A Core Process in Receptor Function, General Anesthesia, Sleep, and Aging

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The diffusion of ligands and proteins was proposed to be guided by chreodes in water organized by protein-surface side chains with varying hydropathic states. These chreodes are proposed to be the target of volatile general anesthetic agents. The similarity between this effect and sleep deprivation leads to a proposal of an external agent responsible for sleep. This agent is elemental nitrogen. An extension of this effect is the concept that elemental nitrogen is a core factor in aging.

Introduction. – Water is the cradle on this planet, holding all of life. The interaction of any two molecules, classified as 'bio', depends on their passage through water. These interactions are not regarded as random events, and so some attributes of guidance have been postulated to account for the specificity and timing of these encounters. Early studies proposed that viscosity variability in water plays a role [1]. These changes in viscosity have been deduced from circular-dichroism studies [2]. Some idea of the role of water near a receptor was presented to explain the occurrence of persistence after a molecule–receptor system was interrupted by washout [3]. It was proposed that a pool or pathway existed near the receptor that held the ligand long enough to resist briefly its washout.

Water Chreodes. – From these observations came a proposal that bulk water near the surface of a protein was organized to hold and to guide a ligand to the receptor [4]. This organization arises from the variety of hydropathic states of amino acid side chains on the protein surface. Each of the 20 possible amino acid side chains has a hydropathic state ranging from very hydrophilic to very hydrophobic. The pattern of these properties creates a pathway through the near bulk water. Water is *ca*. 1/3 void, and so there can exist pathways through the water near the protein surface. These pathways, called '*chreodes*', were proposed to facilitate the passage of a ligand to its specific effector. Because of the rapid H-bond exchange among H_2O molecules, these chreodes are evanescent, yet they may have a recurring propensity to facilitate ligand passage to the effector. The role of the chreodes imparts the specificity and timing of the passage and encounters of ligands with effectors, or between two proteins, or between any two macromolecules in a living system. Further studies support this concept [5–8].

Volatile General Anesthetics. – The vulnerability of this chreode system was modeled to reveal the effect of molecules nearby [5]. The presence of molecules other than those specific for the chreodes may lead to the disruption of the chreodes resulting in the slowing of the ligand passage and encounter with the effector. From this model, there arose the concept of a mechanism of volatile general anesthetic agents [9]. The current view is held that volatile anesthetic agents are not specific for a single receptor, but they interact non-specifically affecting several receptors such as GABA, glutamate, and acetylcholine [10–17]. From this evidence and the proposed chreode concept, a hypothesis was presented invoking chreode interference by volatile general anesthetic agents [9]. The volatile anesthetic agents function as inert molecules interfering with chreode structure by presenting alternative hydropathic states that disrupt the normal chreode patterns arising from the amino acid side chains on the protein surface. This disruption of the chreodes leads to an altered passage of ligand to receptor, thus an altered receptor response. That is the goal and outcome from the administration of these agents, general anesthesia. This effect of halothane on water near proteins has been shown to occur, leading to altered protein dynamics [18].

General Anesthesia and Sleep. – Evidence is growing that reveals many similarities between general anesthesia and sleep. Both involve effects mediated in the central nervous system (CNS) [19–21]. Arousal states are mediated in the pons [22][23]. Sleep has characteristics closely related to anesthesia [24]. The cholinergic system plays a prominent role in each [25–27]. These and other observations led to a recognition that sleep may arise from a mechanism similar to that of general anesthesia [28].

A Theory of Sleep. – A theory of sleep has been proposed based on similarities with general anesthesia. It is based on the postulated interference with chreodes similar to the presence of a general anesthetic agent. It follows that an external agent, like a general anesthetic agent, is participating in the chreode interference. This mechanism proposed for sleep is the effect of elemental nitrogen (N_2) on a variety of chreodes, producing a reduction of function in those effectors involved [29]. The effect is not as severe as with a general anesthetic agent, but sufficient to produce the sleep characteristics. During a period of time referred to as wakefulness, there is a small accumulation of inhaled nitrogen. This reaches a level sufficient to produce an interference with some chreodes similar to those described as general anesthetic targets. Sleep occurs, during which time the respiration rate is reduced to *ca.* 75% of the waking level. This allows for a loss in the level of N_2 in the body, allowing for a return to the wakeful state.

Nitrogen will produce anesthesia, but high pressures must be used [30]. Patients with sleep deprivation require much less general anesthetics to produce anesthesia [31]. Studies on ion channel currents show similar effects of N_2 and general anesthetics [32]. Sleep is a function of all species [33]. It is reported in *D. melanogaster* [34][35], zebra fish [36][37], and *C. elegans* [38].

