

Effects of sleep deprivation in hippocampal neurogenesis

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Abstract

Adult neurogenesis in the hippocampal dentate gyrus (DG) is a process that involves proliferation, differentiation, maturation, migration and integration of young neurons in the granular layer of the DG. These newborn neurons mature in a 3 to 4-week period and then they are incorporated into pre-established hippocampal neural circuits, where they participate in cognitive functions, including spatial memory acquisition and retention, which are consolidated during sleep. In this review, we describe the main findings associating fragmented or total sleep deprivation with changes in DG neurogenesis, as well as their possible consequences on mental processes. In addition, some possible mechanisms implicated in this deterioration are analyzed, such as circadian rhythmicity, melatonin receptors and some growth factors. (Gac Med Mex. 2015;151:90-5)

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Introduction

One of the dogmas that marked last century's neurosciences claimed that replication of new neurons could not occur in adult life. However, since the works by Altman in the sixties, it was possible to overcome this ingrained dogma. One of the first experiments that reported neurogenesis in rodents attempted to observe the glial response upon lateral geniculate body focal damage. In this model, autoradiography with thymidine (an essential nucleotide in the conformation of DNA, which incorporates into the nucleus of the dividing cell) was used, and the presence of mitotic cells, unrelated with the site of injury was observed. These cells presented neuron ultrastructural characteristics, which suggested the existence of adult neuronal reproduction

in specific cerebral areas¹; thus, the term neurogenesis was coined (from *neuro* in reference to nervous system cells, and *genesis*, which means "birth"). Since that moment, numerous studies have reported neurogenesis in different species and cerebral regions. However, in this work we will focus exclusively on findings at the hippocampal level, given their association with sleep-wake cycle-modulating substances.

In 1977, Kaplan et al.² found neurogenesis in the dentate gyrus (DG) and olfactory bulb in a 3-month old rodent. Hippocampal neurogenesis was confirmed by Miller et al. in 1988³. They studied neurogenesis using immunohistochemical detection of bromodeoxyuridine (BrdU), an analog of thymidine that is incorporated into DNA during the S-phase of the cell cycle. With this experimental approach, they were able to determine the presence of proliferative cells in the subgranular zone (SGZ) of the DG and corroborated the findings reported with the 3H thymidine marker. Finally, Eriksson et al.⁴ studied the brains of five cases of patients with thyroid cancer (who had received BrdU injections

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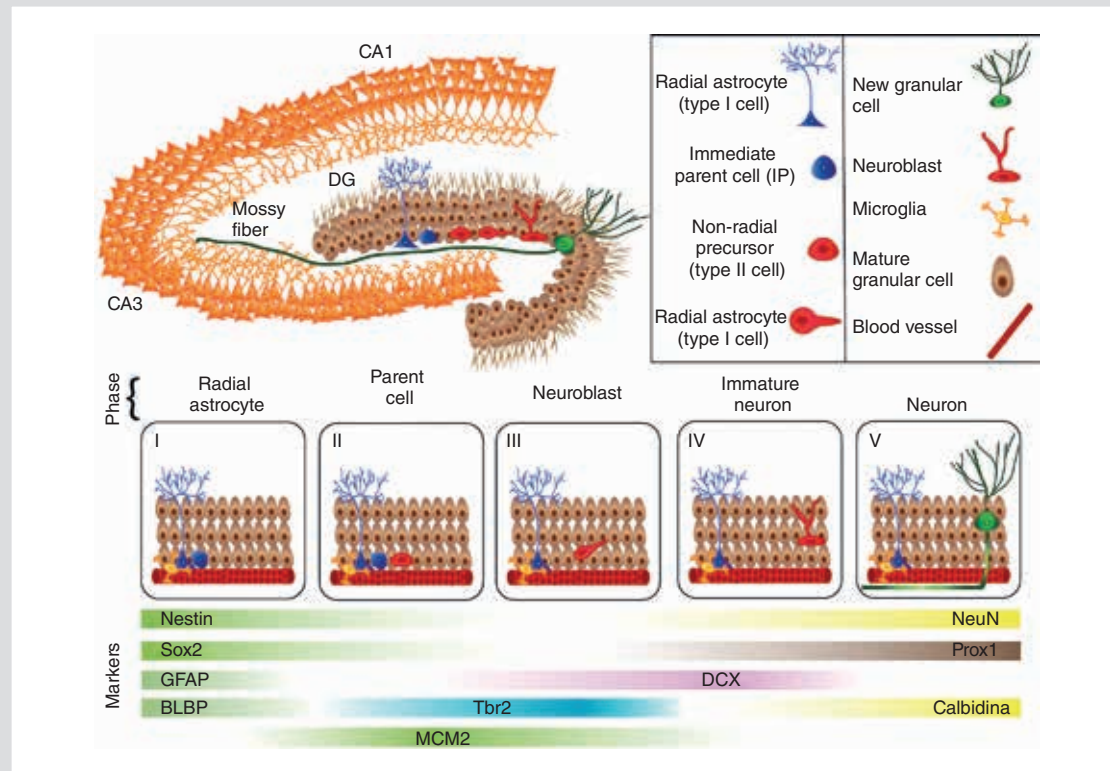


