A Core Molecular Theory of Sleep and Aging

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Abstract: 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 may 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 produced a proposal of a common mechanism. In the case of sleep, it has been proposed that inhaled elemental nitrogen 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 nitrogen with accompanying influences on many processes, leading to a gradual decline of many functions, called aging. The sequence of these concepts is reviewed here.

Keywords: Aging, sleep, water chreodes, cellular automata, elemental nitrogen.

INTRODUCTION

The cradle of life on this planet is water. All systems judged to be "living" are enshrouded in collections of this simple three-atom molecule. All dynamic events taking place in living systems are involved with water in some degree. The coming together of two biomolecules requires some time spent, in water. In our writings we have expressed this event as the core process involving a ligand and an active site [1]. Not much time has been spent studying water when we or our colleagues in the drug design field have pursued an understanding of drug-receptor, enzyme-substrate, protein-protein interactions or QSAR modeling.

Water has always been assumed to be there, everywhere, essential, but not fully understood in the bulk state. Water enters into our studies as an entity that we allude to *via* its properties. We are aware of, and describe water *via* it's temperature, viscosity, compressibility, ionization and so on. We relate these properties to one of it's properties, the temperature. A major interest in a solute and it's relation to water and a lipoidal solvent is the partition coefficient of that solute. The use of this property in drug design was the contribution of Corwin Hansch. He has recently passed away but will be remembered as one of the pioneers in the area of drug design employing mathematical tools.

The properties of water have been used to describe it's influence on events occurring in it's presence. We use water temperature as a descriptor influencing these events. All of these events of interest to us involve bulk water. It is water that is transiently bonded to many other water molecules. Bulk water possesses properties that are more than the simple sum of the parts, individual molecules. Water is a complex system. What is needed is a descriptor of the organization of bulk water that relate to its functions in living systems. We have pursued this goal, of modeling bulk water in order to gain some insight into these functions.

Some models that have been used include molecular dynamics, Monte Carlo simulations and agent based models, primarily cellular automata. We have used cellular automata to model water in order to a) mimic the dynamic, stochastic behavior b) produce estimates of fluctuations from averaged behavior and c) present a visual representation of the dynamic process.

THE CELLULAR AUTOMATA MODEL

The grid in a CA model is a collection of spaces called cells. We have used two-dimensional grids. The movements and actions of an agent on the grid are governed by rules that depend on the nature of the cells. The environment of a cell is called its neighborhood. This neighborhood for a cell refers to the four cells adjoining its four faces. The rules are applied sequentially to each agent in the grid. One complete set of rule applications is one iteration, a unit of time. During each iteration, an agent in the grid has the possibility of moving to an adjacent, unoccupied cell. The movement of every agent on the grid is computed based on rules that involve the status of its neighboring cells i.e. whether these cells are empty or occupied, and, if occupied, by what types of agents. In probabilistic, or stochastic, cellular automata, the movements of the agent are based on rules, stated as probabilities of moving or not moving during each iteration.

The free moving "m" probability $P_m(A)$, defines the probability that an agent A in a cell will move to one of the four adjacent cells, in its neighborhood if that space is unoccupied. The joining parameter, J(AB), defines the propensity of movement of an agent A toward or away from a second agent B. It models a short-range attraction or repulsion component to the interaction between agents A and B. The breaking probability P_B rule assigns the probability $P_B(AB)$ that an agent A, adjacent to an agent B, will break apart from B. Low values of P_B imply a strong cohesion

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between A and B, whereas high values indicate little cohesion.

A CELLULAR AUTOMATA MODEL OF BULK WATER`

A cellular automata model of bulk water was published in 1994 [2]. The water molecules were represented by cells filling 69% of the grid space. This corresponds to the fraction of space occupied by water in the liquid state [3, 4]. The values of these rules were chosen to correspond with experimental evidence. The results of the structure studies were expressed in terms of the fractions of bulk water molecules, f_x, where this fraction describes water cells possessing zero, one two, three or four bonded neighbors.

OTHER CA MODELS OF WATER

Subsequent use of the f_x structure descriptors of bulk water lead to a series of equations with high correlation to several water properties [5]. The property of solute diffusion through water is an intriguing one since this is the mode of transport of all drugs and ligands to an active site. A CA model of aqueous diffusion produced interesting results [6]. It was observed in the model that solutes with high hydrophobicity, diffuse faster through bulk water than those with a low value of this property. This is a result not generally recognized but it is supported by three studies [7-9]. Bulk water is sensitive to the solute character and responds to it.

The hydrophobic effect of a solute is the influence of a molecule in water solution producing an aggregation or structuring of the water near a solute with hydrophobic character.