Sleep deprivation effects are identified as prominent events in society today. Based on the mechanism proposed here, this deprivation is a result of an accumulation of N_2 that was not disposed of because of an insufficient sleep period. Thus in the deprived state, there is more N_2 in the body than would normally remain. This would account for

the symptoms revealed in studies of this state. These effects include cognitive decline and performance impairment at the physical level [39]. Effects at the system level include changes in blood sugar regulation and changes in various hormone concentrations [40]. From these observations, the conclusion has been reached that sleep deprivation effects are closely related to the effects associated with aging [40–43].

Mechanisms of Aging. – The reported similarities of the effects of sleep deprivation and aging led to an examination of proposed mechanisms of aging. Aging, or senescence, is a complex phenomena that basically results from the accumulation of adverse biochemical events, and the failure of self-maintenance and repair [43–46]. It is a process not limited to mammals, but has been observed in more primitive systems such as the *Drosophila* [45][47].

Aging has been studied at the molecular, cellular, and organismal level. Several molecular level mechanisms have been proposed for aging. A current prominent view is that aging results from the accumulation of molecular level interferences, producing retarded or abnormal products from intermolecular encounters. These events include cross-linking alterations, mis-reading of genetic codes, and flawed reaction products from damaged syntheses [43][48]. Cells respond to significant damage that is potentially dangerous to the tissue or organ by initiating apoptosis. While apoptosis may be protective in younger organisms, it contributes to aging when too many cells are eliminated [45]. These aberrant events and the products from them accumulate over time in the living system leading to changes at each level in the hierarchy of molecules, macromolecules, cells, tissues, organs, and the whole body. This describes aging. It is a phenomenon that occurs in all living systems on this planet, for everything ultimately dies.

Studies to date have revealed a variety of molecular level encounters accompanying the aging process. A major system involved in these events is the endoplasmic reticulum. It functions to lower the incidence of protein aggregation by degrading badly folded polypeptides, thus preventing aggregation [49]. Aging reveals an increase in these abnormal proteins, a result of failure in the critical reactions of chaperones with malfunctioning unfolded proteins [50–52]. When proteins that are oxidized, modified, misfolded, or aggregated exceed the availability of chaperones to sequester or degrade them, accumulation of damaged proteins occurs, contributing to aging [53].

These and other mechanisms of aging have been reviewed [43][44]. It is believed that aging is dependent on an interplay of genetic and environmental factors. The focus has been largely on damage accumulation, and the defense and correction of this. The protein structure is the principal actor in the aging process. The alterations of its structure is the main and inevitable manifestations of aging.

Nitrogen: The Primary Cause of Aging. – The reported similarities between sleep deprivation and aging lead us to propose a number of systems in the CNS as key ingredients in both phenomena. Sleep appears to affect a limited number of systems in the CNS, aging is a broad-based phenomenon encompassing many systems in the body. Both involve proteins that function when they are folded in a specific way, or when they encounter another molecule. Both of these events occur in water. Within the water environment, these protein encounters must reach each other from more remote

locations. We have introduced the concept of ligand passage through water, guided by the presence of chreodes created by the hydropathic states of nearby amino acid side chains involved in these encounters [4]. These chreodes facilitate and guide the dynamics of these encountering agents.

The interference of these dynamic events by general anesthetics has been proposed to be a mechanism of general anesthesia. The onset of sleep has been proposed to be the same chreode interference produced by the accumulation of inhaled elemental N_2. Following these presented concepts, we propose that the slow accumulation of flawed protein functions produced by the recurring presence of small overburdens of elemental N_2, occurring over extended periods of time, contributes to aging. This time varies with the species. All living systems experience an aging or senescence, ultimately leading to the demise of the organism. This outcome occurs with every living system on the planet. Nitrogen is present in every one of these systems.

Concluding Remarks. – Models of water in the presence of amino acid side chains have revealed significant variability in the local water structure, reflecting the variations in the hydropathic states of the side chains. These models also reveal patterns of water cavities, termed chreodes, that exist near the surface of a protein. These patterns have been invoked to explain the facilitated diffusion of ligands to an active site on the protein surface. The action of a volatile, general anesthetic agent has been proposed to occur from the interruption of these chreodes producing some loss of function from the receptor. The many similarities reported between the effects of a general anesthetic agent and sleep have led to a proposal of a common mechanism. In the case of sleep, it has been proposed that inhaled elemental N_2 accumulates to produce a mild anesthesia. Sleep is the process of reversal of this accumulation. It is proposed that, over a lifetime, there is a continued accumulation of elemental N_2 with accompanying influences on many processes, leading to a gradual decline of many functions, called aging.

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