Figure 1. Schematic representation of the rodent hippocampus and the cell lineages found in the hippocampal DG SGZ. Radial astrocytes (type I cells) are considered the neural stem cells of this region, which give rise to neuronal precursors (type II cells) that migrate towards superior layers, where they differentiate into mature neurons (post-natal granular). This process lasts approximately 28 days, and during its course, subgranular progenitors express different molecular markers that allow for their typification to be performed. BLBP: brain lipid-binding protein; Tbr2: T-box brain protein; Prox1: prospero homeobox protein 1; MCM2: nuclear replication factor MCM2; DCX: doublecortin.

for diagnostic purposes) and were able to detect the presence of positive cells to BrdU and other neural markers (glial fibrillary acidic protein [GFAP], NeuN and calbindin) in the SGZ and subventricular zone (SVZ) of the human brain.

Neurogenesis at the SGZ in rodents

In the hippocampal DG there is a cellular basal stratum known as SGZ (Fig. 1), which contains multipotential neural progenitors able to produce neurons and astrocytes throughout the individual's entire life⁵. The use of BrdU labeling has allowed to determine that approximately 4,000 to 7,000 new neurons are generated per day, out of which less than a third do survive⁶. This implies an incorporation of around 250,000 new neurons per month in this zone⁷. New-born born subgranular cells start a 2-month maturation process, and during this period they project efferences and receive

afferences from the CA3 (*cornu ammonis* 3) region⁸. This neurogenic process begins with radial astrocytes proliferation, which originate immature neuronal cells (neuroblasts)⁹ that migrate towards the so-called granular layer (Fig. 1)¹⁰. Once there, these young neurons project dendrites towards the DG molecular layer and spread their axons towards CA3 area pyramidal cells and the hilus to establish synaptic contacts with afferent axons of the entorhinal cortex, thus becoming mature neurons¹¹. At each one of these stages, neural precursors express a variety of molecular markers that are used to perform their typification (Fig. 2).

Neurogenesis at the SGZ in humans

DG in the human being is a dorsomedial concave groove that includes the CA4 area. Its medial portion is in front of the lateral fisure, limited by the fimbria and ventrally by the hippocampal fissure subiculum

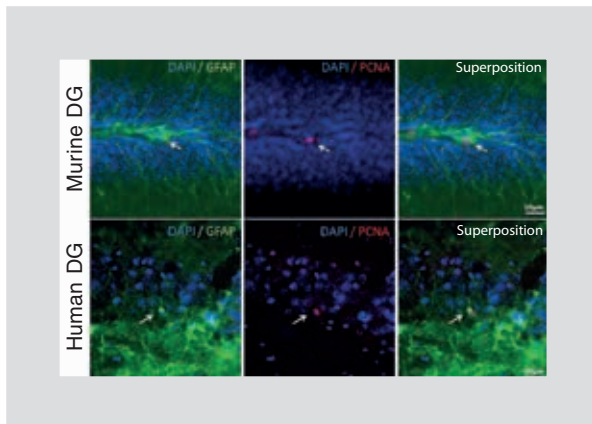


Figure 2. Human and murine DG immunofluorescence protographs. Cell nuclei are labeled with 4',6-diamidino-2-phenylindole (DAPI) (blue), astrocytes (green) were detected with anti-GFAP antibodies and proliferative cells (red) with antibodies against proliferating cell nuclear antigen (PCNA). In both cases, arrows point to a proliferating subgranular astrocyte. Calibration bar = 10 μ m.

