The Dual Role of the Orexin System in Regulating Wakefulness and Stress Responses- A systematic review.

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Abstract:

The orexin/hypocretin neuropeptide system has become a central focus in neurobiology due to its indispensable regulatory roles in physiological and behavioral processes. Operating as potent neuromodulators, orexin peptides coordinate diverse functions—including autonomic regulation, endocrine activity, and complex behavioral responses—across vertebrate species. Beyond their well-established centrality as regulators of vigilance and arousal, these peptides also participate in the modulation of metabolic pathways, feeding behavior, and thermoregulatory responses, although these additional roles require further elucidation.

This review synthesizes the historical progression of orexin research, highlighting key advances from its initial identification to the development of engineered orexin analogs. Particular attention is given to the involvement of the orexin system in stress adaptation, emotional processing, fear, anxiety, and learning. The overview further explores current pharmacological progress, with special focus on orexin-targeted therapies that have demonstrated efficacy, especially in treating sleep-wake disturbances. The authors draw upon their original findings to integrate the diverse activities of orexin peptides and their broad relevance to neuropsychiatric and physiological health.

Overall, understanding the multidimensional functions of orexin neuropeptides and the mechanisms underlying their modulatory effects is pivotal for designing innovative therapeutics. Advancements in orexin pharmacology promise new avenues for intervention in stress-related disorders and sleep pathology.

Keywords: orexin/hypocretin, neuropeptides, stress adaptation, arousal, sleep disorders

Neuropeptides: Guiding and Nurturing the Brain's Interconnected Web

Neuropeptide research originated over a century ago with the initial characterization of vasopressin and oxytocin, followed by the extraction of substance P as the first classical neuropeptide from tissues.[1] This early work paved the way for distinguishing neuropeptides from conventional neurotransmitters, revealing their unique biochemical and functional properties. Unlike the smaller, rapidly acting classic neurotransmitters, neuropeptides are larger molecules that require greater energy for synthesis and trafficking.[2,3] Their release is not limited to the synaptic cleft; rather, neuropeptides can be secreted from dense-core vesicles at multiple neuronal sites and are often co-released with neurotransmitters.[4]

A critical distinction is their metabolic fate: while neurotransmitters are recycled by reuptake mechanisms, neuropeptides are degraded extracellularly by peptidases, often forming biologically active fragments.[5] This metabolism, paired with a prolonged half-life, allows neuropeptides to diffuse across extensive neural territories and exert effects via paracrine, autocrine, or even endocrine mechanisms.[6] Their signalling is generally slower and longer-lasting, more akin to hormone action than rapid neurotransmission.[7]

The neuromodulatory activity of neuropeptides is realized through diverse G-protein-coupled receptors, with ligand diversity enhanced by extensive gene splicing.[8] These features foster plasticity and adaptability within the central nervous system, enhancing the capacity to respond to varied environmental and physiological challenges. The broad distribution and redundancy of neuropeptide families ensure robust neuroendocrine regulation at multiple levels.[9]

Neuropeptides contribute vital flexibility to the neural connectome, modulating receptor and enzyme expression, synaptic plasticity, and dendritic architecture.[10] They represent an essential but underappreciated axis of translational regulation within the CNS, mediating both subtle and long-term changes in neural circuitry.[11] Their actions complement classic neurotransmission and hormonal signalling, collectively underpinning behavioral, autonomic, and endocrine adaptation.[12]

Empirical investigations into the orexin/hypocretin system, among other neuropeptide networks, have highlighted their role in synchronizing autonomic, behavioral, and endocrine responses, especially in the context of arousal and stress adaptation.[13] Continued research into neuropeptide anatomy, physiology, and pathophysiology—particularly in stress, thermoregulation, affect, and learning—offers promising avenues for understanding and harnessing their therapeutic potential in neuropsychiatric and neuroendocrine disorders.[14]

Materials and Methods:

The orexin/hypocretin neuropeptide system has been extensively studied for its crucial role in regulating multiple physiological processes including feeding behavior, metabolism, stress response via the hypothalamic-pituitary-adrenal (HPA) axis, reproduction, and a variety of behavioral functions. Orexin neurons, although localized primarily in the hypothalamus, project widely throughout the central nervous system influencing arousal, wakefulness, and autonomic regulation.[15] Their actions are mediated through two G protein-coupled receptors, OX1R and OX2R, which are differentially distributed and trigger diverse intracellular signaling cascades.[16]

Early research focused on the orexin system's impact on feeding and energy homeostasis, but subsequent studies revealed its integral role in arousal and sleep-wake regulation. Orexinergic activation maintains stable wakefulness by stimulating monoaminergic centers and inhibiting sleep-promoting regions.[17] Beyond arousal, orexins modulate emotional regulation, anxiety, fear, and reward processing through complex neurocircuitry involving limbic structures and dopaminergic pathways.[18] These multifaceted roles position the orexin system as a pivotal integrator of behavioral and physiological homeostasis.[19]

Dysregulation of orexin signaling has been implicated in several human diseases, prominently narcolepsy, obesity, mood and anxiety disorders, cognitive impairments, addiction, and chronic

pain.[20] Notably, narcolepsy results from orexin neuron loss or impaired receptor signaling. Orexin also interacts with other neuropeptides and neurotransmitters, further broadening its physiological effects but complicating therapeutic targeting.[21]

Promising orexin receptor ligands, including approved dual orexin receptor antagonists for insomnia, are under clinical evaluation for multiple indications such as depression, anxiety, binge eating, and narcolepsy.[22] Challenges remain in achieving receptor subtype selectivity, optimizing pharmacokinetics, and minimizing side effects.[23] Furthermore, orexin's interactions with circadian rhythms and immune responses suggest broader therapeutic applications.[24]

Overall, ongoing research advances understanding of orexin's integrative functions in health and disease, supporting the development of novel targeted therapies that may benefit neurological, metabolic, and psychiatric conditions. This review consolidates interdisciplinary insights to guide future orexin-centered investigations and pharmacological innovations.[25]

Hypocretin and Orexin: The Neuropeptides and Their Receptors That Shape Brain Function

The hypocretin/orexin system stands out as one of the central neuropeptide networks in the human brain, marked by its remarkable complexity and influence over a variety of physiological processes. Breakthrough studies that uncovered this system not only identified its core neuropeptides—orexin-A and Orexin-B, also called hypocretin-1 and hypocretin-2—but also revealed their ability to increase feeding behavior and excite neural activity. What truly distinguishes the orexin system is the unique pattern of its neural distribution.[26]

Unlike many other neuropeptide systems, orexin-producing neurons are found almost exclusively within specific regions of the hypothalamus, notably in the lateral, dorsal, dorsomedial, and perifornical areas.[27] Despite their small numbers—estimated at just 50,000 to 80,000 neurons in the human hypothalamus—these cells wield an outsized influence. Their axons branch out to a wide range of areas throughout the central nervous system (CNS), while orexin receptors are distributed nearly everywhere in the brain and spinal cord.[28]

This anatomical arrangement allows a relatively small group of neurons to coordinate large-scale processes like arousal, feeding, and energy regulation.[29] Similar to melanin-concentrating hormone (MCH)-expressing cells, orexin neurons can shape global brain states such as wakefulness and alertness despite their focused origin.[30] Through their intricate web of connections and widespread receptor expression, the hypocretin/orexin system exemplifies how specialized groups of neurons can have far-reaching effects on behavior and physiology, making them a cornerstone of brain function.[31]