The water is not in direct contact with this solute, leaving some space between them. This behavior was modeled with CA using rules to define the solute [10, 11]. In these studies, a solute molecule modeled to be hydrophilic, set up conditions of attraction between solute and water. These models lead to a view that solutes can influence the architecture of bulk water in their environments. This property formed the basis of a new concept relating bulk water to molecular fragments in contact with that water.

LIGAND DIFFUSION ACROSS A PROTEIN LANDSCAPE

Several models of a two-dimensional passage on cell and protein surfaces have been described [12-14]. The conclusion was drawn that amino acid side chains outside of the active site play a major role as “promoters”, facilitating a rapid diffusion to the active site. The participation of the water near the protein surface was discussed by Welch who theorized that the microviscosity of near water was influential on the rate of catalytic reaction [15]. The possibility that the viscosity of water near the protein surface is significantly higher than bulk water creates an ordering in a layer of water that would facilitate faster diffusion of a solute near the protein surface.

A functional model was proposed by Birch who did not specify the nature of the ligand approach to the receptor but described a model of the residence of several ligands near the active site [16]. An experimental observation was made that upon administration of sweet-tasting molecules to observers followed by a washout of the compound, a persistence of the sweet taste results. Birch considered several possible models including a non-specific localized pooling of the compound in the vicinity of the receptor. Based on experimental work he proposed a model in which the sweet molecules are located in a queue held in place near the surface of the protein. After washout, the molecules are retained in the queue and so they continue to move toward the receptor, activating it as long as the queue is occupied. When the queue is empty, the sweet taste vanishes. This model invokes a directional effect focused on the receptor as well as the possibility of sustained residence of several molecules in the queue.

In summary, experimental and modeling evidence may be interpreted as describing a facilitation of reaction rates and receptor activation due to the rapid diffusion of ligands to target sites in essentially a two-dimensional domain. This diffusion most likely occurs near the surface of a protein, involving water and structural features not part of the target site. The forces guiding the ligand to the target site would be expected to result in several effects. These include some period of retention on the protein surface and some influence directing the ligand to the target site. These considerations and the demonstrated role of water led us to propose a model involving the immediate layers of water enshrouding the protein.

CHREODES

A model by Kier proposed that ligand molecules encounter the surface of a protein molecule and are captured within the first few layers of water on the surface [17]. They are then guided to the active site over a series of evanescent cavity paths in the near surface water created by the hydrophobic effects produced by the hydropathic states of each amino acid side chain. These paths are preferences reminiscent of the chreodes envisioned by Waddington, in his description of preferences on an epigenetic landscape [18]. Because this description is close to the dynamic character of the paths created by the hydrophobic effect of the field of surface side chains, Kier adopted the term chreode to characterize the system [17].

A number of attributes are associated with the chreode model that has an impact on diffusion events which they influence. These chreodes are distinct for each type of receptor or enzyme active site. This attribute arises from the fact that the landscape of amino acid side chains around a receptor is just as defined as the receptor itself. A second attribute of these chreodes is that they are evanescent, constantly coming into existence, fading and returning. They exist only as a “most probable” pattern of water passages.

The local structure and topology of segments of a chreode present to surrounding bulk water, asymmetric patterns of side chains. The consequences of this are a different orientation and binding affinity of each chreode segment to chiral isomers captured within the chreode segment. This effect translates into a modest stereoselectivity associated with each segment of a chreode. This coincides

with the experimental observations of Fidler [19], and in a model studied by Kier [20]. The sum of these effects along the chreode may result in a stereoselectivity manifested before the molecule reaches the receptor. The credit for ligand stereoselectivity has traditionally been ascribed exclusively to the receptor.

An attribute of the chreodes is their potential fragility in the presence of other molecules that are of certain size and hydropathic state. These molecules may enter, interfere with and disrupt the structure of the chreode at any segment along their path. Just as the amino acid side chains are the source of the hydrophobic effect creating the chreodes, so another optimally structured molecule may reorganize the water near the protein surface to create a "non-chreode" pattern. This would have some effect on the diffusion of the specific ligand associated with that receptor and its chreode system.

The chreode theory provides a possible explanation of the lag effect of an administered drug in which the onset of activity is delayed until a certain concentration is available to occupy the chreodes and then the receptor. The chreode presence may also be invoked to explain the phenomenon of persistence in which the activity can still be recorded for a short time after the washout of an administered drug. A small concentration may remain in the chreodes so that a few additional receptor encounters may occur.

In the study of chreodes created by protein surface amino acid side chains Kier modeled the effect of amino acid side chain patterns using cellular automata dynamics [20]. With a random distribution of modeled side chains simulating the absence of any chreode pattern, the average diffusion rate of a ligand model was calculated. A pattern of side chains was then modeled, creating a chreode, focused on the receptor. The average rate of diffusion of a ligand was found to increase by about 50%. Modeling studies in other laboratories supported this observation [21-23].

