hypocretin are absorbed by epithelial cells of the choroid plexus of the cerebral ventricles that express hypocretin receptors (195). Hypocretin-conjugated MNPs are then conveyed, via the circulatory system, to peripheral organs where they attach to cells that contain receptors for hypocretin, such as endocrine cells of the pancreas (195). These and related studies reveal that the CSF-circulatory system transports hypocretins from the CNS to the periphery, and, by this route, the hypocretinergic system is able to control the functioning of peripheral organs by nonsynaptic processes (195).

The preceding data demonstrate that the hypocretinergic system activates, selectively, a wide range of visceromotor processes. Complementary correlated patterns of somatomotor control are also promulgated by hypocretinergic actions. In addition, hypocretinergic control of the somatomotor and visceromotor systems is exercised, selectively, only when survival-related behaviors and related processes are being expressed.

Control of Survival Behaviors by the Hypocretinergic System

Prior sections of this article include datasets that describe the manner in which the hypocretinergic system controls synaptic, sensory, somatomotor, visceromotor, hormonal, and other processes and mechanisms in a very specific manner that promotes successful survival behaviors. Also presented are data that demonstrate that these hypocretinergic directives are not activated in the absence of survival or survival-related processes or behaviors. In this section, the integrative functioning of the hypocretinergic system is described with respect to the manner in which it “commands” and “coordinates” the vast panoply of CNS and peripheral organ responses that arise as a result of the presence of adequate survival stimuli (Figs. 1 and 3).

Martinez et al. (98) found that, when prey animals are exposed to a predator, there is an increase in the discharge of hypocretinergic neurons. In a related study, Canteras et al. (28) reported that defensive behaviors in prey that are being attacked by predators are significantly reduced after the lateral hypothalamus is lesioned (28). Complementary studies reveal significantly greater immediate-early gene expression in the hypothalamus of cat-exposed rats compared with confined or handled rats (98). Environmental imperatives of a survival nature that involve explorations of a potentially threatening environment are also accompanied by the discharge of hypocretinergic neurons (160). However, the hypocretinergic system is not engaged during restraint or cold exposure when animals are unable to respond physically and the environment is “reduced,” e.g., to the insides of a refrigerator, even though the animals are highly aroused (56). Thus, the hypocretinergic system is activated and contributes to cold defense when an animal is actively engaged with its environment and is able to react with a variety of somatic and visceral responses (56). On the other hand, when no response is possible in these situations, the hypocretinergic system is not activated (56). Therefore, the critical determinant for hypocretinergic activation is the expression of survival behaviors and/or related processes.

Other studies have shown that the hypocretinergic system promotes adaptive stress responses of the brain and body when an animal is confronted with survival imperatives, which are inherently stressful; however, the hypocretins are not involved in nonsurvival-related stressful responses. For example, the hypocretins are a critical component of stress responses that are activated by corticotropin-releasing factor (CRF) (117). CRF-immunoreactive terminals not only make direct contact with hypocretin-expressing neurons in the lateral hypothalamus, but hypocretinergic neurons also express CRF receptors (174). CRF depolarizes hypocretinergic neurons and increases their firing rate in paradigms that emulate fight-or-flight behaviors (174). The hypocretins also promote the discharge of pituitary corticotropic cells by CRF, which activates the hypothalamic-pituitary-adrenal axis, resulting in the release of glucocorticoids from the adrenal gland (117, 127). In addition, hypocretins in the CSF are transported via the circulatory system to adrenal cells that express hypocretinergic receptors (195). Complementary data also reveal that the excitation of hypocretinergic neurons in response to acute stress is significantly impaired in CRF knockout mice (i.e., mice that do not have a functioning CRF system). As pointed out by Furlong et al., “stress itself is not a critical factor in the activation of the Hert system” (56); these data demonstrate that the hypocretinergic system functions selectively in stressful situations of a survival nature.

Hypocretinergic neurons exhibit a dramatic increase in discharge in conjunction with the presentation of noxious, fear-producing stimuli as animals attempt to escape or avoid these stimuli (126, 197). Nevertheless, after repeated conditioned fear trials, when animals learn that they cannot execute a behavioral (i.e., survival) response to avoid noxious stimuli, there is no increase in the discharge of hypocretinergic neurons (197). In fact, there is a reduction in hypocretinergic activation (197). Thus, activation of the hypocretinergic system only occurs in conjunction with the presence of specific survival-related behavioral responses or the preparation for such responses.

