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Cancer symptom complexes related to alterations in molecular circadian axis signaling.

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Abstract: One of the most common symptoms in cancer patients is fatigue that is often associated with appetite loss and sleep disruption. Quality of life indices and objective measures of these symptoms are now possible and continue to improve our understanding of how these symptoms are caused. Disruption of 24hour rest/activity patterns measured by actigraphy is one example where there is overlap of the objective measurement of symptoms and the circadian axis. This paper reviews new data relevant to understanding mechanisms involving inhibition of the circadian system and the production of symptom complexes in cancer patients through hypothalamic signaling by tumor produced members of the epidermal growth factor receptor.

Cancer patients suffer from a range of physical, affective, and cognitive symptoms that are caused either directly or indirectly by the cancer itself or its treatment [1]. One common symptom cluster is fatigue, appetite loss, and sleep disruption whose causes are possibly multidimensional and that have remained frustratingly elusive. These symptoms would appear to have much in common with the circadian axis since fatigue can easily be understood as a dysregulation or loss of quality in 24 hour rest/activity patterns, and the symptoms of decreased food intake (appetite) and sleep disruption are major survival related activities occurring during the opposed light dark cycle on our planet.

Recent improvements in understanding of the design of the signaling network involved in the circadian axis sheds new light on the role of hypothalamic modulation of the output from the central clock [2]. One of the signaling mechanisms involved here is the epidermal growth receptor family (EGFR) that is also a critical player in cancer mechanisms of growth and proliferation [3,4,5]. This paper discusses recent data supporting the hypothesis that a symptom complex of fatigue, appetite loss and sleep disruption are related to EGFR signaling in the hypothalamic circadian network.

The human circadian timing system, described here in very simplified form, has three functional components. First, there are *signaling inputs* of which the most dominant is the timing of exposure to ambient light, perceived by specialized sensors in the eye and that results in changes in the neurophysiology of the central clock apparatus. The second component of the circadian timing system is the *central oscillator* (the clock) that produces electrophysiologic signals that arise from paired populations of neurons in the suprachiasmatic nuclei (SCN). In the SCN, specialized "core and shell" neurons produce an entrainable ~24 hour rhythm that is expressed in all mammals. Rhythm outputs are produced even in the absence of environmental cues (like that in deep cave isolation studies) that result in "free-running" behavior. Another unique feature of the central oscillations are their constant periodicity over a wide temperature range.

In order to better understand the mechanisms of clock behavior, ablation studies of the SCN have been correlated with behavioral and physiologic changes found in laboratory animals. SCN ablation can cause permanent loss of rhythmic rest/activity, core body temperature, feeding, and sleeping behavior patterns [6,7]. This experimentally induced loss of circadian rhythms can be restored by implantation of embryonic SCN tissue into the lesioned area, while circadian rhythms are only partially restored by encapsulated SCN preparations that prevent axonal connections but allow *diffusion of secreted factors*. Secreted messengers from the SCN have been identified with molecular biology techniques that have isolated SCN peptides that can act as diffusible factors [3]. When these molecules are infused into the third ventricle of a normal animal they inhibit circadian rhythms of core body temperature, eliminate running wheel activity, decrease feeding, and deregulate 24 hour sleep patterns. From over thirty SCN neural peptides identified and tested in this manner, *inhibitory activity* has been shown with Transforming Growth factor – alpha (TGF-a) , Epidermal growth factor (EGF) [3], and neruegulin-1 (NRG-1)[8], that are ligands of the EGFR family.

In addition to these diffusible signaling circuits, three major afferent fiber groups project from the SCN to the hypothalamus. These "hard wired" neural connections and the secreted factors mentioned above comprise the third component of the central circadian timing system and represent a complex *output network.* Through excitatory and inhibitory activity on the hypothalamus, these

connections comprise an output network that modulates the synchronized physiology of the organism. Activation or inhibition of hypothalamic centers facilitate specific behaviors that are associated with rhythmic patterns of arousal and sleep, core body temperature and appetite; through hypothalamic neuroendocrine centers they regulate secretion of reproductive, stress-axis, and physiology regulating hormones; and by effects on the parasympathetic and sympathetic autonomic centers in the brainstem they help maintain physiologic balance.

The concept of *hypothalamic modulation of circadian time structure* is based on studies where ablative lesions have been created in the downstream hypothalamic nuclei that affect circadian output [2,5]. For example, lesions to the subparaventricular zone, either at the dorsal or the ventral nuclei (dSPZ or vSPZ) produce diminished circadian rhythm in rest/activity, sleep, and core body temperature depending on which of these two nuclei are damaged. Other laboratory studies have shown that selective destruction of the hypothalamic dorsal medial nucleus (DMH) can interrupt SCN signal transmission and also results in disruption of circadian output. These laboratory studies show that circadian signaling from the SCN is regulated by these secondary and tertiary relays of the signals from the SCN to the hypothalamic downstream sites. In the human brain, functional loss can occur in a similar fashion to that seen with these laboratory hypothalamic ablation studies. Sleep and activity disturbances have been seen in post-viral illness patients described first by von Economo[2]. These patients have neuropathic behavior that correlates to histologic destruction of areas of the anterior hypothalamus near the junction of the brainstem and the forebrain at the location of circadian sleep-wake centers and not in the SCN.

An important consequence of this design feature is that modulation of circadian rhythms can take place downstream of a central oscillator. This signaling network is subject to other inputs from the brain's visceral, limbic, and cortical systems that act to modulate, amplify, or inhibit signaling of these hypothalamic behavioral centers that are driven by a circadian oscillator. For example, the drive to eat is a circadian regulated pathway that can be masked by the psycho-social inputs. This design feature also theoretically allows for signal inputs from outside the brain like neurally active cytokines or growth factors that arise in diseases like infection, cancer, etc. In these disease conditions modulation of circadian signaling in the hypothalamus could alter basic physiologic drive mechanisms and thus contribute to the production of symptoms clusters like those encountered in cancer patients.

Hypothalamic signaling mediated by ligands of EGFR has been suggested in humans in a study that showed elevated levels of TGF-a were associated with poor 24 hour rest activity patterns. In a retrospective analysis of 80 patients with metastatic colorectal cancer, tumor produced TGF-a found in the serum was shown to be significantly correlated with dampened 24 hour rest/activity patterns, the feeling of fatigue, and appetite loss [9]. These clinical data support the EGFR ligand hypothesis and are being verified with additional clinical studies. In summary, the available laboratory and clinical data support the hypothesis that the symptom complex of fatigue, poor appetite, and sleep disruption in cancer patients are related to altered hypothalamic circadian signaling.

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