Another study repeated these simulations and added a number of solute molecules in addition to the ligand [24]. It was found that the additional molecules interfered with the diffusion rate. The rate of diffusion of the ligand was reduced to the rate modeled for a random distribution of side chains. The presence of the modeled solute molecules interfered with the chreodes, thereby reducing their influence on the diffusion process. This model, along with the other evidence described, led to a proposal of a theory of the action of inhaled volatile anesthetics.

A THEORY OF VOLATILE ANESTHETIC MECHANISM

The current view of weak encounters of volatile anesthetic molecules at many sites on or near protein surfaces appears compatible with the theory of chreodes facilitating and directing ligands to receptors or enzyme active sites [17]. Inhalational anesthetic molecules have sizes approximating those of amino acid side chains, and lipophilicities approximating those of the lipophilic side chains. These two molecular properties are most influential in controlling the creation of the hydrophobic effect. Their presence in or near a chreode is proposed to alter the original chreode pattern, thereby disrupting the normal diffusion of the ligand to the receptor [25]. This effect depends upon a critical concentration and would vary in its intensity from one receptor-chreode complex to another. The interactions of inhaled anesthetic molecules with the chreodes are weak and non-specific. Since chreodes may be associated with many receptors and enzymes, such an interference in their function and influence is expected to be widespread. Their influence may be inhibitory, as at receptor-chreode systems, or reinforcing as at reuptake sites supported by a chreode network.

In summary, the presence of an inhalation anesthetic agent in a chreode system, supporting a ligand diffusion to a receptor, is proposed to alter the chreode structure hence function of the chreode, thereby reducing the diffusion and the receptor response [25]. The summation of these numerous diffusion disruption events leads to the manifestation of clinical anesthesia.

RELATION BETWEEN GENERAL ANESTHESIA AND SLEEP

It is recognized that multiple encounters must be invoked for anesthetic action to account for the variety of observed effects [26]. General anesthesia and sleep share some remarkably similar physiological and behavioral effects [27]. There is strong support for the hypothesis that neuronal networks which regulate natural sleep, are involved in sedation and anesthesia [28]. Sleep and anesthesia eliminate wakefulness *via* many brain regions [29]. Among these the pons has become a focus of attention for arousal states [30]. Cholinergic neurotransmission in the pons is a causal factor in arousal state control [31].

The ideal anesthetic state is a composite of reversible characteristics including analgesia, amnesia, unconsciousness, and skeletal muscle relaxation [32]. Normal sleep also requires the timed coordination of these characteristics [33]. General anesthetics produce the unconscious state by, in part, interfering with CNS cholinergic neuro-transmission [34]. It has been found that cortical acetylcholine release is greater during wakefulness and REM sleep than during non-REM sleep and anesthesia [35]. Cholinergic brain stem neurons produce an activated cortical EEG during wakefulness. During non-REM sleep and general anesthesia there is a decrease in pontine cholinergic neurotransmission and a deactivated cortical EEG. The spindles in the EEG for halothane have the same appearance and frequency as the spindles for non-REM sleep [36].

These observations led us to the conclusion that the mechanism of both sleep and anesthesia is an inhibition of a CNS located neurotransmission system, largely cholinergic, leading to a loss in the waking state. If the mechanism is the same, then we are led to consider the possibility that sleep may be invoked by an exogenous source, just as is general anesthesia.

A THEORY OF SLEEP

From our model of neurotransmitter molecule diffusion and its possible role in the mechanism of general anesthesia, we turn to the closely related natural phenomenon of sleep There is a significant similarity between these two processes, as discussed above. Anesthesia has a primal event, the

introduction of an exogenous agent. From our chreode theory we identify this as a non-specific chreode-modifying drug, a general anesthetic.

The origin of sleep, based on our chreode theory and its role in the mechanism of anesthesia, was proposed by Kier [37]. It is based on the premise that sleep is due to an exogenous substance, sometimes referred to as a sleep factor. The mechanism is the same as in anesthesia, various chreodes associated with receptors in the CNS, and elsewhere are interfered with. These receptors function in many ways, as neurotransmitters, re-uptake sites, and chaperones. These are affected in varying degrees, producing a pattern of physiological responses, collectively called sleep.

