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Circadian Oscillations of Oxidative Stress Affects Nociception Sensitivity and Opioid Induced Antinociception: A Hypothetical Preview

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Abstract

Circadian rhythms are physical, mental, and behavioral changes that follow 24 hr cycle. The production of antioxidants and protective enzymes, have been reported to be regulated or expressed in rhythmic fashions. Thus, oxidative stress seems to have a circadian rhythm connection. Oxidative stress has been implicated in aging and neurodegenerative diseases. Reactive oxygen species have role in pain associated with peripheral nerve injury. Increase in oxidative stress as in aging cause profound decline in opioid system at supraspinal level than at spinal level and also the nociceptive threshold. Oxidative stress decreases the nociceptive threshold and also opioid receptor function leading to decreased opioid induced antinociceptive effects. Thus it is hypothesised that the circadian pattern of nociception is due to oxidative stress level in the brain areas.

Keywords: Circadian Rhythm; Nociception; Oxidative Stress.

Introduction

Circadian rhythms are intimately involved in living systems at environmental, organismal, and cellular levels. Circadian rhythms, by definition, are physical, mental, and behavioral changes that follow a 24 hr cycle. This cycle is generally slightly longer than 24 h (an average of 24.2 h in sighted humans, and 24.5 h in blind humans), but can vary from person to person [1, 2]. It is believed that the development of circadian rhythms is a response to the earth's rotation, both around its axis and around the sun, which dictates daily light and temperature changes [3]. The production of antioxidants and protective enzymes, have been reported to be regulated or expressed in rhythmic fashions. Thus, oxidative stress seems to have a circadian rhythm connection.

Oxidative Stress and Circadian Pattern

Reactive Oxygen Species (ROS), such as superoxide radicals (O_2^-), peroxides (ROOR), and hydroxyl radicals (OH^-), are by products of normal cellular metabolism, mainly in the mitochondria. These molecules can benefit the cell by playing critical roles in cellular defense and other important cellular processes [4, 5]. One such role that many of the ROS have, especially O_2^- and hydrogen peroxide (H_2O_2), is in cellular signalling controlling a variety of biological processes. The ROS have many features that make them excellent signalling molecules, and have been shown to be involved in many pathways, from kinase activation to insulin action [6, 7].

However, a tight regulation of ROS is needed, as they may inflict serious detrimental effects if left unchecked. To place checks and balances on ROS, the cellular machinery has a sophisticated system to neutralize them before they become problematic. This includes producing protective enzymes (e.g., catalases [CATs], superoxide dismutase [SODs], and glutathione peroxidases [GPxs]) and physiologically generated small molecule antioxidants (e.g., Vitamins C and E, glutathione [GSH], and uric acid) [8, 9]. If these protective measures are not enough, due to exposure to environmental stresses (such as

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ultraviolet [UV] light, chemical pollutants, or heat) or due to other physiological reasons (poor or inappropriate diet, life style, etc.), the cell enters a state of oxidative stress. When this happens, it can be disastrous for the cells, causing DNA damage, lipid peroxidation, oxidation of amino acids, and ultimately death of the cell or disease in the host [5].

Reactive nitrogen species (RNS), including nitric oxide (NO) and peroxynitrite (ONOO-), also play an important role in oxidative stress. NO is produced in normal cells as an integral part of cellular signalling and is a mediator of cellular damage [10]. NO can diffuse easily through cells, which makes it especially useful as a biological messenger, and although it is only mildly reactive, its chemical properties make it a very potent intermediate messenger for production of more reactive RNS [11, 12], as well as other biological processes such as vasodilation [10]. Excess NO is normally inactivated by various cellular responses, including in the blood by a reaction with oxyhemoglobin to form nitrate [12]. However, since NO is poorly reactive, it has been suggested that much of the cellular damage that occurs during oxidative stress comes from the oxidation products of NO, especially peroxynitrite [13, 5]. This compound is formed from the reaction of O_2 - and NO, is a particularly active oxidative molecule, and has been implicated in several diseases and disorders, including hypertension, arthritis, and cancer [12, 5].