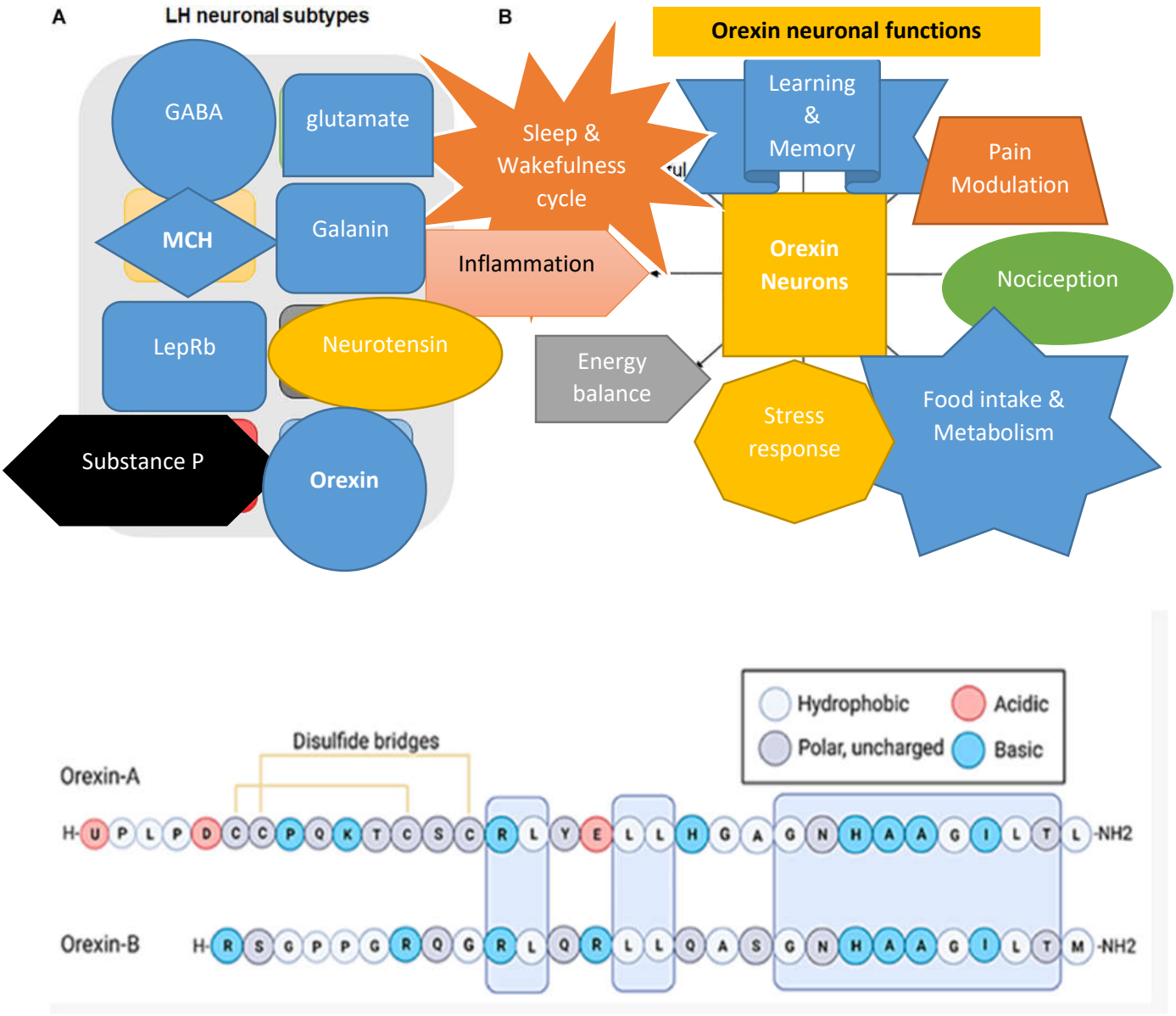

Fig:1 *The hypocretin/orexin neuropeptide system, at the cellular level, consists of two principal ligands—orexin-A and Orexin-B—and two corresponding receptors, OX1R and OX2R. Although both peptides belong biochemically to the incretin family, they bear limited structural similarity to other members of this group. Remarkably, orexin-A and Orexin-B differ by approximately 50% at the primary amino acid sequence level. They are both derived by cleavage from a common precursor protein known as pre-pro-orexin (PPO) and feature amidated C-termini. Orexin-A is the longer peptide, composed of 33 amino acids, while Orexin-B consists of 28 residues.*

Distinct physicochemical properties further differentiate the two peptides. Orexin-A possesses an N-terminal pyroglutamate residue and two disulphide bridges, rendering it more resistant to proteolytic breakdown than Orexin-B. Moreover, its enhanced hydrophobicity facilitates more efficient passage across the blood-brain barrier. These molecular characteristics influence the peptides' stability, bioavailability, and receptor engagement.[32]

Binding affinities to their receptors differ notably between the peptides. Orexin-A preferentially binds to OX1R with an affinity markedly higher (5–100 fold) than Orexin-B, whereas both ligands exhibit comparably high affinity for OX2R, which has less ligand specificity.[33] This receptor preference is partly attributed to the approximately 64% amino acid sequence identity shared between OX1R and OX2R. Such divergence generates functional diversity within cellular signal transduction pathways.[34]

Both receptors belong to the G protein-coupled receptor (GPCR) family, primarily coupling to the Gq/11 subtype, which activates phospholipase C (PLC), phospholipase A (PLA), and phospholipase D (PLD).[35] These enzymatic activations lead to intracellular calcium mobilization and protein kinase C (PKC) activation, critical mediators of downstream cellular responses.[36] Additionally, OX1R can elevate cytosolic calcium through activation of non-selective cation channels, while OX2R is capable of inhibiting adenylate cyclase and protein kinase A (PKA) pathways via Gi/o proteins, adding further complexity.[37]

The functional versatility of the orexin system is enhanced by receptor dimerization and significant structural homology with other neuropeptide GPCRs, including neuropeptide Y (NPY), thyrotropin-releasing hormone (TRH), cholecystokinin (CCK), and neurokinin receptors. Among these, the neuropeptide FF (NPFF) receptor displays the highest sequence similarity (approximately 35–37%) with orexin receptors.[38]

Immunohistochemical studies reveal that the distribution of orexin peptides and their receptors, OX1R and OX2R, only partially overlap in the central nervous system. This spatial segregation, combined with differences in ligand pharmacokinetics and receptor signalling profiles, likely underpins the distinct physiological and pathophysiological actions attributed to orexin-A and Orexin-B.[39] Together, these features shape the orexin/hypocretin system's role in regulating wakefulness, energy homeostasis, stress responses, and various neuroendocrine functions.[40]

This intricate ligand-receptor interplay forms the basis for ongoing research aimed at targeting orexin receptors for therapeutic modulation in sleep disorders, metabolic dysfunction, and neuropsychiatric conditions.[41]

The Vital Role of Orexin in Synchronizing Arousal with the Body's Internal Clock

The orexin neurons exert widespread influence across numerous brain regions, providing vital clues about the diverse physiological roles of orexins at the systemic level. Early studies identified orexins as critical mediators of hedonic feeding behavior—in other words, the pleasure-driven consumption of food.[42] However, subsequent research revealed that a more prominent function of the orexin system lies in the regulation of arousal and wakefulness.[43]

One of the key discoveries was that the orexin system receives essential inputs from the brain's central circadian clock, the suprachiasmatic nucleus (SCN). This connection fosters the precise synchronization of circadian rhythms and arousal states in mammals.[44] The mammalian circadian system is intricately organized with a hierarchical arrangement comprising input signalling pathways (light sensed through the retina), a central pacemaker (SCN), and output pathways that influence multiple physiological processes such as the sleep–wake cycle, feeding, and neuroendocrine functions.[45]

The SCN (supra chiasmatic nucleus) acts as the master clock, orchestrating the timing of local clocks throughout the brain and body.[46] Its outputs target several hypothalamic autonomic centers that regulate vigilance, body temperature, fluid intake, and hormone secretion. Beyond hypothalamic targets, SCN signals reach brainstem nuclei and higher cortical areas involved in mood, cognition, and memory.[47] The bidirectional communication between the SCN and orexin neurons, both at the neural circuit and endocrine levels, establishes the temporal framework for arousal and related autonomic functions.[48]

Orexinergic cells modulate the ascending reticular activating system (ARAS), which comprises cholinergic and monoaminergic nuclei essential for wakefulness.[49] By stimulating these nuclei, orexins disinhibit arousal-promoting centers and suppress sleep-inducing regions such as the ventrolateral preoptic nucleus (VLPO), facilitating the transition from sleep to waking.[50] Notably, orexin receptor type 2 (OX2R) plays a predominant role in this arousal modulation, as pharmacological antagonism of OX2R induces sleep, while blocking type 1 receptors has a lesser effect.[51]

The indispensable role of orexins in maintaining vigilance is best exemplified by the sleep disorder narcolepsy. Deficiency of orexin signalling causes narcolepsy and cataplexy in multiple species, including humans, where it is linked to disrupted hypothalamic development or autoimmune destruction of orexin neurons.[52] Narcolepsy is characterized by inappropriate intrusion of REM sleep into wakefulness, a process regulated by interactions between orexin and histaminergic neurons within the ARAS.[53]

Beyond arousal and sleep regulation, the orexin system influences multiple homeostatic processes, including food and fluid intake, energy metabolism, body temperature, and reproductive functions. Orexin neurons innervate hypothalamic centers such as the arcuate nucleus (ARC) and paraventricular nucleus (PVN), which coordinate neuropeptide signals governing[54] feeding behavior through stimulatory (e.g., neuropeptide Y, agouti-related peptide) and inhibitory (e.g., cocaine- and amphetamine-regulated transcript, melanocortins) factors.[55,56]

Notably, orexin-A activates OX1R in these feeding centers to promote food consumption.[57] Paradoxically, chronic orexin deficiency is associated with weight gain, attributable to orexin's dual role in both stimulating thermogenic heat production and promoting heat dissipation.[58] Orexinergic projections to the preoptic area and dorsomedial hypothalamus regulate these competing processes, balancing energy expenditure and storage.

In thermoregulation, orexins enhance sympathetic vasodilation through OX1R and modulate brown adipose tissue metabolism by activating or inhibiting thermogenesis via distinct receptor pathways. This dynamic balance prevents excessive fat accumulation by simultaneously increasing heat generation and loss.[59]

The orexin system also regulates the hypothalamic-pituitary-gonadal axis and reproductive behavior in a brain-region-specific and cycle-dependent manner.[60] This system integrates nutritional and metabolic cues with reproductive status, optimizing the balance between self-preservation and species continuation.

Lastly, orexins are key orchestrators of the stress response, modulating adaptive behavioral reactions to threats and fear-related learning via complex neuroendocrine pathways.[61]

Together, these findings highlight the orexin system as a versatile central regulator, integrating circadian, metabolic, reproductive, and stress-related processes to maintain physiological homeostasis and adaptive responsiveness.