It was proposed that this exogenous substance leading to sleep is molecular nitrogen, N_2 [37]. Nitrogen makes up 78% of the air we breathe, drawn in with the oxygen which is considered essential for life. Nitrogen is inert, apparently playing no role in any life process, at least as far as current studies have revealed. But all terrestrial life has evolved in the presence of nitrogen. It must have some role. It was proposed that nitrogen is taken into the body with each breath and is distributed throughout just like a non-specific volatile anesthetic drug. Over the course of a waking period, there is an increasing accumulation of nitrogen in tissues. At some point there is enough nitrogen accumulated to interfere with a wide variety of chreodes, causing a significant decline in their function. This is the onset of sleepiness, ultimately leading to sleep. During sleep there are intermediate states that occur, as a result of variations in the level of the nitrogen overburden. The nitrogen overburden is influenced by the respiration rate that is slower during sleep. This produces a net decline in the accumulated nitrogen concentration from a shift in the equilibrium, producing a lessened effect on the chreodes, ultimately allowing a return to a waking state. The chreode targets of the nitrogen may be associated with several neurotransmitters in the CNS, recognized as being important in the sleep state, and they may also be a cascade of receptors throughout the body.

Nitrogen is known to produce anesthesia and is well known as the cause of the deep diving condition of nitrogen narcosis. Trudell and his colleagues have studied the anesthetic effect of noble gasses along with H_2 and N_2 [38]. The common features among these gases is their chemical inertness, approximately spherical atomic (molecular) shape and their relatively small size. The gases H_2, He, and Ne are not anesthetic, while Ar, Kr, Xe and N_2 are. The study produced the conclusion that the anesthetic effect was a chemically non-specific encounter at certain sites in the living system. The minimum alveolar concentration (MAC) of the four anesthetic gases showed that the value for N_2 was the highest, indicating a low level of potency. Thus at one atmosphere there is no immediate anesthesia or sleep produced. An accumulation over a considerable period of time would be the only way to account for an influence on sleep.

It is known that sleep-deprived individuals require less volatile anesthetic to produce anesthesia or to potentiate the onset and duration of anesthesia produced by isoflurane [39]. It is possible that sleep deprivation is an excess accumulation of nitrogen, thus the patient needs only a small amount of anesthetic drug to create the conditions for chreode disruption. Nitrogen was studied for its effect on the decrease in sodium channel currents due to increases in the percentage of channels in the inactive state [40]. The results were the same as with volatile general anesthetics. Abraini has reported that some of the mechanisms of nitrogen and argon narcotic action appear to be similar to those of clinical inhaled anesthetics [41].

RELATION BETWEEN SLEEP AND AGING

Several molecular level mechanisms have been studied and proposed for aging. A current prominent view is that aging results from the accumulation of molecular level interferences, producing abnormal products from molecular encounters. Sleep deprivation effects are identified as prominent events in society today, based on the mechanism proposed here, sleep deprivation is a result of an accumulation of nitrogen that was not diposed of because of an insufficient sleep event. Thus in the deprived state there is more nitrogen in the body than would normally exist. This would account for the symptoms revealed in studies of this state. These effects include cognitive decline and performance impairment at the physical level [42]. Effects at the system level include changes in blood sugar regulation and changes in various hormone concentrations [43]. From these observations the conclusion has been reached that sleep deprivation effects are closely related to the effects associated with aging [43, 44].

FACTORS IN AGING

The reported similarities of effects of sleep deprivation and aging have stimulated a focus on the essential mechanisms of aging [45]. The general conclusion is that aging, or senescence, is basically a function of the accumulation of certain biochemical events. It is a process not limited to mammals, but has been observed in more primative systems such as the *Drosophila* [46]. These events include cross-linking alterations, misreading of genetic codes, and the unrepairability of flawed reaction products from damaged syntheses [45, 47]. 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 [48]. Aging reveals an increase in these abnormal proteins, a result of failure in the critical reactions of chaperones with malfunctioning unfolded proteins [49, 50]. These and other mechanisms of aging have been reviewed [45]. It is believed that aging is dependent on an interplay of inherent 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 and

encounters are 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 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. These chreodes facilitate and focus the dynamics of these encountering agents.

The interference of these dynamic events by general anesthetics has been proposed to be the mechanism of general anesthesia. The onset of sleep has been proposed to be the same chreode interference produced by the accumulation of inhaled elemental nitrogen. Following these proposed concepts, we propose that aging is the slow accumulation of flawed protein functions produced by the recurring presence of small over burdens of elemental nitrogen, occurring over extended periods of time. The time various 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.

ACKNOWLEDGEMENT

I am so very honored to be selected for this attention to one of my birthdays. For all of us authoring in this issue, birthdays come once a year accompanied by a bit of what is called aging. I thought it would be appropriate to make this contribution where I speak to a possible core mechanism for the aging process. Like every study in science it represents a viable contribution to existing ideas. Time and studies like those made by the distinguished authors in this edition, will speak to the validity of all current concepts and contribute new ideas.

I want to express my warm thanks to Subhash Basak for his idea and work to create this special edition. I want to thank the scientists, colleagues and friends who have made contributions to this edition. I wish all of you success in your studies and I hope that you experience what I have for many years, the pleasure and excitement of doing science.

CONFLICT OF INTEREST

Declared none.

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