(Fig. 3)^{12,13}. This area has been associated with the processing of declarative memory¹⁴. In the human DG there are cells with similar characteristics to those reported in rodents and non-human primates, although their general architecture shows important morphological differences. Similarly as in rodents, most cells concentrate in the granular layer, but their numbers vary considerably; for example, in rats, the number is approximately 1.2 million neuronal cells¹⁵, whereas in humans it reaches 18 million¹⁶. Also the number and

distribution of mossy cells of the hilus are different in each species; in rats, total number of neurons is estimated to be 10,000¹¹, whereas in the human this figure is approximately 1.72 million¹⁶. From a morphological point of view, mossy cells dendritic spines are proportionally larger in humans than in rodents and monkeys¹⁸. In addition, some ramifications of these cells have been observed to penetrate into the molecular layer, which suggests they receive afferences from the hippocampal perforant pathway, a finding not confirmed in rodents, which, in addition, possess a well-defined hilus¹⁹. In humans, the number of neurons generated every day has been calculated to possibly reach approximately 700 per day²⁰, although this number could decrease dramatically with increasing age^{4,21}. Nevertheless, there are still little data on neural maturation dynamics in the human SGZ (Fig 2)^{21,22}.

Effects of SD on neurogenesis

Sleep deprivation (SD) entails a number of physiological disturbances in different organs and systems²³⁻²⁵. By means of electroencephalographic activity records, three biological basic states of the sleep-wake cycle have been determined in humans and other mammals: alertness state (awakeness *per se*), rapid eye movement (REM) sleep with and sleep with no rapid eye movement (NREM). These cycles are produced by activation of reciprocally connected thalamic and cortical neurons^{26,27}.

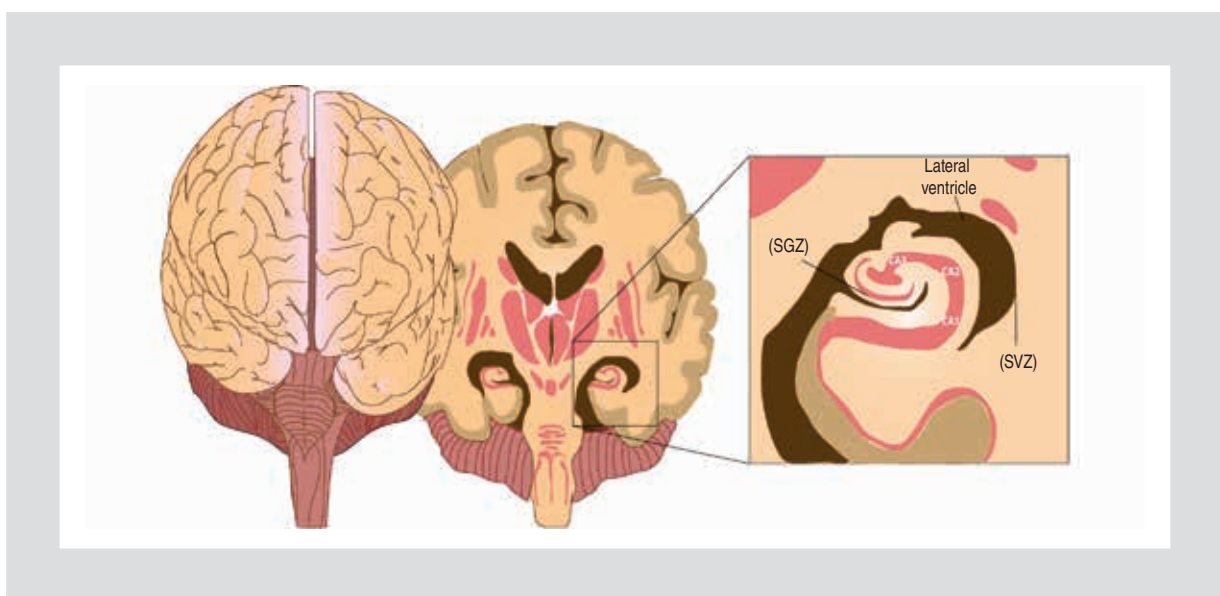


Figure 3. Schematic representation of the hippocampus of the human adult brain. The panel shows an amplification of the anatomical localization of the hippocampal SGZ and its relationship with the Ammon's horn (cornu ammonis) (CA1, CA2 and CA3).

Sleep seems to have an important function in memory consolidation, a dynamical process produced by interaction of hippocampal neuronal networks and the neocortex²⁸. At the cortical level, pyramidal cell networks are modified (plasticity) as a result of calcium influx in the dendrites during the NREM cycle of sleep, which is characterized by the presence of slow waves that favors long-term memory²⁹. Once memory is consolidated in the neocortex, the hippocampus gradually removes some pre-existing connections (short-term memory), presumably restoring the hippocampal capacity to generate networks³⁰.

One of the most notorious negative consequences of SD in humans is the deterioration of memory^{31,32} resulting from a reduced acquisition of temporal memory³³ and declarative memory^{34,35}, as well as low consolidation of hippocampus-dependent memory³⁶⁻⁴⁰. Hippocampus-dependent memory consolidation in rodents is assessed as memory of objects, places and settings⁴¹⁻⁴³, and its efficacy decreases after SD^{44,45}. These tasks are comparable to the declarative memory test in humans, who also show deficiencies after SD³⁴.