As mentioned above, these reactive species can be produced in the mitochondria as a by product of metabolism or by environmental stressors such as exposure to UV light or exposure to chemical pollutants. Since it is difficult to directly measure the very short-lived ROS, much research has focused on studying the presence of the antioxidants and other enzymes produced by the body that work against the oxidant radicals [8]. Interestingly, the cellular concentrations or activity levels of many of these antioxidants and protective mall molecules (such as SOD, GPx, melatonin, and several others discussed in the next section) have been found to have circadian rhythmicity [14, 15, 16]. This suggests an importance of both oxidative stress and the circadian rhythm in human diseases.

The cyclic pattern in the expression of circadian proteins and other rhythmic elements is dependent on a number of external cues or melatonin, including light exposure, feeding patterns, exercise, and temperature change [17, 18]. The strongest zeitgeber, light, initiates synchronization of rhythms when the retinorecipient cells within the suprachiasmatic nucleus (SCN) in the hypothalamus region of the brain receive the light impulses from the retina [17]. The SCN has been found to be the main regulator of circadian rhythms, which then sends signals to peripheral cells throughout the body, causing that rhythm to be passed on to the proper cells and tissues [19]. However, the SCN can be stimulated by zeitgebers other than light, especially by serotonin and melatonin, although these are thought to be internal feedback regulators as opposed to primary circadian rhythm initiators [20, 21, 22]. Melatonin has also been found to be one of the signalling molecules used by the body to synchronize certain peripheral cells. However, it is believed that many more molecules and hormones, including insulin and glucocorticoids, may be involved in this process [23, 24].

Rhythmicity of the Cellular Antioxidant System

Data from various studies suggest that the circadian regulation of protein expression plays a significant role in the cellular response to oxidative stress. Several studies have shown evidence of differences in DNA damage, lipid peroxidation, and protein oxidation at different times of the day, thus indicating circadian oscillations of oxidative stress responses [25, 26, 27, 28, 29]. These oscillations relate directly to the daily rhythm of antioxidant expression and protective enzyme activity levels. This rhythmicity in antioxidant levels may be exploited for a more precise targeting of the ROS, thereby offering better protection for the cells.

One of the biggest causes of oxidative damage in the cell is the O_2- molecule, many of the enzymes used to transform it into less-reactive species are rhythmically expressed. One key group of antioxidant enzymes that oscillate with circadian rhythmicity is SODs. These enzymes protect against oxidative damage by catalyzing the dismutation of O_2 – into O_2 and H_2O_2. In eukaryotes, there are two main types of SODs: copper / zinc (Cu / Zn), found cytoplasmically and extracellularly, and manganese (Mn), found mitochondrially (30). Mn SOD is thought to be especially important in maintaining and influencing the redox status of the cell, since it is the form present in the mitochondria where most ROS are produced. Also, it can directly influence the flux of certain ROS in some instances [31]. Daily rhythmicity in SOD activity was first reported by Diaz-Munoz et al. in 1985. They found that in the rat cerebral cortex, SOD activity peaks in the dark phase, coinciding with the peak level of malondialdehyde, which is a product of lipid peroxidation [32]. SOD

converts O_2 - into O_2 and H_2O_2, CAT is one enzyme that offers further protection by catalyzing the decomposition of H_2O_2 to H_2O and O_2 [33].

The rhythmicity of CAT activity was established over 25 years ago, and has been studied in many model organisms, as well as in humans [34, 33]. CAT activity oscillation has been shown to peak in the middle of the dark phase in the liver and kidneys of nocturnal mice [33]. However, in diurnal humans, the peak occurs in the beginning of the light phase as detected in plasma samples [35], illustrating the difference in circadian oscillation between nocturnal and diurnal species that would be expected due to their opposing patterns of sleep / wake cycles and the differences in their feeding patterns and light exposure.

