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# Stem Cells on Hippocampus – A Short Review

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**Abstract**

Multipotential cells have been identified both in vitro and in vivo in the central nervous system of human being. Defined mitogens cause the proliferation of multipotential cells in vitro, the magnitude of which is sufficient to account for the number of cells in the brain. Factors that control the differentiation of fetal stem cells to neurons and glia have been defined in vitro, and multipotential cells with similar signaling logic can be cultured from the adult central nervous system. Neural stem cells can also be derived from more primitive embryonic stem cells. Transplanting cells to new sites emphasizes that neuroepithelial cells have the potential to integrate into many brain regions. These results focus attention on how information in external stimuli is translated into the number and types of differentiated cells in the brain. The development of therapies for the reconstruction of the diseased or injured brain will be guided by our understanding of the origin and stability of cell type in the central nervous system. The term "neural stem cell' is used specifically to describe cells that (a) can generate neural tissue or are derived from the nervous system, (b) have some capacity for self-renewal, and (c) can give rise to cells other than themselves through asymmetric cell division.

**Key Words-**
Hippocampus, Neuroepithelial Cells, Culture, Multipotential, Stem Cells.

## INTRODUCTION

Neurons, astrocytes and oligodendrocytes arise from precursors in the germinal layer of the developing brain, the ventricular and subventricular zones. Ongoing anatomical reorganization is now widely accepted as a fundamental mechanism of adult neural plasticity. An example of this reorganization is the birth of new granule neurons in the dentate gyrus of adult hippocampus in all mammals, including humans[1-3]. Although adult neurogenesis in the CNS of mammals has been seen for over three decades [4,5], little is known about the extent to which adult-derived neurons are mature and functional[6]. Recent advances in stem cell technology have led to purification and *in vitro* propagation of stem cells from embryonic and adult tissues of various species, including humans[1-3]. Several groups have isolated adult cells whose progeny express, *in vivo* and *in vitro*, neuronal antigens[7-15]. Rarely addressed, however, is the question of whether adult stem cells can give rise to fully differentiated and functional neurons. It is not yet known whether adult-derived neurons have even basic functional properties of mature CNS neurons, such as action potential firing. A few studies have reported that neurons derived from adult progenitor cells show rather limited neuronal maturation *in vitro*, as evidenced by the small voltage-dependent Na+ currents[13] and the inefficient formation of synapses[16]. Furthermore, adult-derived neurons have never been shown to be capable of releasing classic neurotransmitters. Embryonic stem (ES) cells[17] and neuronal progenitors from developing brains[18], in contrast, retain the ability to develop into fully functional neurons *in vitro*, bringing into question the functional potential of adult-derived neural stem cells. Mature CNS neurons share certain characteristic properties[19]. Neurons are polarized, non-mitotic cells, normally with a single axon and multiple dendrites. They are able to fire tetrodotoxin (TTX)-sensitive action potentials and, most importantly, to communicate with other cells by releasing and detecting neurotransmitter at their synapses. The mechanisms of differentiation, maturation and synapse formation of neural progenitors during development have been thoroughly investigated [20-22], but little is known about these processes in adult neurogenesis. It is not clear whether the set of cues responsible for neuronal maturation and synapse formation during development persists in adults, or whether the neural progeny of adult stem cells retain the ability to respond to these cues. Here we established an *in vitro* co-culture system to examine the functional potential of neural progeny of stem cells derived from adult hippocampus. We also investigated the underlying mechanisms of their maturation. Our findings demonstrate that, qualitatively, neural progeny of adult stem cells show the same key properties as do mature CNS neurons. Moreover, we report that astrocytes from postnatal hippocampus promote neuronal maturation and formation of functional synapses by adult stem cells.

## DISCUSSION

Cell proliferation in the adult mammalian brain is ubiquitous but is primarily confined to the measured production of glia. Except for discrete regions in the hippocampus and the subventricular zone (SVZ), neurogenesis is conspicuously absent [23]. The reasons why these areas continue to generate neurons are unknown, but primary cell cultures from the adult rodent brain are beginning to provide some insights. Cultures initiated from adult SVZ or hippocampal (HC) tissues contain proliferative neuronal and glial-restricted progenitors, as well as multipotent precursors with the characteristics of neural stem cells, i.e., the ability to self-renew and the ability to generate both neurons and glia [24]. More recently, Johansson et al. (1999) has shown evidence that some of these stem-like cells may actually be ependyma. If ependymal cells are actually stem cells, it seems increasingly unlikely that neurogenesis is absent in other regions because of the lack of multipotent stem cells. In past work, we have suggested that stem cells may be more widely distributed because cells from non-neurogenic areas

