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Role of Sex Hormones in Influencing Neurogenesis Through Astrocyte Activity

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Abstract: ***Neurogenesis is most likely to occur in the hippocampal area of the brain due to its conductive environment. Particularly the subgranular and subventricular zones of the dentate gyrus zone. The process of neurogenesis can be divided into 3 stages. These stages include proliferation, differentiation and maturation. The cells involved in these stages are neural stem cells. These cells can be influenced by a variety of different factors, both intrinsic and extrinsic. Hormones are an intrinsic factor. In particular, sex hormones can influence the proliferation and differentiation stages of neurogenesis. These sex hormones include estrogen and androgens. There are different types of estrogen molecules such as estradiol and other estrogen - like molecules that can play the role of estrogen in influencing a particular neural stem cell, astrocytes. Astrocytes are largely responsible for maintaining a balanced internal environment for the proliferation of cells to take place in order to result in a mature neuron. Through the particular hormone receptors present on astrocytes, its proliferation is influenced positively causing the rate of neurogenesis to increase. The data available is limited to animals such as primates and rats but there is enough evidence to conclude a link between hormones and neurogenesis.***

Keywords: neurogenesis, hippocampus, estrogen, astrocytes

1. Introduction

Neurogenesis is a fascinating concept that introduces the capacity of a mammalian brain to create new neurons from neural stem cells (NSC's) and progenitor cells in the brain. This process was traditionally viewed to occur primarily in embryonic and prenatal stages in mammals. [1] In the 1960's, Altman and Das proved that neurogenesis does not occur only during the brain development stage but also postnatal, specifically in the adult hippocampal region. [2] By using this study as the foundation for further research, the introduction of bromodeoxyuridine (BrdU), a nucleotide analog, as a lineage tracer [3] and demonstrating that neurogenesis continues throughout a mammals lifespan [4] setting the discovery in stone. Significant progress has been made since then.

Adult neurogenesis has been said to occur majoritarily in the subgranular (SGZ) and subventricular zones (SVZ) of the dentate gyrus region of the adult mammalian hippocampus. [4] These specific areas of the hippocampus compose of a large number of neural stem cells which are responsible for neurogenesis. Some of these cells include radial glial cells comprising of both pluripotent and different lineage - restricted neural progenitors that give rise to new neural stem cells which are responsible for neurogenesis. [5] A type of glial cells called astrocytes also play a major role in neurogenesis. They secrete various signaling molecules that promote the survival and proliferation of neural stem cells like radial glial cells. [6]

The entire process of neurogenesis can be divided into three major parts. In simple terms, we can describe these phases as proliferation, differentiation and maturation phases. [7] A radial glia - like precursor cell proliferates a postmitotic matured cell through high proliferative activity and comes to be a new granule cell, a type of neuron. [8]

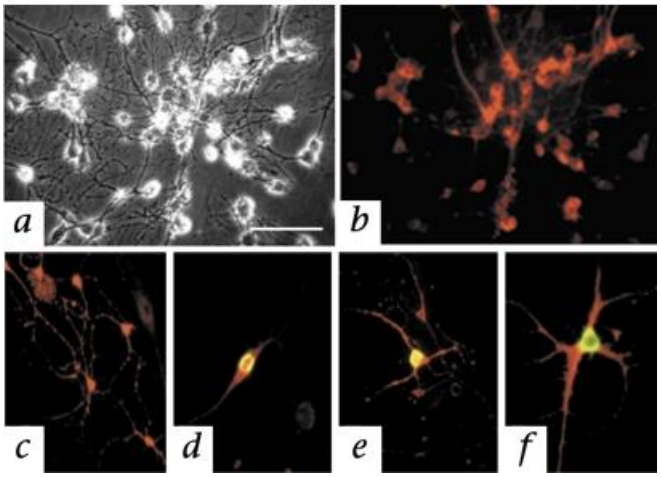


Figure 1 [9] The adult human hippocampus containing mitotic neuronal progenitor cells
a & b - monolayer dissociate of adult human dentate gyrus, removed from a 33 - yr old man after temporal lobectomy
Phase (a) and fluorescence (b) images of a cluster of neurons at 7 d in vitro; c, Hippocampal culture from a 35 - year - old
Scale bar represents 50 µm.

The proliferation stage involves NSC's undergoing asymmetrical division to produce progenitor cells. Due to this division, a higher number of precursor cells are available for further differentiation. Since these progenitor cells are present in between the differentiation and proliferation stages of neurogenesis, they are called intermediate progenitor cells (IPC's). These IPC's further divide to produce neuroblasts, a more differentiated version of IPC's that exit the continuous cycle of division to develop into mature neurons.