Input Region(s)	**Core Region(s)**	**Target Region(s)**	**Receptor(s)**	**Function(s)**
Thalamus, TMN, SCN	PFA, Lateral Hypothalamic Area (LHA)	Thalamus, Locus Coeruleus (LC), Dorsal Raphe (DR), Ventral Tegmental Area (VTA), TMN	OX2R	Circadian regulation, arousal, wakefulness
Peripheral signals, Arcuate Nucleus (ARC), Paraventricular Nucleus (PVN), Suprachiasmatic Nucleus (SCN)	LHA, Dorsomedial Hypothalamus (DMH)	Ventromedial Hypothalamus (VMH), ARC, PVN, Nucleus Accumbens (NAc)	OX1R	Regulation of food intake
Peripheral receptors, Brainstem, Septum	LHA, Perifornical Area (PFA)	Periaqueductal Gray (PAG), Nucleus of the Solitary Tract (NST), Preoptic Nucleus (PON), PVN, Rostral Ventrolateral Medulla (RVLM), Rostral Ventromedial Medulla (RVMM), VTA	OX1R, OX2R	Autonomic regulation: thermoregulation, cardiovascular responses
Thalamus, Hippocampus, PVN, Bed Nucleus of the	PFA, DMH	Central Amygdala (CeA), Lateral Amygdala (LA), LC, Pedunculopontine Tegmental	OX1R	Emotional regulation: anxiety, fear, mood

Input Region(s)	Core Region(s)	Target Region(s)	Receptor(s)	Function(s)
Stria Terminalis (BNST)		Nucleus (PPT), Paraventricular Thalamic Nucleus (PVT), BNST, Medial Temporal Lobe (MTL)		
Thalamus, Hippocampus, SCN	LHA, DMH	VTA, NAc, Dorsal Raphe (DR), Insular Cortex (IC), Prefrontal Cortex (PFC)	OX1R, OX2R	Cognitive functions, reward processing, addiction
Pituitary, Adrenal Gland, Thalamus, Brainstem, SCN	LHA, DMH	PVN, PON	OX1R, OX2R	General Adaptation Syndrome (GAS), fight-or-flight response
Pituitary, Ovary, Brainstem, SCN	LHA, DMH	ARC	OX1R, OX2R	Gonadal functions and reproductive regulation

Table 1: *This table illustrates the extensive network through which orexin neurons influence diverse physiological systems via their projections and receptor-specific signalling. Orexin neuron's targets include key autonomic, limbic, reward, and endocrine centers that contribute to arousal, metabolism, emotional regulation, and stress responses.*

The orexin system plays a crucial regulatory role not only in circadian and arousal processes but also in physiological and pathophysiological functions with less obvious temporal patterns. Among these are pain perception, anxiety, mood regulation, reward processing, and addiction. Despite the small number of orexin-producing neurons, their projections influence a wide array of evolutionarily conserved functions involved in maintaining homeostasis and behavioral adaptation.[62] Notably, the orexin system is considered a prime example of neuropeptide-mediated regulation: it originates from a limited neuronal population but exerts widespread control over distant target areas throughout the central nervous system. Fundamentally, its principal role appears to be the temporal gating of brainstem functions, coordinating diverse responses in accordance with internal and external cues.[63]

Supporting this, recent studies have illustrated orexinergic projections modulate pain pathways at spinal and supraspinal levels, providing analgesic effects. Additionally, orexin neurons affect anxiety and mood centers in limbic regions and mediate reward and addiction via dopaminergic circuits. The orexin system's influence on physiological processes thus extends far beyond sleep and feeding into critical domains shaping emotional and nociceptive responses.[64] This integrative functionality highlights the importance of this neuropeptide network as a master regulator synchronizing complex brain activities with organismal demands.[65]

The Influence of Orexin Neuropeptides on How We Handle Stress

The neuroendocrine response to stress relies on the coordinated interaction of two major systems: the sympathoadrenal (SA) system and the hypothalamic-pituitary-adrenal (HPA) axis. While both serve as critical regulators for adapting to adverse challenges, their roles are often intertwined in practice and literature. The SA system, identified by Cannon, encompasses the rapid "fight or flight" response, mediated by the autonomic nervous system and adrenal medulla, releasing catecholamines like adrenaline. Conversely, the HPA axis, characterized by Selye's General Adaptation Syndrome (GAS), orchestrates longer-term hormonal adaptation, governed by interactions among the hypothalamus, pituitary gland, and adrenal cortex, ultimately leading to glucocorticoid release.[66]

Despite overlapping functions, distinguishing these stress pathways is essential for accurately describing neuroendocrine reactions. The HPA axis regulation begins with corticotrophin-releasing hormone (CRH) and arginine vasopressin (AVP) secretion within the hypothalamic paraventricular nucleus (PVN), stimulating pituitary adrenocorticotropic hormone (ACTH) release and subsequent adrenal glucocorticoid production.[67] Feedback mechanisms through CRH, ACTH, and glucocorticoids ensure homeostatic restraint, preventing over activation and damage from excessive inflammation or immune suppression.[68]

Various neuropeptides, including NPY, neurotensin, ghrelin, and others, fine-tune the HPA axis, with oxytocin and natriuretic peptides acting as inhibitors. The orexin system, in particular, promotes both SA and HPA activity in response to stress, with orexin-A activating OX1R receptors found in the nucleus of the solitary tract, locus coeruleus, and sympathetic neurons.[69] In effect, orexins function as both instigators and integrators of heightened arousal responses, linking classic "fight or flight" and GAS adaptations, and showing dense innervation of limbic structures like the bed nucleus of the stria terminalis (BNST).[70]

Inputs to the HPA axis are remarkably diverse—systemic challenges such as osmotic or immune disturbance are relayed from the periphery directly to the brainstem, whereas neurogenic stressors like fear or pain are processed through cerebral circuits.[71] The PVN contains distinct neuronal populations that mediate acute versus chronic stress responses, reflecting the complexity of this regulation.[72] Additionally, neuropeptide signalling complements the negative feedback loops of the HPA system, contributing to stress resilience and adaptation.[73]

Acute stress events generate robust activation of orexin neurons, as evidenced by heightened c-fos expression after aversive challenges, novelty, or fear stimuli.[74] Chronic or repeated stress, however, elicits mixed or attenuated orexinergic activity, possibly reflecting adaptive mechanisms to persistent adversity. Studies have shown that the orexin response is also

modulated by species, sex, and individual resilience—females and animals with better-coping phenotypes typically exhibit less orexin release under stress.[75]

Regarding the HPA axis, orexins have a direct stimulatory influence at multiple levels—hypothalamic, pituitary, and adrenal—helping maintain sufficient basal hormone activity and avoid exaggerated hypothalamic responses.[76] This stabilizing effect is especially relevant for continuous stress exposure, preventing maladaptive outcomes. The reciprocal connections between orexin and CRH populations illustrate bi-directionality, with noradrenaline and neuropeptide Y further diversifying the system's outputs.[77]

The orexin/hypocretin system is a vital coordinator for neuroendocrine stress adaptation. By actively stimulating both sympathetic and HPA axes, it shapes organismal responses to acute and chronic stressors, helps manage negative feedback and inflammatory restraint, and ensures integrated adaptation through its widespread projections and limbic connectivity. This flexible regulatory function—spanning arousal, mood, homeostasis, and immune balance—underscores the importance of orexin signalling for maintaining mental and physiological health in the face of adversity.

The Influence of Orexins on Anxiety and the Process of Learning Through Reward

The orexin system is widely regarded in neuroscience as the most pivotal peptidergic modulator of the ascending reticular activating system (ARAS), which is central to the regulation of arousal and wakefulness. This view is supported by the fact that the loss of orexin neurons or signalling causes severe sleep and arousal disorders, such as narcolepsy and cataplexy, both in genetic and acquired forms.[78] While initial research focused on the importance of orexins in sustaining wakefulness, it soon became clear that their functional reach extends to the fine-tuning of arousal-related behaviors, including attention, motor activities, and a range of anxiety-related and stereotypic responses like grooming and freezing.[79]

Arousal is intimately tied to threat detection. Imminent danger triggers the strongest arousal responses and leads to heightened alertness, attention, and emotional experiences such as fear.[80] These affect mood, cognition, and behavior, and this broad behavioral adaptation is closely linked to increased activity in the orexin system—a master controller of vigilance and emotional state.[81]

When the brain processes threatening stimuli, a robust activation of the orexinergic network occurs, primarily via the ARAS. The hypothalamic centers then modulate the release of neurotransmitters across brainstem and limbic structures that underlie the regulation of emotions, motivation, and higher cognitive processes.[82] Animal studies have shown that orexin signalling is essential for mounting behavioral responses to both acute threats and to stressors that persist over time.[83,24]

The neurocircuitry underlying the integration of fear- and reward-related learning consists of three broad domains: sensory input (centered on the thalamus), primary emotional modulation (the amygdala), and modality-specific output regions.[84] For reward learning, the ventral striatum and the ventral tegmental area (VTA) play key roles, whereas the medial temporal lobe (MTL), including the hippocampus and related cortices, orchestrates fear-based learning and memory. The amygdala, especially its central (CeA) and extended (BNST) areas, is essential for encoding fear memories and emotional learning, often in conjunction with orexinergic or noradrenergic input.[85]

Orexin activity in these circuits is not unidirectional. Limbic areas such as the septum, BNST, basal forebrain, central amygdala, and hippocampus provide substantial feedback to orexin neurons, creating a bidirectional dialogue. For instance, when animals are exposed to anxiogenic conditions (such as predator odour or novel environments), orexin neuron activity increases, which in turn can heighten startle responses, passive avoidance behaviors, and emotional memory consolidation.[86] Direct and indirect orexinergic projections, particularly via OX1 receptors, influence the lateral amygdala and hippocampus, affecting memory consolidation and emotional learning, often through noradrenergic transmission from the locus coeruleus (LC).

Importantly, recent research has highlighted the orexin system's involvement in reward processing and the development of addiction. Orexins have been established as key facilitators of hedonic behaviors, promoting natural rewards like food, fluids, and reproduction. Particularly, they enhance binge-like intake of palatable substances. Anatomical studies have shown that critical nodes in the reward system—like the VTA, NAc, BNST, CeA, and PFC—receive rich orexinergic innervation, and this network can fine-tune reward system activity, even in the absence of circadian cues from the SCN.[87]

Furthermore, orexins modulate behavioral adaptation (stress resilience), especially during chronic or repeated stress.[88] The link between orexin and other "hedonistic" peptides such as ghrelin supports synergistic effects that could buffer psychological stress. Alterations in orexin signalling are associated not only with obesity but also with substance dependence, impacting reinforcement, drug-seeking, and self-administration.[89] The orexin network is upregulated in the context of cocaine and opiate abuse, while responses to other substances (alcohol, cannabinoids, nicotine) vary depending on the duration and phase of exposure, reflecting the system's adaptive (coping) drive.[89]

The orexin system stands as a master integrator at the intersection of arousal, emotional regulation, reward, and adaptive behavior.[90] Its widespread projections ensure the flexible synchronization of vigilance, learning, motivation, and behavioral coping mechanisms in mammals, highlighting its importance for both mental health and resilience to daily challenges.[91]

Interactions Between Orexin-Producing Neurons and Other Peptide-Signalling Brain Networks