Circadian rhythms and oxidative stress components oscillate in humans. Many antioxidants and enzymes that protect the cell from oxidative stress exhibit daily cycles in their expression or activity levels. Levels of by products of oxidative stress, such as those indicating DNA damage, protein damage, or lipid peroxidation, also oscillate with circadian rhythmicity. In addition, the peak time of expression for the circadian period and CRY proteins are listed for comparison. Those that peak in the morning include glutathione peroxidise (GPx) [36], glutathione reductase (GR) [36], catalase [36], superoxide dismutase (SOD) [36], uric acid [36], and peroxiredoxins (Prxs) [38]. Peaks in the evening have been observed in melatonin [39], plasma thiols [40], lipid peroxidation [40, 36], ascorbic acid [36], Period 1 and 2 [37], and the CRYs [37].

Another group of enzymes that regulate the effects of oxidative stress on the cell by removing peroxides is the Prxs. In Syrian hamsters, Prxs have been shown to oscillate with circadian rhythmicity in both the SCN region of the brain, as well as in the peripheral tissue of the liver, although the two rhythms are not in sync with each other [29]. As mentioned earlier, Prxs have also been studied in mature red blood cells (as they do not have a nucleus or most other organelles, including mitochondria), and O'Neill and Reddy found that there was still rhythmicity of the Prxs, in the absence of external cues [38].

Finally, circadian oscillation is highly involved in the regulation of the GSH system. GSH is a powerful antioxidant that neutralizes ROS in a process catalyzed by one of the 4 selenium-dependant GPx proteins, thereby converting GSH to the oxidized state of glutathione disulfide (GSSG). Glutathione reductase (GR) then catalyzes the reaction in which GSSG is reduced to GSH, allowing for additional neutralization of ROS (41). An additional component of the GSH system, the glutathione S-transferases (GSTs), is a group of enzymes separated into three major classes in mammals (cytosolic, mitochondrial, and microsomal), with at least 18 different isoforms expressed in humans. They play important roles in oxidative stress defense through the inactivation of cytotoxic and mutagenic byproducts of the process, including a,b-unsaturated aldehydes, quinones, epoxides, and hydroperoxides [42, 43).

Oxidative Stress: Nociception Sensitivity and Opiod Antinociception

Oxidative stress has been implicated in aging and neurodegenerative diseases [44, 45, 46, 47]. The aging process is associated with cellular damage caused by reactive oxygen species. There was a significant increase in protein oxidation in aged mice brain regions such as the cortex, hippocampus, striatum, and midbrain [48, 49, 50]. The cortex, striatum, hippocampus, and midbrain express opioid receptors [51, 52, 53, 54] and contribute to pain processing [55], therefore age-related oxidative damage in these regions increase pain sensitivity and decrease opioid analgesia. Recent studies suggested a mediatory role of reactive oxygen species in pain associated with peripheral nerve injury [56, 57].

As per Raut and Ratka [58] due to increase in oxidative stress as in aging the protein carbonyl content which is the marker for protein oxidation and TBARS content a marker for lipid peroxidation showed a gradual increase in cerebral cortex, hippocampus, striatum, and midbrain. Further there was a significant negative correlation between the antinociceptive effect of morphine (15 mg / kg at 60 minutes) and protein oxidation and lipid peroxidation in the cortex, striatum, midbrain and hippocampus also a significant negative correlation was observed between fentanyl-induced antinociception at 30 minutes after 50 mg / kg, and protein oxidation and lipid peroxidation in the cortex, striatum, midbrain and in the hippocampus. Oxidation of opioid receptor proteins can result in decreased opioid receptor function. One study reported significantly reduced binding density of mu opioid receptors (MOR) in the striatum. Increase in oxidative stress as in aging may cause profound decline in opioid system at supraspinal level than at spinal level and also the nociceptive threshold.

Conclusion and Hypothesis

As evident by these studies it is concluded that oxidative stress decreases the nociceptive threshold and also opioid receptor function leading to decreased opioid induced antinociceptive effects. Further, there is circadian oscillation of oxidative stress level. Thus it is hypothesised that the circadian pattern of nociception is due to oxidative stress level in the brain areas.

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