Another data set reveals different, but equally important, integrative functions of the hypocretinergic system that provide essential support for survival behaviors. Studies of attentional performance demonstrate that the hypocretins enhance the accuracy of signal detection in survival-type situations, such as when predators and prey interact; however, the hypocretins are not involved in the detection or evaluation of similar kinds of signals that are nonsurvival related (20). In addition, the surprising omission of an expected event enhances attention to cues that occur at the moment of surprise, which facilitates subsequent learning regarding the nature and importance of the relevant cue. Hypocretinergic input is critical for this pattern of surprise-induced learning, which does not occur in hypocretin-lesioned animals (69). Thus, the hypocretinergic system does...
not simply enhance general neural performance, rather, it is essential for the integration of meaningful stimuli of a survival nature.

The superior colliculus and the periaqueductal gray (PAG) play well-established roles in the execution of the survival behavior of predatory hunting: these sites first integrate visual, auditory, somatosensory, and olfactory cues and then generate appropriate motor responses of a survival nature (107). For example, it has been shown that hypocretinergic neurons control cells in the superior colliculus and PAG with respect to the execution of predatory hunting (107, 108). Both the superior colliculus and PAG are massively innervated by hypocretinergic neurons and, in turn, send substantive projections to them (55, 107, 132). Studies of fos expression indicate that cells in the superior colliculus and PAG as well as hypocretinergic neurons discharge at accelerated rates during predatory hunting and related behaviors, but not during nonsurvival motor behaviors (29, 38, 55, 107, 122). On the other hand, animals with lesions of the superior colliculus and/or PAG are unable to orient themselves toward moving prey and exhibit significant deficits in their ability to capture, hold, and kill prey (55, 108).

It is also important to highlight the converse finding that hypocretin-lesioned animals perform in a manner that is equivalent to intact animals in situations that are not survival-related, e.g., in open field tests of arousal or locomotion (28, 108).

From an evolutionary perspective, a rewarding stimulus can be considered as a directional force with a high survival value for the species. Therefore, it is of significance that the greatest concentration of hypocretinergic neurons overlaps precisely with the area in the lateral hypothalamus that has been identified as the “reward” or “pleasure” zone, which is responsible for promoting self-stimulation and generating positively rewarding feelings and emotions (37). The importance of the hypocretinergic system in defense and survival behaviors has also been proposed by Choi et al. (36) and Benoit et al. (14) based upon elevated hypocretinergic activity in conjunction with risk-reward seeking survival-related behaviors (14, 36, 42). It was therefore not surprising to find that the dopaminergic system is a special target of hypocretin projections that enhance motivated, positively rewarding survival-related activities, including food consumption and reproduction (87). In addition to predatory hunting, the hypocretinergic system, together with the superior colliculus and the PAG, also mediates related survival behaviors such as reward seeking (107, 108). The complementary behavioral studies of Muschamp et al. (109) led them to conclude that “activation of the hcrtr/orx system is an integral component of motivated behaviors” and that hypocretinergic neurons are activated by natural rewards such as food and sex (109). Thus, hypocretinergic neurons constitute the core of the “emotional motor system,” described by Holstege, which is responsible for promoting the emotional, somatomotor, and visceromotor components of survival behaviors (70).

In animals wherein there is a deficit in the functioning of the hypocretinergically regulated reward system, survival and related behaviors are severely compromised (14). In humans with cataplexy who lack hypocretin, there is a corresponding reduction in reward-based behaviors, such as drug addiction (9). Hypocretin knockout mice exhibit attenuated morphine dependence and withdrawal; similarly, hypocretin neuron-ablated mice fail to show increased arousal and motor activity when food deprived (86). Thus, hypocretinergically driven, positively rewarding directives are an essential component of survival behaviors. It would certainly be nonproductive if animals sought to avoid behaviors that enhanced their ability to survive!

The preceding studies reveal that the hypocretinergic system controls the output of numerous systems at all levels of the neuraxis, as well as the activities of peripheral organs, in the performance of survival behaviors that are stressful but also highly rewarding. In addition, as described above, the integrative actions of the hypocretinergic system encompass all of the command and control directives that comprise the multifaceted components of survival behaviors.