The cell bodies of orexin (also known as hypocretin) neurons are tightly clustered in the caudal hypothalamus, specifically within regions such as the lateral hypothalamic area, perifornical area, dorsomedial hypothalamus, and posterior hypothalamic zone.[92] Despite this localized origin, their axonal projections—and receptors for their peptides—are widely dispersed throughout the central nervous system. This spatial architecture is reminiscent of other neuropeptides like melanin-concentrating hormone (MCH), ghrelin, and neuromedin-S, whose cell bodies also occupy discrete hypothalamic locales but send broad, functional outputs across multiple brain regions.[93]

The concentrated somata with extensive projecting terminals allow orexin neurons to act as pivotal integrators and influencers of diverse physiological processes including feeding, arousal, stress response, and behavior. Orexins interact closely with other peptidergic systems such as MCH, neuropeptide Y (NPY), apelin, ghrelin, and neuromedin networks.[94] These

partnerships are thought to enhance the functional diversity and plasticity of orexin-mediated regulation, particularly in key hypothalamic circuits involved in energy homeostasis and neuroendocrine control.[95]

Orexin neurons receive important afferent inputs from monoamines, NPY, and ghrelin, which modulate their excitability. In turn, orexinergic neurons project to and functionally cooperate with networks expressing corticotrophin-releasing hormone (CRH)/urocortin, NPY, pro-opiomelanocortin (POMC), and monoamines.[96] This extensive fibre interplay orchestrates adaptive neuroendocrine and behavioral responses in both acute and homeostatic challenges, refining functions such as thermoregulation, mood, anxiety, and learning.[97]

Interestingly, orexin receptor expression reveals additional complexity. The two primary orexin receptors, OX1R and OX2R, exhibit overlapping but distinct distributions and affinities, with different neuronal subpopulations expressing one or the other receptor type.[98] This receptor heterogeneity adds further layers of control to orexin signalling dynamics.

A striking feature of the orexin system is its sensitivity to damage and the limited compensatory capacities of other neuropeptides. While deficiencies in other neuropeptide systems often result in minimal functional disruption due to redundancy, orexin deficiency—whether congenital or acquired—leads to profound pathophysiological consequences such as narcolepsy and impaired stress responses.[99] This vulnerability is linked to the small number of orexin neurons (approximately 50,000–80,000 in humans) and their relatively unique molecular properties, including limited homology with other neuropeptides.

Though some G-protein-coupled receptors (GPCRs) of other neuropeptides like neuropeptide Y receptor type-2, thyrotropin-releasing hormone receptor, cholecystokinin receptor, and neurokinin receptors share modest sequence similarity with orexin receptors, their ligand binding affinities to orexins are negligible. The neuropeptide FF receptor of the RF-amide peptide family stands out as an exception with higher sequence homology and significant affinity for orexins. The orexin/hypocretin system's anatomical localization, selective receptor distribution, and extensive interaction with multiple neuropeptidergic and monoaminergic pathways define it as a specialized and indispensable regulator of CNS functions. The system's integration across afferent and efferent pathways amplifies its ability to finely coordinate arousal, metabolism, stress, and behavioral processes, making it central to maintaining physiological balance and adaptability.

Human Pathophysiological aspects: The Orexin receptor ligands in its present form and future implications

The orexin/hypocretin system, discovered through early experimental studies, has been linked to various human diseases by alterations in its neurons. The most obvious connections first identified were with disorders of the ascending reticular activating system (ARAS) and related sleep pathologies, such as obstructive sleep apnea and hypopnea syndrome. Since then, dysfunction in the orexin system has been firmly established in narcolepsy with cataplexy, a condition caused by the loss of orexin neurons, and in obstructive sleep apnea–hypopnea syndrome. Notably, narcolepsy in its acquired form is recognized as a neuroinflammatory disorder often triggered by infections like H1N1 influenza or vaccinations, which provoke an autoimmune attack on the orexin-producing neurons.[100]

The orexin system also plays a significant role in disorders of the reward system, particularly in cooperation with the ghrelin network. This interaction has been implicated in conditions like Prader–Willi syndrome, a rare genetic form of obesity characterized by excessive appetite and weight gain.[101] However, the orexin system's functions are complex and dual-faceted, as it simultaneously promotes feeding behavior and energy expenditure based on environmental and physiological signals. Consequently, orexin dysregulation is involved in both weight gain and weight loss conditions, manifesting in eating disorders such as binge eating, bulimia, and anorexia nervosa.[102]

In hypersomnia disorders like Kleine–Levin syndrome, fluctuating levels of orexin in cerebrospinal fluid correlate with the cyclical phases of hypersomnia and intense hunger, suggesting orexin involvement in these alternating stages.[103] Similar to the hypothalamic-pituitary-adrenal (HPA) axis, the specific eating disorder phenotype appears influenced by the type and duration of psychological stressors.[104]

Research has also revealed hypoactivity of the orexin system in reproductive disorders, including gestational diabetes and polycystic ovary syndrome (PCOS). These conditions often show increased body weight and elevated leptin, which suppresses orexin expression, linking metabolic and reproductive dysfunctions.[105]

Regarding drug addiction, orexin upregulation is commonly observed during withdrawal phases across different substance dependencies. Withdrawal is perceived by the brain as a stress stimulus, heightening arousal, attention, and drug-seeking behaviors, all modulated by orexinergic signalling.[106]

In the nervous system, orexin dysfunction contributes to various neuropsychiatric and neurological diseases such as attention deficit hyperactivity disorder (ADHD), anxiety, epilepsy, panic disorders, and phobias. Therapeutic interventions with orexin receptor antagonists have been effective in reducing exaggerated startle responses seen in anxiety. These disorders often display circadian patterns, reinforcing the hypothesis that alterations in the orexin system contribute causally to their development.[107]

Chronic over activation of neuronal circuits involving orexin may result in “burnout,” with progression to conditions such as major depression, post-traumatic stress disorder (PTSD), hypertension, and even various neurodegenerative diseases, including Parkinson’s, Huntington’s, Alzheimer’s disease, multiple sclerosis, and amyotrophic lateral sclerosis (ALS).[108] The vulnerability of orexin neurons in these disorders is partly due to their small population confined to a limited hypothalamic region, making them among the first neuronal populations to be depleted by neuroinflammation and protein aggregation.

Symptoms such as cataplexy and impaired postural reflexes are common across Parkinson’s, Huntington’s, and prion diseases, while altered sleep-wake cycles and fluctuating vigilance characterize Alzheimer’s, multiple sclerosis, and prion-related disorders. Behavioral symptoms including mood swings, anxiety, irrational fears, and irritability are widespread and can be linked to both hyperactivity and hypoactivity of the orexin system.[109]

Cognitive impairments and altered pain perception have also been associated with orexin system dysfunction. In pain modulation, orexin receptors share similarities with RF-amide family receptors, which may mediate analgesic functions both directly and indirectly. Conditions such as fibromyalgia and primary headaches, including migraines and cluster

headaches, exhibit abnormal orexin-mediated pain signalling, with clear daily rhythmicity explained partly through hypothalamic suprachiasmatic nucleus (SCN) influence.[110]

Beyond neurological and behavioral disorders, the orexin system may impact reproductive health and cancer. Structural receptor similarities suggest orexin may interact with RF-amide peptide systems, known for their roles in inhibiting cancer metastasis and regulating gonadal axis metabolism. The rhythmic activity of these peptides possibly extends to orexin modulation, either directly or through intermediate pathways.

Finally, dysfunctions of the orexin network have been documented in major neuropsychiatric, neuroinflammatory, and neurodegenerative diseases like schizophrenia, Parkinson's, Alzheimer's, Huntington's diseases, multiple sclerosis, and amyotrophic lateral sclerosis. In these diseases, widespread neural network damage occurs, but the orexin system's limited neuron number and localized brain region make it especially vulnerable. Consequently, orexin network failure contributes to characteristic symptoms across these conditions, including sleep disturbances, motor dysfunction, and affective instability.

Overall, the orexin/hypocretin system is a fundamental regulator whose dysfunction plays a considerable role in a broad range of human pathologies. With its pivotal influence on arousal, metabolism, behavior, and neuroprotection, this system offers promising avenues for understanding disease mechanisms and developing targeted therapies.

“Encouraging Advances in Orexin-Based Medicine: From Research to Real-World Treatments"

One major challenge in developing drugs for the brain is the blood-brain barrier (BBB), which prevents most molecules, especially larger or less lipid-soluble ones, from entering the central nervous system from the blood. Many promising neuropeptide-based compounds—despite having excellent biochemical properties like strong receptor affinity or stability—fail to cross this barrier effectively. Only specialized brain areas such as the lamina cribrosa and circumventricular organs naturally allow peptides access to cerebrospinal fluid, and in many cases, advanced delivery systems like liposomes and nanoparticles are required to transport drugs through the BBB.[112]

However, orexin peptides (orexin-A and Orexin-B) and some of their synthetic analogs are unique in their ability to cross the BBB freely. This distinct property has made orexin receptor ligands particularly successful candidates in pharmacology. Indeed, several orexin receptor antagonists, designed to regulate the sleep–wake cycle, have already been approved by the FDA for treating insomnia, demonstrating strong clinical efficacy.[113]

Research is also ongoing into orexin antagonists for other conditions, including panic disorder, major depressive disorder, anxiety, and binge eating. Additionally, orexin receptor agonists are being tested in clinical trials as potential treatments for narcolepsy.

The ability of orexin ligands to bypass the BBB naturally or through clever chemical designs makes them valuable in brain therapeutics. It removes a critical pharmacokinetic roadblock faced by many neuropeptide drugs, enabling them to exert desired effects in the brain more efficiently. This characteristic positions orexin receptor ligands at the forefront of neuropharmacology and translational medicine for central nervous system disorders.