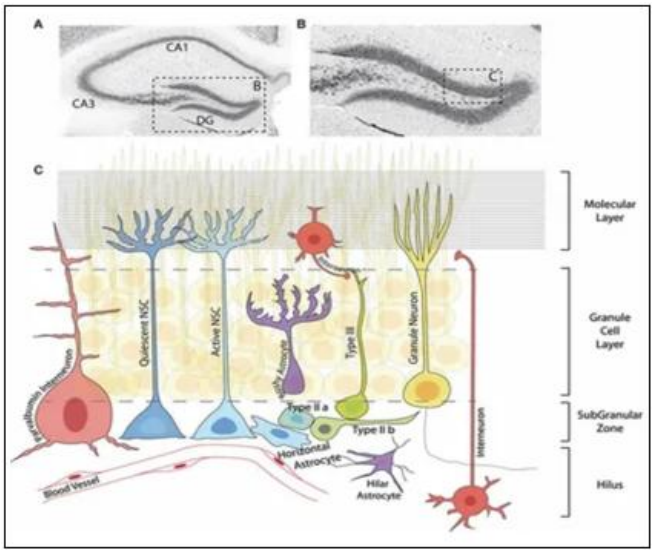


Figure 2: [10] (C) Graphic representation of the area marked in (B) depicting the neurogenic lineage

Consists of quiescent and active NSCs, IPCs, neuroblasts and granule neurons. Neural stem cells and IPCs reside in the SGZ, while neuroblasts and neurons are found in the granule cell layer. Several types of interneurons (red) and astrocytes (purple) are located in different regions of the DG, and together with granule neurons are essential parts of the adult hippocampal niche.

The maintenance of a conductive internal environment is crucial for these processes to occur chronologically. This responsibility is undertaken by astrocytes. Furthermore, astrocytes also secrete growth factors to aid in the maturation of neuroblasts. Some of these include Fibroblast Growth Factor, Heparin - Binding Epidermal Growth factor - like Growth Factor and Bone Morphogenetic proteins. [11] They each contribute slightly differently to the maturation of neuroblasts. [12]

During differentiation, progenitor cells undergo a series of changes that help in their identification as a neuron. [7] This involves the expression of specific transcription factors and neuronal markers. Synapses begin to form and acquire specific electrophysiological properties such as resting membrane potential and action potential. [13] Biochemically, synaptic firing requirements are set. These involve voltage gated ion channels and calcium dynamics.

The maturation stage involves neuroblasts to undergo significant morphological processes. Synaptic connections are established through extension of their dendrites and axons. This process is called synaptogenesis. [7] They each allow inputs to be received by other neurons and connect with target cells. This maturation also involves changes in the ion channel expression and synaptic plasticity. Neuroblasts begin to form synapses and allow an integration of new neurons into existing neural circuits allowing them to contribute to various brain functions. [14]

Multiple different factors can positively influence these stages of neurogenesis. However, the timing of neurogenesis from active NSCs has been difficult to analyze, as viral labeling and thymidine analog incorporation are not restricted to NSCs and transgenic lineage tracing has been hampered by a lack of cell - type specificity. Several intrinsic factors such as hormones, lower stress levels, trophic factors and glia contribute to the maintenance and regulation of NSC's proliferation. This review aims to explore the influence of hormones such as estrogen on astrocytes that alter neurogenesis in response to estrogen receptors and concentrations in different areas of the adult mammalian hippocampus.

Hormonal role in neurogenesis

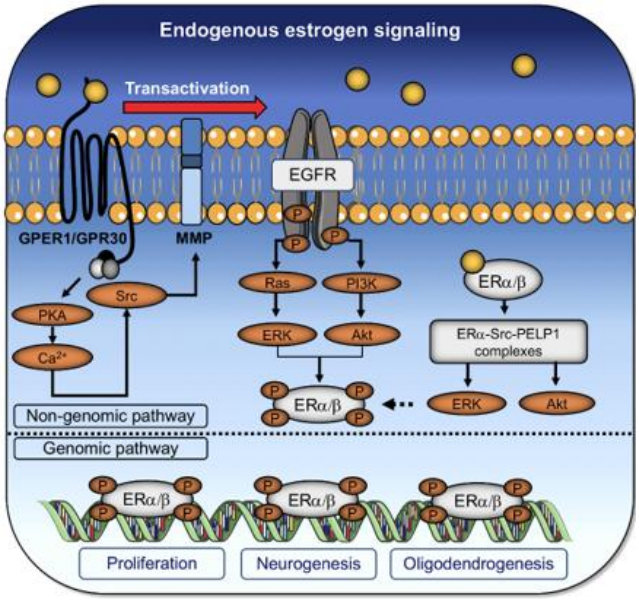
Hormones play a significant role in influencing various stages of neurogenesis. Estrogen and androgens are particularly influential. Androgens are hormones that influence male reproductive activity. The action of these hormones are also through receptors particular to this hormone present on the cell surface of astrocytes and other neural stem cells. Short - term androgen replacement increased the cell proliferation in male meadow voles without altering the number of adult - generated cells in the hippocampus. [15] Long - term androgen replacement increased the survival of cells in the ganglion cell layer, but not hilus, in male Sprague - Dawley rats without altering GCL neuronal differentiation. On the other hand, one acute mating encounter in male C57BL mice did not alter cell survival in the accessory or main olfactory bulb, but it increased neuronal differentiation in the glomerular cell layer of the main olfactory bulb. [15] In these ways, we can determine a connection between androgen molecules and the stage of differentiation in neurogenesis occurring in rats.

