Gravity in the Brain May be Revealed by Sleep Deprivation Studies Using Time-Lapsing Diurnal Brain Magnetic Resonance Imaging to Analyse White Matter Microstructural Changes

A group of Norwegian sleep investigators recently reported[1] on a cohort of healthy volunteers in whom they studied sleep deprivation using novel brain magnetic resonance imaging (MRI) techniques to examine the white matter microstructure compared to a control group. They found significant white matter changes during sleep deprivation compared to during a normal sleep/wake cycle which they considered to represent changes in intra-axonal and extra-axonal diffusivity. These, in turn, they reported, may represent changes in axonal membrane integrity and myelin maintenance.

Vascular laboratory investigators elsewhere, studying endothelial function, may have something to add to that. They have spent the last decade establishing an association between sleep deprivation and endothelial dysfunction.[2] This would include the microvasculature of white matter in the brain, as well as the coronary vasculature. Moreover, one of their clinical trials,[3] analogous to that of the Norwegian investigators,[1] uses peripheral vascular sonography in healthy volunteers studied during sleep deprivation.

The works of these two seemingly divergent groups of investigators, viewed side by side, might raise the question of whether vascular endothelial dysfunction plays a role in the brain white matter changes seen during sleep deprivation.[4] However, more importantly, why is sleep deprivation associated with white matter changes in the brain and also with vascular endothelial dysfunction? Part of the answer may be gravity or more specifically, gravitational ischemia, a potentially reversible injury. Recent reports have suggested that gravitational ischemia in the brain may explain these relations and also explain why we need to sleep.[5,6]

Something's Weighing on My Mind

Unlike the heart and lungs, the brain sits on a hard floor of bone, where it is almost entirely motionless. The brain is analogous to a bed-ridden hospital patient who can avoid ischemic skin breakdown and decubitus ulcer formation only by the relentless efforts of a skin nurse to intermittently roll him from side to side, and reposition his arms and legs, to relieve under-lying skin pressure resulting from the weight of over-lying body mass in the earth's gravitational field.[5] The meninges and cerebrospinal fluid surrounding the brain may provide some cushioning for the brain, but do not mitigate the effects of gravity.

The brain needs to limit the severity of ischemic injury to its weight-bearing surface caused by gravity. How does the brain do it? Does the brain roll itself from side to side? Maybe so by sleeping 8 h/day, which encourages a horizontal positioning of head and body and by maintaining wakefulness for 16 h/day, which encourages a vertical positioning of head and body.[5]

"Gravitational ischemia in the brain," results from the mass effect of one part of the brain upon another in a gravitational field. In any given head position, the "top" half of the brain (farthest from the center of the earth) is sitting on the "bottom" half as a weight burden. In healthy individuals, head and body positions are roughly vertical for 16 h a day, and then roughly horizontal for 8 h at night during sleep. Pancaking layers of progressively increasing weight [Figure 1] from the overlying brain tissue compress blood vessels and reduce blood flow in the bottom layers, resulting in regional gravitational ischemia on the bottom side of the brain[5] which is potentially reversible, if it does not become too severe. Some have suggested that gravitational ischemia in the brain may play a role in dreaming and in some psychiatric illnesses.[5]

In healthy individuals, the horizontal body positioning associated with sleep helps to redistribute both gravitational ischemia and blood flow in the brain after a 16-h period of vertical head positioning during the waking hours of the day. Restoration of blood flow by reopening of capillary vascular

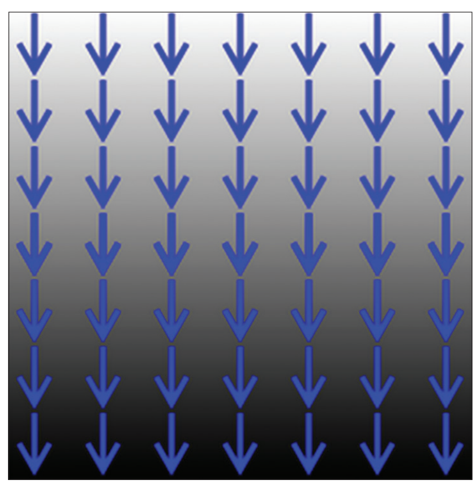

Figure 1: Gravity schematic stratification of biological tissue into pancaking layers under the influence of gravity. Lower layers incur progressively increasing weight burden from upper layers, and thus increasing compression of blood vessels and reduction of blood flow, possibly resulting in regional ischemia

beds follows repositioning (unloading of ischemic regions) of the brain relative to gravity by head tilting, which is significant through the 24-h sleep/wake cycle. Other factors such as intra-cranial carbon dioxide levels and metabolic rate in the autonomic nuclei may play a role in ischemia there as well.[7-18]