Orexin Analog Class	**Therapeutic Indication**	**Clinical Trial Phase**
OX2R Agonists	Narcolepsy	Phase II
OX2R Antagonists	Major Depressive Disorder (MDD)	Phase III
Dual Orexin Receptor Antagonists (DORAs)	Insomnia	Approved (e.g., Suvorexant, Lemborexant)
OX1R Antagonists	Binge Eating Disorder	Phase II
OX1R Antagonists	Panic Disorder, MDD, Anxiety	Phase II

Table 2: *summarizes the developmental stages of various orexin receptor ligands targeting distinct human disorders. OX2 receptor agonists aim to restore orexin signaling in narcolepsy patients, currently in mid-stage clinical trials. OX2 receptor antagonists are being evaluated for efficacy in major depressive disorder. Approved dual antagonists, including suvorexant and lemborexant, are in clinical use for insomnia, modulating both OX1 and OX2 receptors. Selective OX1 receptor antagonists are undergoing trials for binge eating and anxiety-related disorders such as panic and depression, demonstrating the broad therapeutic potential of orexin system modulation.*

In neuroendocrine research, one of the most exciting goals is to develop orexin-derived compounds that can help correct sleep-wake disturbances seen in neurodegenerative diseases like Alzheimer's and Parkinson's. These compounds could revolutionize supportive care, as traditional sleep aids tend to depress brain function, possibly worsening symptoms in already compromised nervous systems.[114] Because of this, current and future orexin derivatives rank among the most promising and advanced therapies in neuropeptide drug development.

Additionally, non-invasive brain stimulation methods such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) are emerging as potential therapeutic tools. These methods target localized brain regions where orexin neurons reside, offering an opportunity to alleviate symptoms linked to orexin dysfunction. Conditions such as narcolepsy, cluster headaches, and various mood and cognitive disorders might benefit from such innovative approaches.[115]

This progress in both pharmaceutics and neuromodulation highlights orexin system modulation as a powerful frontier in treating neurological and psychiatric disorders with fewer side effects and better efficacy compared to conventional therapies. Ongoing studies deepen our understanding and bring hope for improved quality of life for patients afflicted with complex brain disorders.

Discussion:

Orexin, also known as hypocretin, is a neuropeptide system crucially involved in regulating a broad range of physiological processes including food intake, metabolism, the hypothalamic-pituitary-adrenal (HPA) axis, reproductive functions, and various behaviors. Initially, orexins were primarily studied for their role in feeding stimulation and energy expenditure. However, ongoing research has revealed their extensive involvement in homeostatic functions such as thermogenesis, heat dissipation, and importantly, the regulation of arousal and sleep-wake transitions.[116]

The orexin neurons are located exclusively in the hypothalamus but project widely across the brain, engaging target regions responsible for maintaining wakefulness, including monoaminergic centers like the locus coeruleus and the tuberomammillary nucleus. These neurons activate multiple neurotransmitter systems and facilitate neural excitability, thereby promoting a stable wakeful state and preventing unwanted sleep episodes. Research using optogenetics has demonstrated that selective activation of orexin neurons triggers transitions from sleep to wakefulness, highlighting their critical role in arousal regulation.[117]

Moreover, orexins have a multidimensional role beyond arousal, impacting emotional regulation, stress responses, anxiety, fear, and reward processing. Orexinergic modulation of limbic and cortical circuits contributes to adaptive responses to environmental stimuli, including reinforcing behavioral changes in addiction and pain perception. This complex neurochemical communication underscores orexin’s influence in both physiological homeostasis and behavioral adaptation.

Dysfunctions in the orexin system have been associated with a variety of human diseases. Loss of orexin neurons leads to narcolepsy, characterized by excessive daytime sleepiness and cataplexy. Orexin alterations have also been implicated in obesity, anxiety disorders, mood fluctuations, cognitive impairments, and several neuropsychiatric conditions. Furthermore, orexin’s regulatory role in addiction and pain pathways highlights its potential as a pharmacological target for treating substance abuse disorders and chronic pain syndromes.[118]

The intrinsic complexity of orexin signaling, involving multiple receptor subtypes (OX1R and OX2R) and interactions with other neuropeptides and neurotransmitters, presents both challenges and opportunities for therapeutic development. While preclinical findings have advanced our understanding substantially, translating these insights into safe, selective, and effective drugs requires further research into orexin’s molecular mechanisms and in vivo functions.

Several orexin receptor ligands have reached clinical development, demonstrating promising efficacy and safety profiles in managing sleep disorders, depression, anxiety, and eating disorders. Dual orexin receptor antagonists, now approved to treat insomnia, exemplify this progress. Ongoing development of selective orexin agonists and antagonists reflects their potential across a spectrum of CNS and metabolic disorders.[119]

This comprehensive review integrates diverse data on orexin physiology and pharmacology, contributing to a better understanding of its role in health and disease. It addresses existing knowledge gaps and encourages continued investigation into orexin's therapeutic applications. Given orexin's pivotal roles, advancing this field holds promise for improved treatments benefiting millions affected by sleep disruptions, mood disorders, metabolic syndromes, and addiction, marking it as a vital frontier in neuroscience and medicine.[120]

Conclusion:

This review, adopting an interdisciplinary perspective, advances our comprehension of the orexin/hypocretin neuropeptide family and its expanding therapeutic potential. Orexins are involved in critical physiological processes such as feeding behavior, energy homeostasis, thermoregulation, cognitive functions, stress response, anxiety, and arousal regulation. These multifaceted roles position the orexin system as a promising target for treating diverse disorders including sleep disturbances, obesity, addiction, and anxiety.

Despite significant progress, there remain theoretical and methodological challenges, notably the development of orexin receptor agonists and antagonists exhibiting superior selectivity and efficacy. Advances in drug delivery systems targeting the orexin system are essential to enhance therapeutic precision and minimize off-target effects. Further research is also warranted to unravel the complex interactions between orexins and other physiological systems such as the immune system and circadian regulation, which could inform novel therapeutic strategies.[121]

Promisingly, several orexin receptor antagonists have gained regulatory approval for insomnia treatment, and ongoing clinical trials investigate their utility in mood disorders, binge eating, and narcolepsy. As orexin ligands possess the ability to cross the blood-brain barrier, they circumvent a major pharmacokinetic obstacle limiting many neuropeptide drugs.

This comprehensive synthesis of existing preclinical and clinical research underscores the orexin system's translational significance. Understanding its integrative role in neurobiology and behavior opens pathways for identifying innovative drug targets and designing pharmacological interventions.[122] Overall, continued exploration of orexin physiology and pharmacology holds substantial promise for advancing treatments that improve patient outcomes across neurological, metabolic, and psychiatric domains. This review aims to serve as a foundation for future investigations and therapeutic developments targeting the orexinergic system.

Funding: Self-Funding

Conflict of Interest: The author declares no conflict of Interest with any person or organization.

Abbreviations:

ACTH adrenocorticotropic hormone

ALS amyotrophic lateral sclerosis

ARAS ascending reticular activation system

ARC arcuate nucleus

BAT brown adipose tissue

BBB blood–brain barrier

BNST bed nucleus of stria terminalis

CeA central amygdala

CCK cholecystokinin

CNS central nervous system

CSF cerebrospinal fluid

CRH corticotrophic-releasing hormone

DMH dorsomedial hypothalamus

DR dorsal raphe

FDA the Food and Drug Administration

GABA γ

-amino-butyric-acid

GAS general adaptation syndrome

GPCRs G-protein-coupled receptors

HPA hypothalamic–pituitary–adrenal cortex

HPG hypothalamic–pituitary–gonadal axis

IC insular cortex

LA lateral amygdala

LC locus coeruleus

LDT lateral dorsal tegmental nuclei

LHA lateral hypothalamic area

MCH melanin-concentrating hormone

MDD major depressive disorder

MnPO median preoptic nucleus

MPO medial preoptic nucleus

MS multiple sclerosis

MT mesopontine tegmentum

MTL medial temporal lobe

NAc nucleus accumbens

NIBS non-invasive brain stimulation techniques

NK neurokinin

NM neuromedin

NMS neuromedin S

NPY neuropeptide Y

NST nucleus of the solitary tract

NT neurotensin

OVLT organum vasculosum laminae terminalis

OX1R orexin-1 receptor

OX2R orexin-2 receptor

OXR orexin receptor

PAG periaqueductal gray

PCOS polycystic ovary syndrome

PFA perifornical area

PFC prefrontal cortex

POMC pro-opiomelanocortin

PON preoptic nucleus

PPT pedunculopontine tegmental nucleus

PVN paraventricular nuclei

RVLM rostral ventrolateral medulla

RVMM rostral ventromedial medulla

SA sympathoadrenal

SCN suprachiasmatic nucleus

SON supraoptic nucleus

tDCS transcranial direct current stimulation

TMs transcranial magnetic stimulation

TMN tuberomammillary nucleus

VMH ventromedial hypothalamus

VTA ventral tegmental area

VLPO ventrolateral preoptic nucleus

References:

1. Soya, S.; Sakurai, T. Evolution of Orexin Neuropeptide System: Structure and Function. *Front. Neurosci.* 2020, *14*, 691. [Google Scholar] [CrossRef] [PubMed]
2. Sakurai, T.; Amemiya, A.; Ishii, M.; Matsuzaki, I.; Chemelli, R.M.; Tanaka, H.; Williams, S.C.; Richardson, J.A.; Kozlowski, G.P.; Wilson, S.; et al. Orexins and orexin receptors: A family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior. *Cell* 1998, *92*, 573–585. [Google Scholar] [CrossRef] [PubMed]
3. de Lecea, L.; Kilduff, T.S.; Peyron, C.; Gao, X.; Foye, P.E.; Danielson, P.E.; Fukuhara, C.; Battenberg, E.L.; Gautvik, V.T.; Bartlett, F.S., 2nd; et al. The hypocretins: Hypothalamus-specific peptides with neuroexcitatory activity. *Proc. Natl. Acad. Sci. USA* 1998, *95*, 322–327. [Google Scholar] [CrossRef]
4. Peyron, C.; Tighe, D.K.; van den Pol, A.N.; de Lecea, L.; Heller, H.C.; Sutcliffe, J.G.; Kilduff, T.S. Neurons containing hypocretin (orexin) project to multiple neuronal systems. *J. Neurosci.* 1998, *18*, 9996–10015. [Google Scholar] [CrossRef] [PubMed]
5. Bittencourt, J.C.; Presse, F.; Arias, C.; Peto, C.; Vaughan, J.; Nahon, J.L.; Vale, W.; Sawchenko, P.E. The melanin-concentrating hormone system of the rat brain: An immuno- and hybridization histochemical characterization. *J. Comp. Neurol.* 1992, *319*, 218–245. [Google Scholar] [CrossRef]
6. Lopez-Lopez, C.; Dietrich, M.O.; Metzger, F.; Loetscher, H.; Torres-Aleman, I. Disturbed cross talk between insulin-like growth factor I and AMP-activated protein kinase as a possible cause of vascular dysfunction in the amyloid precursor protein/presenilin 2 mouse model of Alzheimer's disease. *J. Neurosci.* 2007, *27*, 824–831. [Google Scholar] [CrossRef]
7. Couvineau, A.; Nicole, P.; Gratio, V.; Voisin, T. The Orexin receptors: Structural and anti-tumoral properties. *Front. Endocrinol.* 2022, *13*, 931970. [Google Scholar] [CrossRef]
8. Kastin, A.J.; Akerstrom, V. Orexin A but not orexin B rapidly enters brain from blood by simple diffusion. *J. Pharmacol. Exp. Ther.* 1999, *289*, 219–223. [Google Scholar]
9. Sutcliffe, J.G.; de Lecea, L. The hypocretins: Excitatory neuromodulatory peptides for multiple homeostatic systems, including sleep and feeding. *J. Neurosci. Res.* 2000, *62*, 161–168. [Google Scholar] [CrossRef]
10. Wang, C.; Wang, Q.; Ji, B.; Pan, Y.; Xu, C.; Cheng, B.; Bai, B.; Chen, J. The Orexin/Receptor System: Molecular Mechanism and Therapeutic Potential for Neurological Diseases. *Front. Mol. Neurosci.* 2018, *11*, 220. [Google Scholar] [CrossRef]
11. Carrive, P. Orexin, orexin receptor antagonists and central cardiovascular control. Front. Neurosci. 2013, 7, 257. [Google Scholar] [CrossRef] [PubMed]

12. Soya, S.; Takahashi, T.M.; McHugh, T.J.; Maejima, T.; Herlitze, S.; Abe, M.; Sakimura, K.; Sakurai, T. Orexin modulates behavioral fear expression through the locus coeruleus. Nat. Commun. 2017, 8, 1606. [Google Scholar] [CrossRef]

13. Baimel, C.; Bartlett, S.E.; Chiou, L.C.; Lawrence, A.J.; Muschamp, J.W.; Patkar, O.; Tung, L.W.; Borgland, S.L. Orexin/hypocretin role in reward: Implications for opioid and other addictions. Br. J. Pharmacol. 2015, 172, 334–348. [Google Scholar] [CrossRef]

14. Becker-Krail, D.D.; Walker, W.H., 2nd; Nelson, R.J. The Ventral Tegmental Area and Nucleus Accumbens as Circadian Oscillators: Implications for Drug Abuse and Substance Use Disorders. Front. Physiol. 2022, 13, 886704. [Google Scholar] [CrossRef] [PubMed]

15. Samson, W.K.; Taylor, M.M.; Follwell, M.; Ferguson, A.V. Orexin actions in hypothalamic paraventricular nucleus: Physiological consequences and cellular correlates. Regul. Pept. 2002, 104, 97–103. [Google Scholar] [CrossRef] [PubMed]

16. Holland, P.; Goadsby, P.J. The hypothalamic orexinergic system: Pain and primary headaches. Headache 2007, 47, 951–962. [Google Scholar] [CrossRef]

17. Hoffmann, J.; May, A. Diagnosis, pathophysiology, and management of cluster headache. Lancet Neurol. 2018, 17, 75–83. [Google Scholar] [CrossRef]

18. Villano, I.; La Marra, M.; Di Maio, G.; Monda, V.; Chieffi, S.; Guatteo, E.; Messina, G.; Moscatelli, F.; Monda, M.; Messina, A. Physiological Role of Orexinergic System for Health. Int. J. Environ. Res. Public. Health 2022, 19, 8353. [Google Scholar] [CrossRef]

19. Vaseghi, S.; Zarrabian, S.; Haghparast, A. Reviewing the role of the orexinergic system and stressors in modulating mood and reward-related behaviors. Neurosci. Biobehav. Rev. 2022, 133, 104516. [Google Scholar] [CrossRef] [PubMed]

20. Melmed, S.; Auchus, R.J.; Goldfine, A.B.; Koenig, R.J.; Rosen, C.J. Williams Textbook of Endocrinology, 14th ed.; Elsevier: Philadelphia, PA, USA, 2020. [Google Scholar]

21. Cannon, W.B. The emergency function of the adrenal medulla in pain and the major emotions. Am. J. Physiol.-Leg. Content 1914, 33, 356–372. [Google Scholar] [CrossRef]

22. Selye, H. A Syndrome produced by Diverse Nocuous Agents. Nature 1936, 138, 32. [Google Scholar] [CrossRef]

23. Wade, N. Guillemin and schally: A race spurred by rivalry. Science 1978, 200, 510–513. [Google Scholar] [CrossRef] [PubMed]

24. Vale, W.; Spiess, J.; Rivier, C.; Rivier, J. Characterization of a 41-residue ovine hypothalamic peptide that stimulates secretion of corticotropin and beta-endorphin. Science 1981, 213, 1394–1397. [Google Scholar] [CrossRef] [PubMed]

25. Selye, H. The general adaptation syndrome and the diseases of adaptation. J. Allergy 1946, 17, 231. [Google Scholar] [CrossRef] [PubMed]

26. Bujdoso, E.; Jaszberenyi, M.; Tomboly, C.; Toth, G.; Telegdy, G. Behavioral and neuroendocrine actions of endomorphin-2. Peptides 2001, 22, 1459–1463. [Google Scholar] [CrossRef]

27. Carrive, P. Orexin, orexin receptor antagonists and central cardiovascular control. Front. Neurosci. 2013, 7, 257. [Google Scholar] [CrossRef] [PubMed]

28. Soya, S.; Takahashi, T.M.; McHugh, T.J.; Maejima, T.; Herlitze, S.; Abe, M.; Sakimura, K.; Sakurai, T. Orexin modulates behavioral fear expression through the locus coeruleus. Nat. Commun. 2017, 8, 1606. [Google Scholar] [CrossRef]

29. Baimel, C.; Bartlett, S.E.; Chiou, L.C.; Lawrence, A.J.; Muschamp, J.W.; Patkar, O.; Tung, L.W.; Borgland, S.L. Orexin/hypocretin role in reward: Implications for opioid and other addictions. Br. J. Pharmacol. 2015, 172, 334–348. [Google Scholar] [CrossRef]

30. Becker-Krail, D.D.; Walker, W.H., 2nd; Nelson, R.J. The Ventral Tegmental Area and Nucleus Accumbens as Circadian Oscillators: Implications for Drug Abuse and Substance Use Disorders. Front. Physiol. 2022, 13, 886704. [Google Scholar] [CrossRef] [PubMed]

31. Samson, W.K.; Taylor, M.M.; Follwell, M.; Ferguson, A.V. Orexin actions in hypothalamic paraventricular nucleus: Physiological consequences and cellular correlates. Regul. Pept. 2002, 104, 97–103. [Google Scholar] [CrossRef] [PubMed]

32. Holland, P.; Goadsby, P.J. The hypothalamic orexinergic system: Pain and primary headaches. Headache 2007, 47, 951–962. [Google Scholar] [CrossRef]

33. Hoffmann, J.; May, A. Diagnosis, pathophysiology, and management of cluster headache. Lancet Neurol. 2018, 17, 75–83. [Google Scholar] [CrossRef]

34. Villano, I.; La Marra, M.; Di Maio, G.; Monda, V.; Chieffi, S.; Guatteo, E.; Messina, G.; Moscatelli, F.; Monda, M.; Messina, A. Physiological Role of Orexinergic System for Health. Int. J. Environ. Res. Public. Health 2022, 19, 8353. [Google Scholar] [CrossRef]

35. Vaseghi, S.; Zarrabian, S.; Haghparast, A. Reviewing the role of the orexinergic system and stressors in modulating mood and reward-related behaviors. Neurosci. Biobehav. Rev. 2022, 133, 104516. [Google Scholar] [CrossRef] [PubMed]

36. Melmed, S.; Auchus, R.J.; Goldfine, A.B.; Koenig, R.J.; Rosen, C.J. Williams Textbook of Endocrinology, 14th ed.; Elsevier: Philadelphia, PA, USA, 2020. [Google Scholar]

37. Cannon, W.B. The emergency function of the adrenal medulla in pain and the major emotions. Am. J. Physiol.-Leg. Content 1914, 33, 356–372. [Google Scholar] [CrossRef]

38. Selye, H. A Syndrome produced by Diverse Nocuous Agents. Nature 1936, 138, 32. [Google Scholar] [CrossRef]

39. Wade, N. Guillemin and schally: A race spurred by rivalry. Science 1978, 200, 510–513. [Google Scholar] [CrossRef] [PubMed]

40. Vale, W.; Spiess, J.; Rivier, C.; Rivier, J. Characterization of a 41-residue ovine hypothalamic peptide that stimulates secretion of corticotropin and beta-endorphin. Science 1981, 213, 1394–1397. [Google Scholar] [CrossRef] [PubMed]

41. Selye, H. The general adaptation syndrome and the diseases of adaptation. J. Allergy 1946, 17, 231. [Google Scholar] [CrossRef] [PubMed]

42. Bujdoso, E.; Jaszberenyi, M.; Tomboly, C.; Toth, G.; Telegdy, G. Behavioral and neuroendocrine actions of endomorphin-2. Peptides 2001, 22, 1459–1463. [Google Scholar] [CrossRef]

