What happens to the brain when we don't sleep?

Everyone has experienced it at some point, staying up all night to finish an assignment, play video games or just not being able to sleep. The consequences of sleep deprivation are easily felt, reduced attention span, lack of energy, mood changes, stress, and irritability etc. How do such changes to cognition and mental states represent themselves in the brain and are there ways to mitigate some of these changes?
In this essay I will focus on one neurophysiological change that happens as sleep deprivation starts to mount, namely the lack of adenosine triphosphate and the build-up of adenosine in the brain.

Adenosine triphosphate (ATP) is the energy concurrency of the human body and most living systems. This molecule is built such that the three phosphate groups in the molecule can be released one by one and in the process release energy that can be utilized. The adenosine molecule acts as a carrier of the phosphate molecules, and these can be utilized to produce energy in either muscle cells for contraction or to neurons and cause ion channels to transport ions across the membrane potential hereby either polarizing or hyperpolarizing the neuron (Owen & Sunram-Lea, 2011). When phosphate molecules are utilized for energy in the cells from ATP the remaining molecule will, with help from the mitochondria, be made back into ATP, hereby restoring the homeostatic balance of energy in the overall system.
The simplistic view of adenosine and its phosphatic relatives as the energy currency in the brain and body, with ATP being the most valuably and adenosine being the least valuable has proven remarkably useful for understanding how these molecules influence physiology and into the investigation of why we sleep.
One tenable hypothesis is that as we are awake, we use up the phosphate groups in ATP to produce the energy needed for daily activity, and when we go to sleep, we resynthesize this ATP. A key assumption here is that the mitochondria cannot synthesize as much ATP from its phosphate relatives as is being used up when being awake and therefore needs a period (sleep) to resynthesize the ATP from adenosine (Lazarus et al., 2019) (Bjorness & Greene, 2009),

Adenosine:

One of the effects of adenosine in the brain is that it works as an inhibitory neuromodulator. This means that increases in adenosine concentrations in the brain leads to decreased neural excitability especially in on acetylcholine and norepinephrine diffuse modulatory systems, which appear to promote wakefulness (Dulla et al., 2005) (bear et al p. 672-673). Several other converging lines of evidence support this notion that increased adenosine concentration is involved in the sleep-wake cycle (Basheer et al., 2008). In this essay I will be focusing on neuropharmacological studies and especially on the molecules creatine and caffeine. These will be the focus as they are easily supplemented in humans and have been shown to cross the blood brain barrier which is a necessity for the molecules to have a direct effect in the brain (McCall et al., 1982) (Ohtsuki et al., 2002) (Christie, 2007).

Caffeine is one of the most studied stimulants in the world, and effects of caffeine range from increased alertness, to increased reaction time (McLellan et al., 2016). Caffeine's effect is though to be mediated by being an adenosine antagonist, meaning it binds to adenosine receptors and inhibits the decreased neural excitability caused by the accumulation of adenosine in the brain (McLellan et al., 2016). Some of the most convincing mechanistic animal evidence of this antagonistic effect of caffeine comes from knock-out mice and rats where one of the 4 known adenosine receptors have been inactivated. The results from these studies suggest a dose-dependent relationship between the percent of knocked out receptors and the wakefulness effects of induced caffeine (Lazarus et al., 2011). A tenable hypothesis could be that antagonists to these adenosine receptors would reduce feelings of sleepiness and reverse some of the negative cognitive effects seen in prolonged sleep deprivation. This hypothesis would therefore be able to explain the increased alertness and reaction time findings described earlier and supports the notion that the effects are more notable when individuals are sleep deprived (Souissi et al., 2014).

Creatine does not directly influence adenosine receptors as caffeine does, however creatine is thought to work as a buffer of phosphate, the energy storing component of ATP, essentially working as an energy reserve. The way that creatine is thought to help maintain a homeostatic ATP level is that creatine binds to a phosphate group and thereby becoming creatine phosphate (PCR) which enters the cells and can donate the phosphate group to adenosine diphosphate or adenosine monophosphate, basically functioning as an energy

reverse.

Studies in humans utilizing muscle biopsies have found that creatine-phosphate levels in most humans are not fully saturated, because supplementation with creatine increases the concentration of PCR in muscle cells and increases physical performance in high intensity tasks where the PCR energy system is thought to be mostly active as the transfer of phosphate from PCR is much quicker than the synthetization of ATP (Casey & Greenhaff, 2000).

Creatine can also cross the blood brain barrier and it has been hypothesized that it therefore might influence cognitive aspects and especially when lots of energy is needed or much energy has been consumed, as with prolonged sleep deprivation. Magnetic resonance spectroscopy has been used to determine that oral supplementation of creatine can increase brain phosphor creatine levels as well as inorganic creatine levels in the brain. (Lyoo et al., 2003)

One of the most convincing lines of evidence indicating that creatine supplementation has cognitive implications is studies done on patients suffering from cerebral creatine deficiency syndrome, making them unable to produce and synthesize creatine. Symptoms of these conditions include autism like behaviors and intellectual disability of variable severity. These symptoms are treated with creatine supplementation which strongly improves many of the symptoms of the patients (Stockler et al., 2007).

Other studies have shown that creatine supplementation in healthy individuals can reduce the negative effects on executive function from sleep deprivation in healthy individuals (McMorris et al., 2007, McMorris et al., 2006) and that these effects are more pronounced in vegetarians and vegans that do not get creatine from their diets hereby further decreasing their creatine availability (Cooper et al., 2012).

One of the reasons that we sleep seems to be to replenish the molecules that the body uses for energy. So, when we do not sleep the remains built up and interfere with normal functioning. There are several ways to combat this built up of remains, some temporary, caffeine supplementation and some more long lastly, creatine supplementation.

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