Control of Survival-Related Processes by the Hypocretinergic System

Survival-related actions of the hypocretinergic system. Based upon the established actions of the hypocretins in promoting arousal, food consumption, motor activity, antinoception, etc., as well as its key role in the control of integrated survival behaviors, one might not necessarily assume that the hypocretinergic system also functions to mitigate diseases such as cancer or prevent processes such as neurodegeneration. Nevertheless, from the perspective that the hypocretins act in a multitude of ways to promote the survival of individual animals as well as the species, such data could have been anticipated. For example, it has been shown that, in addition to playing a key role in food consumption, the hypocretins also enhance gastric defense mechanisms and ulcer healing, especially during stress such as that which occurs in conjunction with fight-or-flight behaviors (25). In addition, the hypocretins induce both neurogenesis (31, 74) and angiogenesis (83).

Surprisingly, the hypocretins have also been shown to be anti-carcinogenic. For example, it is known that cells of the epithelium of the normal, disease-free colon do not contain receptors for hypocretin; however, when these epithelial cells become cancerous, they begin to express, de novo, receptors for hypocretin (90, 138). Amazingly, when these aberrant hypocretinergic receptors in the colon are activated by hypocretin, instead of functioning as normal receptors that promote cellular activity (166), they initiate intracellular processes that result in cell death by a process of apoptosis (167). Thus, hypocretinergic receptors that are generated by cancerous cells in the colon, by acting as “suicide” receptors, have potent cellular effects that are life-preserving. The hypocretinergic system has also been found to prevent neurodegeneration that is induced by hypoxia (110, 187). This finding is especially significant because almost every known neuroprotective substance acts by suppressing or inhibiting neural activity. Consequently, even though hypocretin is an excitatory neuropeptide, in this case its effects are more closely related to those produced by inhibitory neurotransmitters (54, 189).

Anticipated survival-related actions of the hypocretinergic system. As described above, in a multitude of ways the hypocretinergic system provides protection from injury and disease and promotes survival-related processes at subcellular, cellular, systems, and behavioral levels. As our knowledge of the central and peripheral as well as the synaptic and nonsynaptic actions of the hypocretins increases, based upon concepts that
are inherent in the Unified Hypocretinergic Survival Theory, a host of other phenomena/processes can logically be anticipated to be discovered, such as enhanced immune directives, blood coagulation, recovery from trauma, the prevention or reduction in Traumatic Brain Injury (11, 172), etc. It has already been shown that there are surges of hypocretinergic activity that are correlated with critical periods of infant and adolescent development (8, 159). In addition, hypocretinergic neurons have been shown to be relatively resistant to the deleterious effects of the aging process, compared with other neuronal phenotypes (192, 193).

Many other positive actions of the hypocretins will likely emerge based upon their role in mediating survival behaviors. For example, there is a fascinating phenomenon called time dilation wherein, under certain situations of a life-threatening nature, such as those that occur in combat or when one loses control of a speeding automobile, information is processed in a unique mode (50). When these situations arise, there is a profound subjective impression that time slows down (i.e., that it dilates); individuals feel as if they have “all the time in the world” to make reasoned critical decisions of a life-preserving nature. Since time dilation occurs exclusively during survival-type situations, it is likely to be mediated by the hypocretinergic system, which simultaneously promotes arousal, motor activity, surprise-induced learning, etc. under similar circumstances. For example, CSF and plasma concentrations of hypocretin in combat veterans with posttraumatic stress disorder (PTSD) are significantly lower than in healthy control subjects (156). These data may reflect a paucity of effective hypocretinergic control mechanisms that result in an inability of individuals to cope with the wide range of physiological and psychological responses that arise in fight or flight (e.g., combat) situations (76). It would be interesting to determine if there is a cause and effect relationship, i.e., do combat veterans that develop PTSD have low levels of hypocretin before their engagement in warfare? Clearly, data detailing the actions of the hypocretinergic system, when presented from the perspective of its role in promoting survival and related behaviors and processes, have the potential to impact many new and diverse areas of basic and clinical research.

Potential Limitations of the Unified Survival Theory of the Functioning of the Hypocretinergic System

Novel theories are based upon a consideration of existing data that, by their very nature, are insufficient to transform the theory into established fact. Therefore, in this section, potential “limitations” of the Unified Hypocretinergic Survival Theory that are due to a lack of data are examined, and a number of experiments are proposed that would resolve these limitations.