Hippocampal memory consolidation and retention tasks are modulated by young neurons produced at the SGZ of the hippocampus^{46,47}. Recent research indicates that SD significantly reduces proliferation, survival, differentiation and even maturation of these new neurons. In this regard, Guzmán-Marín et al. have reported a decrease in the proliferation rate at the hippocampal DG occurring in animals deprived of sleep for 96 h⁴⁸. Other study where the sleep REM phase was deprived reported an 82% decrease in the percentage of BrdU+ cells and 80% decrease in Ki67+ (a G1, G2 and S cell-cycle phases proliferation marker) cells in this same neurogenic niche⁴⁹. Furthermore, fragmented sleep deprivation (FSD) during eight days significantly decreased the number of Ki67+ cells at the SGZ. Similar results have been reported in adrenalectomized animals subjected to FSD⁵¹, in which the effects of stress (generated by FSD *per se*) on corticosteroid-mediated neurogenic processes are neutralized. A similar study, where the SD model was used over a 12-h period under light conditions showed no modification in the average of BrdU+ and Ki69+-expressing cells⁵², and even the same SD time applied during the night produced an increase in the number of BrdU+ cells^{53,54}. Taken together, these results indicate that total and partial (REM phase) deprivation of sleep greater than 56 h decrease new neuron proliferation at the hippocampus and that the mechanism regulating their proliferation is disturbed by SD.

The molecular mechanisms underlying the decrease in SD animal models are not completely clarified. It has been suggested that these mechanisms are affected by circadian rhythmicity. Recent studies report variations in the subgranular cell proliferation rate in different deprivation periods (light/darkness) with the SD experimental model⁵²⁻⁵⁴. Such variations seem to be more significantly modified during the night^{55,56}. In fact, the circadian rhythmicity processes that promote mitosis during the night have been suggested to act on the transition of the G2/M phase (G2-to-mitosis phase) and to be determinant for the continuity of the cell cycle or to induce apoptosis⁵⁷.

Currently, emphasis has been placed on the possible modulating role of melatonin in the neurogenesis process. Continuous exposure to light for 24 h reduces melatonin expression⁵⁸ and proliferation at the hippocampal SGZ⁵⁹. This neurohormone promotes cell proliferation during the process of aging⁶⁰ by decreasing the amount of free-radicals and this way avoid cell death caused by oxidative stress. The hippocampus is a region that is susceptible to the effects of stress and cell oxidation^{61,62}. These events decrease the levels of brain-derived neurotrophic factor (BDNF) and calmodulin-dependent protein kinase II (CaMKII). In this regard, administration of melatonin to sleep-deprived rats increases the levels of these proteins in the hippocampus, which suggests that this antioxidant favors the neurogenic process.

In addition to its functions as antioxidant, melatonin modifies neurogenesis through the melatonin receptors 1 (MT1), present in subgranular neural precursors⁶³. In this regard, the administration of melatonin for seven days promotes DG neuronal parent cells survival and differentiation⁶⁴. The number of BrdU+ cells has been reported to decrease by 39.6% after a 96-h period of SD⁶⁵. Similar effects are observed during an eight-day period of FSD, with a reduction occurring of a third of these cells⁶⁶. FSD also produces a considerable decrease in neuroblast differentiation⁴⁵, although such changes have not been observed with total deprivation⁵. Curiously, the neuronal maturation process in the SGZ is also affected by SD, a phenomenon observed with a 96-h total SD model⁶⁵. Other events implicated in SD-mediated neurogenesis reduction involve the inhibitory effect exerted by long-term potentiation on SGZ⁶⁷, through reduction of the cAMP response element-binding (CREB) protein, BDNF^{68,69}, calcium kinases calmodulin II and IV (CaMKII and CaMKIV)⁷⁰.

Conclusions

During the phases of sleep, episodic and spatial memory are consolidated in the hippocampus, a process likely coadjuvated by the generation of new cells in the DG. Different investigations show that SD in rodents modifies neurogenesis. In fact, long deprivation periods decrease hippocampal cell proliferation, survival or maturation, without altering their integration into the DG circuitry. Circadian rhythmicity has been found to promote mitosis of neural progenitors, especially during the night, which has been associated with the levels of melatonin receptors and BDNF in the SGZ. These cellular changes can be highly relevant, since current rhythms of life have motivated changes in populational periods of sleep, which produce different systemic and cognitive alterations, such as memory acquisition and retention, which are associated with hippocampal neurogenesis.

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