Hormonal influence in the hippocampus of an embryonic brain

Estrogen in specific acts by binding to estrogen receptors, under the family of nuclear receptors. These receptors are present in the SVZ and SGZ of the dentate gyrus region of the hippocampus and ERβ (Beta Estrogen Receptor) levels are shown to remain largely constant during both developmental and adult NSC's. To determine whether estrogen acts on proliferating neural stem cells [16], the estrogen receptor's (ER) expression was observed. A RT - PCR analysis, a reverse transcription polymerase chain reaction, was used to reveal that the proliferating NSC's expressed both ERα and ERβ, two ER subtypes. The ratio of ER - positive and TH - positive (Tyrosine hydroxylase, a present marker for dopamine, norepinephrine, and epinephrine - containing [catecholamine]) neurons was 85.5% and 81.7% for ERα and ERβ receptors respectively. [16] This evidence suggests that estrogen does act on NSCs derived from the human embryonic brain in vitro and in vivo. This supports the hypothesis that hormones like estrogen have an effect on neurogenesis through the cells involved in the stages, particularly NSCs.

Impact of Estrogen and Estrogen - like molecules

Estrogen in particular modulates a balance between the different stages of neurogenesis. Particularly, the proliferation and differentiation stages. Short - term estrogen replacement increased DG cell proliferation in female Sprague - Dawley rats and meadow voles.



[19] Figure 3: Endogenous estrogen regulates the proliferation and differentiation of NSPCs. Endogenous estrogen binds to both classical and non - classical ERs. There are multiple processes of translocation, cell signaling and activation throughout this mechanism that concludes with an influence on the expression of genes associated with cell proliferation and in turn, neurogenesis

Short - term estrogen replacement increased cell proliferation in the prairie vole SVZ. Long - term estrogen treatment did not alter hippocampal cell proliferation in female and male rats. [16]

There are three main forms of estrogens: estrone, estradiol and estriol. These are produced by different organs. These molecules have a high affinity for ER receptors including ERα and ERβ. [17] ERα interacts with the intercellular protein: Estradiol 2 (E2). [18] Both ERα and ERβ are classical receptors that are expressed in the NSCs present in the hippocampus. [19] Primate - derived neurons and neurons derived from human NSPCs exhibit rapid oscillation in the intracellular calcium concentration after being stimulated with estrogens or ERβ selective agonists [19] Evidence indicates that estradiol is also able to play an important role in differentiating the human brain during early prenatal stages and even after birth. [20]

Some estrogen - like molecules include phytoestrogens and xenoestrogens. These are similar in structure and function of estrogen molecules. Phytoestrogens are plant derived molecules that have an effect quite like estrogen molecules in the human brain. The reason these are crucial to research is because they allow a comparison to be made in terms of growth and capacity to undergo basic cognitive functions that have been noticed in plants. Although these cannot be called cognitive functions, they are induced by phytoestrogens and can be altered and influenced depending upon certain factors in relation to plants. [19] Xenoestrogens are chemicals that act as disruptors by binding to classical ER's. Since these ER's are present in plants, its consumption is also an area of focus since it can influence brain health and disease. They influence estrogenic activity through binding to ERs present.

2. Conclusion

Estrogens appear to play a key role in the growth of the brain and the maturation of differentiated neural stem cells. This opens novel perspectives on the effect of these hormones on brain activity and cognitive processes, laying emphasis on brain homeostasis.

3. Discussion

Multiple factors play a role in inducing the proliferation of NSCs thus contributing to neurogenesis. Hormones, specifically estrogen, plays a role in influencing the rate of neurogenesis. There are a huge number of factors to consider when discussing the influence of a hormone. Receptors are the most common and simplest method through which an undeniable connection can be made. Yet, in the adult mammalian brain, there is immense research yet to be made especially in the area of hormones and their influence on neurogenesis.

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