Together with the findings of the vascular pathophysiology investigators,[2] the recent perspective on gravity in the brain[4-6] suggests how compressive ischemic changes in the weight-bearing brainstem autonomic nuclei may contribute to the autonomic causation of vascular endothelial dysfunction and disease in the brain and elsewhere in the body following sleep deprivation.[4]

Inconsistencies in the data of the Norwegian sleep investigators[1] are likely related to patients being placed in supine (horizontal) position for MRI scanning, and also to wait in queue for that scanning. MRI scanning is typically done in the supine position whereas sleep deprivation occurs naturally in the upright position. There are significant gravitational implications here. Horizontal positioning disrupts ischemic architecture that developed during vertical head positioning, even if wakefulness is maintained, as it was through stimulation by the investigators.[1] Open upright MRI is potentially available, yet may introduce other problems such as resolution capability.

Three lines of investigation, taken together, suggest that the Norwegian group[1] may have seen events which combined the forces of gravity with microstructural changes in axonal membranes, and microvascular endothelial changes. Ischemia may be playing a large role. Ischemia has long been an important pathological process in the heart, related to vascular stenosis, occlusion, and other phenomena and so has vascular endothelial dysfunction. However, observations about gravity in the brain are challenging the presumed role of these two processes there, and whether each process (ischemia and vascular endothelial dysfunction) has two separate roles in the brain a "normal" physiological role in sleep, and a pathological role in stroke.

The Norwegian investigators[1] may have visually chronicled the slowly accumulating diurnal effects of gravity in the brain its fluid shifts possibly related to the gradually worsening ischemia of weight-bearing strata of neuronal axons in tracts, situated "underneath" the mass of higher strata of brain tissue.

Ischemia previously considered to be strictly a pathological process and in the brain associated mostly with new strokes and their surrounding ischemic penumbrae (shadows), resulting from occlusive cerebrovascular disease may also function as an important and pervasive component of normal neurophysiology caused by gravity.

Vascular endothelial dysfunction previously considered to be strictly a pathological process, may also function as an important and pervasive component of normal neurophysiology caused by gravity, and helping to mediate sleep.

Something's Weighing on My Heart

And what about the role of sleep deprivation in cardiac disease? Preliminary research suggests that it may be significant.[19] Sleep deprivation clearly seems to be associated with vascular endothelial dysfunction and disease,[2,3] including the coronary vasculature. How does it interact with sleep apnea of different types to influence cardiac disease?[20-29] The answers to these questions may take many years to sort out. However, it appears today that the indirect effects of gravity on the heart, via its direct effects upon the brain, may be significant.[4]

During the last decade, however, significant research[30-37] has been done in both animals and humans regarding obesity and body mass index (BMI), and their effects on the brain. As a generalization, fat does not accumulate in the brain, in the same manner, it does elsewhere in the body, due to limitations of both space and pressure. However, as the BMI increases, the brain incurs many subtle changes in composition and in cellular architecture. These changes may be very influential physiologically and they may affect the brain at the same time other changes related to obesity and BMI are affecting the heart.[38-40]

Several investigators have described lipid accumulation in the hypothalamus and how it may be affected by variables such as diet and diabetes.[32-35] The specific effects of this accumulation on gravitational ischemia there are as yet unexplored. However, they are interesting because the supra-chiasmatic nucleus of the hypothalamus is thought by many to be the central pacemaker of the circadian timing system, which regulates most circadian rhythms in the body. This may correlate with the role that some consider gravitational ischemia to play in the body's most prominent circadian phenomenon sleep.

In some reports[31] of changes in the brain associated with obesity and increased BMI, the investigators have suggested a pathophysiological origin for those changes which relates to their neural function regarding obesity. After finding that increased BMI was associated with significant thinning of the cortex in two areas: The left lateral occipital cortex (LOC) and the right ventromedial prefrontal cortex (vmPFC), they concluded that "Consistent implications of the latter region in reward valuation, and goal control of decision and action suggest a possible shift in these processes with increasing BMI." They suggested no etiology for the former occipital changes.

Although this may seem logical, these changes may instead relate specifically to gravitational ischemia. Obese individuals may spend an excessive amount of time resting in the supine position, which places a weight burden on the occipital region. Most will likely be right-handed, and spend some time lying on their side, with the left side down so that their right hand is available to interact with their environment. This would be consistent with thinning of the LOC. At the same time, the right vmPFC would be lying again the falx cerebri which may be acting as a hard surface, analogous to the inside of the skull, resulting in a thinned cortex. In summary, gravitational ischemia in the brain may be an important physical process, causing microstructure changes, which are visible on serial MRI scans throughout the day, and which are currently unexplored. It may cause or influence many aspects of metabolism in normal physiology, like sleep and it may also influence pathophysiology, like eating disorders, and diabetes. Brain investigators might logically be recommended to consider the influence of gravitational ischemia in their work.

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