The Unified Hypocretinergic Survival Theory has not yet encompassed the manner in which the hypocretinergic system, as with other primitive systems, developed over time to include more functions than those subsumed early in its phylogenetic development. For example, a role in stabilizing the states of sleep and wakefulness may be an evolved function of the hypocretinergic system that provides a background for the “stable” expression of survival behaviors, especially those that are related to this system’s interactions with forebrain structures involved in the control of arousal as well as other waking and sleep states. The influence of the hypocretins on circadian processes may also be complementary to its role in stabilizing sleep and waking states since there are strong reciprocal connections between hypocretinergic neurons and various sites that are involved in the regulation of circadian rhythms (94, 118, 119). These are complex processes as evidenced by the fact that hypocretins and their receptors are present in the retina, and photosensitive retinal ganglion cells play a role in setting the suprachiasmatic circadian clock (146). Stable circadian rhythms, as with the states of sleep and wakefulness, provide an important foundation for the expression of survival and related behaviors, which are highlighted by the deficits in survival-related processes and states that arise in hypocretin knockout animals (82, 89). Additional studies are required to determine the precise manner in which survival behaviors are dependent on hypocretinergic/circadian/sleep/wakefulness interactions; experiments that define the deficits in survival behaviors that arise when these interactions are not maintained would therefore be of great value.

The importance of the hypocretinergic system in controlling respiratory activities is well established in survival situations that take place during arousal (82, 89). However, the hypocretins also play a critical role in the control of CO2 sensitivity in a state-dependent manner by preserving ventilatory stability during sleep (110, 111). These actions of the hypocretins during sleep may be viewed as supporting the Unified Hypocretinergic Survival Theory insofar as they represent an example of a survival-related function of this system that maintains/stabilizes sleep, and this assures optimal functioning during wakefulness/arousal. In this regard, the finding that there is a high incidence of apneic episodes during sleep in hypocretin knockout mice, and the consequences that arise with respect to survival behaviors that take place during wakefulness, has been relatively unexplored (152). The Unified Hypocretinergic Survival Theory may also be expanded by conducting clinically related studies involving an evaluation of the therapeutic potential of hypocretin for the treatment of sleep- and waking-related breathing disorders (178).

Other aspects of the Unified Hypocretinergic Survival Theory would benefit from additional studies dealing with the various behaviors/reactions of animals that occur when the hypocretinergic system is rendered nonfunctional either by ablation of its constituent neurons, the generation of hypocretin knockout animals, the administration of receptor antagonists, etc. Data must also be examined over an extended period of time in behaving animals. In addition, studies of hypocretin knockout animals should take into account the possible impact of processes such as neuronal plasticity as well as compensatory actions by alternate sites. Although there is a consensus that the locus coeruleus-noradrenergic system plays a causal role in the induction of arousal states, lesions of the noradrenergic system have an inconsistent impact on indexes of arousal, which is thought to be due to the presence of time-dependent lesion-induced compensation by other systems (15, 16).

The ontogenetic development of the hypocretinergic system as well as its response to aging processes have not been examined to any significant extent from the perspective of the Unified Hypocretinergic Survival Theory (192, 193). Destruction of the hypocretinergic system in newborn animals and the aged in conjunction with behavioral survival-related tests could clarify the role of the hypocretins in promoting survival behaviors across the life span. In addition, the Unified Hypo-
Hypocretinergic Survival Theory has not addressed, to any significant extent, gender differences vis-à-vis the functioning of the hypocretinergic system. Although there is a paucity of relevant behavioral data, it is known, for example, that the expression of hypocretin receptors in the adrenal cortex is gender specific and is magnified not only by plasma glucose, but also by gonadal steroids during conditions that are survival related (81). Thus, the Unified Hypocretinergic Survival Theory is currently limited by a lack of data as opposed to existing data that do not support the Theory.

Summary

The Unified Hypocretinergic Survival Theory proposes that hypocretinergic neurons, and their receptors, function to “command” and “coordinate” the activity of CNS sites as well as peripheral organs to ensure the animal’s survival. In a complementary fashion, the data reveal that, when there is a deficit in the functioning of the hypocretinergic system, survival behaviors and related processes are compromised, whereas processes and behaviors that are not involved in survival remain relatively intact. Importantly, the Unified Hypocretinergic Survival Theory also accounts for all of the diverse and often paradoxical-appearing results that have been reported to arise in conjunction with the activation of hypocretinergic neurons.

The Unified Hypocretinergic Survival Theory also provides a perspective to interpret data emanating from previous studies of the hypocretinergic system. In addition, it establishes a foundation for the generation of experiments to further explore the vast array of CNS and peripheral actions that occur as a consequence of the hypothalamic control of survival and related behaviors.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author.

AUTHOR CONTRIBUTIONS

Author contributions: M.H.C. analyzed data; M.H.C. prepared figures; M.H.C. drafted manuscript; M.H.C. edited and revised manuscript; M.H.C. approved final version of manuscript.

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