43. Carrive, P. Orexin, orexin receptor antagonists and central cardiovascular control. Front. Neurosci. 2013, 7, 257. [Google Scholar] [CrossRef] [PubMed]

44. Soya, S.; Takahashi, T.M.; McHugh, T.J.; Maejima, T.; Herlitze, S.; Abe, M.; Sakimura, K.; Sakurai, T. Orexin modulates behavioral fear expression through the locus coeruleus. Nat. Commun. 2017, 8, 1606. [Google Scholar] [CrossRef]

45. Baimel, C.; Bartlett, S.E.; Chiou, L.C.; Lawrence, A.J.; Muschamp, J.W.; Patkar, O.; Tung, L.W.; Borgland, S.L. Orexin/hypocretin role in reward: Implications for opioid and other addictions. Br. J. Pharmacol. 2015, 172, 334–348. [Google Scholar] [CrossRef]

46. Becker-Krail, D.D.; Walker, W.H., 2nd; Nelson, R.J. The Ventral Tegmental Area and Nucleus Accumbens as Circadian Oscillators: Implications for Drug Abuse and Substance Use Disorders. Front. Physiol. 2022, 13, 886704. [Google Scholar] [CrossRef] [PubMed]

47. Samson, W.K.; Taylor, M.M.; Follwell, M.; Ferguson, A.V. Orexin actions in hypothalamic paraventricular nucleus: Physiological consequences and cellular correlates. Regul. Pept. 2002, 104, 97–103. [Google Scholar] [CrossRef] [PubMed]

48. Holland, P.; Goadsby, P.J. The hypothalamic orexinergic system: Pain and primary headaches. Headache 2007, 47, 951–962. [Google Scholar] [CrossRef]

49. Hoffmann, J.; May, A. Diagnosis, pathophysiology, and management of cluster headache. Lancet Neurol. 2018, 17, 75–83. [Google Scholar] [CrossRef]

50. Villano, I.; La Marra, M.; Di Maio, G.; Monda, V.; Chieffi, S.; Guatteo, E.; Messina, G.; Moscatelli, F.; Monda, M.; Messina, A. Physiological Role of Orexinergic System for Health. Int. J. Environ. Res. Public. Health 2022, 19, 8353. [Google Scholar] [CrossRef]

51. Vaseghi, S.; Zarrabian, S.; Haghparast, A. Reviewing the role of the orexinergic system and stressors in modulating mood and reward-related behaviors. Neurosci. Biobehav. Rev. 2022, 133, 104516. [Google Scholar] [CrossRef] [PubMed]

52. Melmed, S.; Auchus, R.J.; Goldfine, A.B.; Koenig, R.J.; Rosen, C.J. Williams Textbook of Endocrinology, 14th ed.; Elsevier: Philadelphia, PA, USA, 2020. [Google Scholar]

53. Cannon, W.B. The emergency function of the adrenal medulla in pain and the major emotions. Am. J. Physiol.-Leg. Content 1914, 33, 356–372. [Google Scholar] [CrossRef]

54. Selye, H. A Syndrome produced by Diverse Nocuous Agents. Nature 1936, 138, 32. [Google Scholar] [CrossRef]

55. Wade, N. Guillemin and schally: A race spurred by rivalry. Science 1978, 200, 510–513. [Google Scholar] [CrossRef] [PubMed]

56. Vale, W.; Spiess, J.; Rivier, C.; Rivier, J. Characterization of a 41-residue ovine hypothalamic peptide that stimulates secretion of corticotropin and beta-endorphin. Science 1981, 213, 1394–1397. [Google Scholar] [CrossRef] [PubMed]

57. Selye, H. The general adaptation syndrome and the diseases of adaptation. J. Allergy 1946, 17, 231. [Google Scholar] [CrossRef] [PubMed]

58. Bujdoso, E.; Jaszberenyi, M.; Tomboly, C.; Toth, G.; Telegdy, G. Behavioral and neuroendocrine actions of endomorphin-2. Peptides 2001, 22, 1459–1463. [Google Scholar] [CrossRef]

59. Carrive, P. Orexin, orexin receptor antagonists and central cardiovascular control. Front. Neurosci. 2013, 7, 257. [Google Scholar] [CrossRef] [PubMed]

60. Soya, S.; Takahashi, T.M.; McHugh, T.J.; Maejima, T.; Herlitze, S.; Abe, M.; Sakimura, K.; Sakurai, T. Orexin modulates behavioral fear expression through the locus coeruleus. Nat. Commun. 2017, 8, 1606. [Google Scholar] [CrossRef]

61. Baimel, C.; Bartlett, S.E.; Chiou, L.C.; Lawrence, A.J.; Muschamp, J.W.; Patkar, O.; Tung, L.W.; Borgland, S.L. Orexin/hypocretin role in reward: Implications for opioid and other addictions. Br. J. Pharmacol. 2015, 172, 334–348. [Google Scholar] [CrossRef]

62. Becker-Krail, D.D.; Walker, W.H., 2nd; Nelson, R.J. The Ventral Tegmental Area and Nucleus Accumbens as Circadian Oscillators: Implications for Drug Abuse and Substance Use Disorders. Front. Physiol. 2022, 13, 886704. [Google Scholar] [CrossRef] [PubMed]

63. Samson, W.K.; Taylor, M.M.; Follwell, M.; Ferguson, A.V. Orexin actions in hypothalamic paraventricular nucleus: Physiological consequences and cellular correlates. Regul. Pept. 2002, 104, 97–103. [Google Scholar] [CrossRef] [PubMed]

64. Holland, P.; Goadsby, P.J. The hypothalamic orexinergic system: Pain and primary headaches. Headache 2007, 47, 951–962. [Google Scholar] [CrossRef]

65. Hoffmann, J.; May, A. Diagnosis, pathophysiology, and management of cluster headache. Lancet Neurol. 2018, 17, 75–83. [Google Scholar] [CrossRef]

66. Villano, I.; La Marra, M.; Di Maio, G.; Monda, V.; Chieffi, S.; Guatteo, E.; Messina, G.; Moscatelli, F.; Monda, M.; Messina, A. Physiological Role of Orexinergic System for Health. Int. J. Environ. Res. Public. Health 2022, 19, 8353. [Google Scholar] [CrossRef]

67. Vaseghi, S.; Zarrabian, S.; Haghparast, A. Reviewing the role of the orexinergic system and stressors in modulating mood and reward-related behaviors. Neurosci. Biobehav. Rev. 2022, 133, 104516. [Google Scholar] [CrossRef] [PubMed]

68. Melmed, S.; Auchus, R.J.; Goldfine, A.B.; Koenig, R.J.; Rosen, C.J. Williams Textbook of Endocrinology, 14th ed.; Elsevier: Philadelphia, PA, USA, 2020. [Google Scholar]

69. Cannon, W.B. The emergency function of the adrenal medulla in pain and the major emotions. Am. J. Physiol.-Leg. Content 1914, 33, 356–372. [Google Scholar] [CrossRef]

70. Selye, H. A Syndrome produced by Diverse Nocuous Agents. Nature 1936, 138, 32. [Google Scholar] [CrossRef]

71. Wade, N. Guillemin and schally: A race spurred by rivalry. Science 1978, 200, 510–513. [Google Scholar] [CrossRef] [PubMed]

72. Vale, W.; Spiess, J.; Rivier, C.; Rivier, J. Characterization of a 41-residue ovine hypothalamic peptide that stimulates secretion of corticotropin and beta-endorphin. Science 1981, 213, 1394–1397. [Google Scholar] [CrossRef] [PubMed]

73. Selye, H. The general adaptation syndrome and the diseases of adaptation. J. Allergy 1946, 17, 231. [Google Scholar] [CrossRef] [PubMed]

74. Bujdoso, E.; Jaszberenyi, M.; Tomboly, C.; Toth, G.; Telegdy, G. Behavioral and neuroendocrine actions of endomorphin-2. Peptides 2001, 22, 1459–1463. [Google Scholar] [CrossRef]

75. Carrive, P. Orexin, orexin receptor antagonists and central cardiovascular control. Front. Neurosci. 2013, 7, 257. [Google Scholar] [CrossRef] [PubMed]

76. Soya, S.; Takahashi, T.M.; McHugh, T.J.; Maejima, T.; Herlitze, S.; Abe, M.; Sakimura, K.; Sakurai, T. Orexin modulates behavioral fear expression through the locus coeruleus. Nat. Commun. 2017, 8, 1606. [Google Scholar] [CrossRef]

77. Baimel, C.; Bartlett, S.E.; Chiou, L.C.; Lawrence, A.J.; Muschamp, J.W.; Patkar, O.; Tung, L.W.; Borgland, S.L. Orexin/hypocretin role in reward: Implications for opioid and other addictions. Br. J. Pharmacol. 2015, 172, 334–348. [Google Scholar] [CrossRef]

78. Becker-Krail, D.D.; Walker, W.H., 2nd; Nelson, R.J. The Ventral Tegmental Area and Nucleus Accumbens as Circadian Oscillators: Implications for Drug Abuse and Substance Use Disorders. Front. Physiol. 2022, 13, 886704. [Google Scholar] [CrossRef] [PubMed]

79. Samson, W.K.; Taylor, M.M.; Follwell, M.; Ferguson, A.V. Orexin actions in hypothalamic paraventricular nucleus: Physiological consequences and cellular correlates. Regul. Pept. 2002, 104, 97–103. [Google Scholar] [CrossRef] [PubMed]

80. Holland, P.; Goadsby, P.J. The hypothalamic orexinergic system: Pain and primary headaches. Headache 2007, 47, 951–962. [Google Scholar] [CrossRef]

81. Hoffmann, J.; May, A. Diagnosis, pathophysiology, and management of cluster headache. Lancet Neurol. 2018, 17, 75–83. [Google Scholar] [CrossRef]

82. Villano, I.; La Marra, M.; Di Maio, G.; Monda, V.; Chieffi, S.; Guatteo, E.; Messina, G.; Moscatelli, F.; Monda, M.; Messina, A. Physiological Role of Orexinergic System for Health. Int. J. Environ. Res. Public. Health 2022, 19, 8353. [Google Scholar] [CrossRef]

83. Vaseghi, S.; Zarrabian, S.; Haghparast, A. Reviewing the role of the orexinergic system and stressors in modulating mood and reward-related behaviors. Neurosci. Biobehav. Rev. 2022, 133, 104516. [Google Scholar] [CrossRef] [PubMed]

84. Melmed, S.; Auchus, R.J.; Goldfine, A.B.; Koenig, R.J.; Rosen, C.J. Williams Textbook of Endocrinology, 14th ed.; Elsevier: Philadelphia, PA, USA, 2020. [Google Scholar]

85. Cannon, W.B. The emergency function of the adrenal medulla in pain and the major emotions. Am. J. Physiol.-Leg. Content 1914, 33, 356–372. [Google Scholar] [CrossRef]

86. Selye, H. A Syndrome produced by Diverse Nocuous Agents. Nature 1936, 138, 32. [Google Scholar] [CrossRef]

87. Wade, N. Guillemin and schally: A race spurred by rivalry. Science 1978, 200, 510–513. [Google Scholar] [CrossRef] [PubMed]

88. Vale, W.; Spiess, J.; Rivier, C.; Rivier, J. Characterization of a 41-residue ovine hypothalamic peptide that stimulates secretion of corticotropin and beta-endorphin. Science 1981, 213, 1394–1397. [Google Scholar] [CrossRef] [PubMed]

89. Selye, H. The general adaptation syndrome and the diseases of adaptation. J. Allergy 1946, 17, 231. [Google Scholar] [CrossRef] [PubMed]

90. Bujdoso, E.; Jaszberenyi, M.; Tomboly, C.; Toth, G.; Telegdy, G. Behavioral and neuroendocrine actions of endomorphin-2. Peptides 2001, 22, 1459–1463. [Google Scholar] [CrossRef]

91. Carrive, P. Orexin, orexin receptor antagonists and central cardiovascular control. Front. Neurosci. 2013, 7, 257. [Google Scholar] [CrossRef] [PubMed]

92. Soya, S.; Takahashi, T.M.; McHugh, T.J.; Maejima, T.; Herlitze, S.; Abe, M.; Sakimura, K.; Sakurai, T. Orexin modulates behavioral fear expression through the locus coeruleus. Nat. Commun. 2017, 8, 1606. [Google Scholar] [CrossRef]

93. Baimel, C.; Bartlett, S.E.; Chiou, L.C.; Lawrence, A.J.; Muschamp, J.W.; Patkar, O.; Tung, L.W.; Borgland, S.L. Orexin/hypocretin role in reward: Implications for opioid

and other addictions. Br. J. Pharmacol. 2015, 172, 334–348. [Google Scholar] [CrossRef]

94. Becker-Krail, D.D.; Walker, W.H., 2nd; Nelson, R.J. The Ventral Tegmental Area and Nucleus Accumbens as Circadian Oscillators: Implications for Drug Abuse and Substance Use Disorders. Front. Physiol. 2022, 13, 886704. [Google Scholar] [CrossRef] [PubMed]

95. Samson, W.K.; Taylor, M.M.; Follwell, M.; Ferguson, A.V. Orexin actions in hypothalamic paraventricular nucleus: Physiological consequences and cellular correlates. Regul. Pept. 2002, 104, 97–103. [Google Scholar] [CrossRef] [PubMed]

96. Holland, P.; Goadsby, P.J. The hypothalamic orexinergic system: Pain and primary headaches. Headache 2007, 47, 951–962. [Google Scholar] [CrossRef]

97. Hoffmann, J.; May, A. Diagnosis, pathophysiology, and management of cluster headache. Lancet Neurol. 2018, 17, 75–83. [Google Scholar] [CrossRef]

98. Villano, I.; La Marra, M.; Di Maio, G.; Monda, V.; Chieffi, S.; Guatteo, E.; Messina, G.; Moscatelli, F.; Monda, M.; Messina, A. Physiological Role of Orexinergic System for Health. Int. J. Environ. Res. Public. Health 2022, 19, 8353. [Google Scholar] [CrossRef]

99. Vaseghi, S.; Zarrabian, S.; Haghparast, A. Reviewing the role of the orexinergic system and stressors in modulating mood and reward-related behaviors. Neurosci. Biobehav. Rev. 2022, 133, 104516. [Google Scholar] [CrossRef] [PubMed]

100. Melmed, S.; Auchus, R.J.; Goldfine, A.B.; Koenig, R.J.; Rosen, C.J. Williams Textbook of Endocrinology, 14th ed.; Elsevier: Philadelphia, PA, USA, 2020. [Google Scholar]

101. Cannon, W.B. The emergency function of the adrenal medulla in pain and the major emotions. Am. J. Physiol.-Leg. Content 1914, 33, 356–372. [Google Scholar] [CrossRef]

102. Selye, H. A Syndrome produced by Diverse Nocuous Agents. Nature 1936, 138, 32. [Google Scholar] [CrossRef]

103. Wade, N. Guillemin and schally: A race spurred by rivalry. Science 1978, 200, 510–513. [Google Scholar] [CrossRef] [PubMed]

104. Vale, W.; Spiess, J.; Rivier, C.; Rivier, J. Characterization of a 41-residue ovine hypothalamic peptide that stimulates secretion of corticotropin and beta-endorphin. Science 1981, 213, 1394–1397. [Google Scholar] [CrossRef] [PubMed]

105. Selye, H. The general adaptation syndrome and the diseases of adaptation. J. Allergy 1946, 17, 231. [Google Scholar] [CrossRef] [PubMed]

106. Bujdoso, E.; Jaszberenyi, M.; Tomboly, C.; Toth, G.; Telegdy, G. Behavioral and neuroendocrine actions of endomorphin-2. Peptides 2001, 22, 1459–1463. [Google Scholar] [CrossRef]

107. Carrive, P. Orexin, orexin receptor antagonists and central cardiovascular control. Front. Neurosci. 2013, 7, 257. [Google Scholar] [CrossRef] [PubMed]

108. Soya, S.; Takahashi, T.M.; McHugh, T.J.; Maejima, T.; Herlitze, S.; Abe, M.; Sakimura, K.; Sakurai, T. Orexin modulates behavioral fear expression through the locus coeruleus. Nat. Commun. 2017, 8, 1606. [Google Scholar] [CrossRef]

109. Baimel, C.; Bartlett, S.E.; Chiou, L.C.; Lawrence, A.J.; Muschamp, J.W.; Patkar, O.; Tung, L.W.; Borgland, S.L. Orexin/hypocretin role in reward: Implications for opioid and other addictions. Br. J. Pharmacol. 2015, 172, 334–348. [Google Scholar] [CrossRef]

110. Becker-Krail, D.D.; Walker, W.H., 2nd; Nelson, R.J. The Ventral Tegmental Area and Nucleus Accumbens as Circadian Oscillators: Implications for Drug Abuse and Substance Use Disorders. Front. Physiol. 2022, 13, 886704. [Google Scholar] [CrossRef] [PubMed]

111. Samson, W.K.; Taylor, M.M.; Follwell, M.; Ferguson, A.V. Orexin actions in hypothalamic paraventricular nucleus: Physiological consequences and cellular correlates. Regul. Pept. 2002, 104, 97–103. [Google Scholar] [CrossRef] [PubMed]

112. Holland, P.; Goadsby, P.J. The hypothalamic orexinergic system: Pain and primary headaches. Headache 2007, 47, 951–962. [Google Scholar] [CrossRef]

113. Hoffmann, J.; May, A. Diagnosis, pathophysiology, and management of cluster headache. Lancet Neurol. 2018, 17, 75–83. [Google Scholar] [CrossRef]

114. Villano, I.; La Marra, M.; Di Maio, G.; Monda, V.; Chieffi, S.; Guatteo, E.; Messina, G.; Moscatelli, F.; Monda, M.; Messina, A. Physiological Role of Orexinergic System for Health. Int. J. Environ. Res. Public. Health 2022, 19, 8353. [Google Scholar] [CrossRef]

115. Vaseghi, S.; Zarrabian, S.; Haghparast, A. Reviewing the role of the orexinergic system and stressors in modulating mood and reward-related behaviors. Neurosci. Biobehav. Rev. 2022, 133, 104516. [Google Scholar] [CrossRef] [PubMed]

116. Melmed, S.; Auchus, R.J.; Goldfine, A.B.; Koenig, R.J.; Rosen, C.J. Williams Textbook of Endocrinology, 14th ed.; Elsevier: Philadelphia, PA, USA, 2020. [Google Scholar]

117. Cannon, W.B. The emergency function of the adrenal medulla in pain and the major emotions. Am. J. Physiol.-Leg. Content 1914, 33, 356–372. [Google Scholar] [CrossRef]

118. Selye, H. A Syndrome produced by Diverse Nocuous Agents. Nature 1936, 138, 32. [Google Scholar] [CrossRef]

119. Wade, N. Guillemin and schally: A race spurred by rivalry. Science 1978, 200, 510–513. [Google Scholar] [CrossRef] [PubMed]

120. Vale, W.; Spiess, J.; Rivier, C.; Rivier, J. Characterization of a 41-residue ovine hypothalamic peptide that stimulates secretion of corticotropin and beta-endorphin. Science 1981, 213, 1394–1397. [Google Scholar] [CrossRef] [PubMed]

121. Selye, H. The general adaptation syndrome and the diseases of adaptation. J. Allergy 1946, 17, 231. [Google Scholar] [CrossRef] [PubMed]

122. Bujdoso, E.; Jaszberenyi, M.; Tomboly, C.; Toth, G.; Telegdy, G. Behavioral and neuroendocrine actions of endomorphin-2. Peptides 2001, 22, 1459–1463. [Google Scholar] [CrossRef]