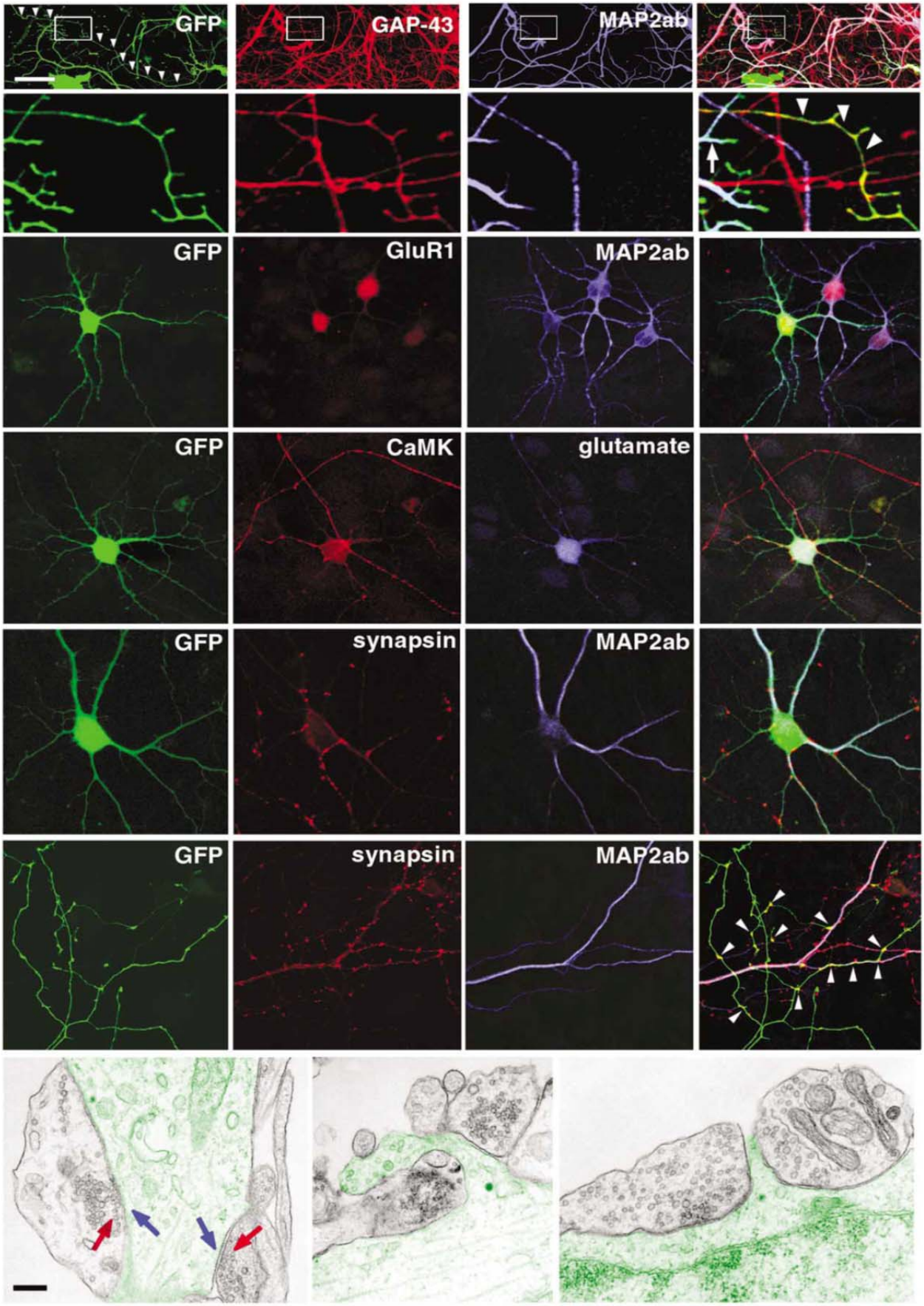
GFP
GAP-43
MAP2ab
GFP
GluR1
MAP2ab
GFP
CaMK
glutamate
GFP
synapsin
MAP2ab
GFP
synapsin
MAP2ab

**FIG -1**

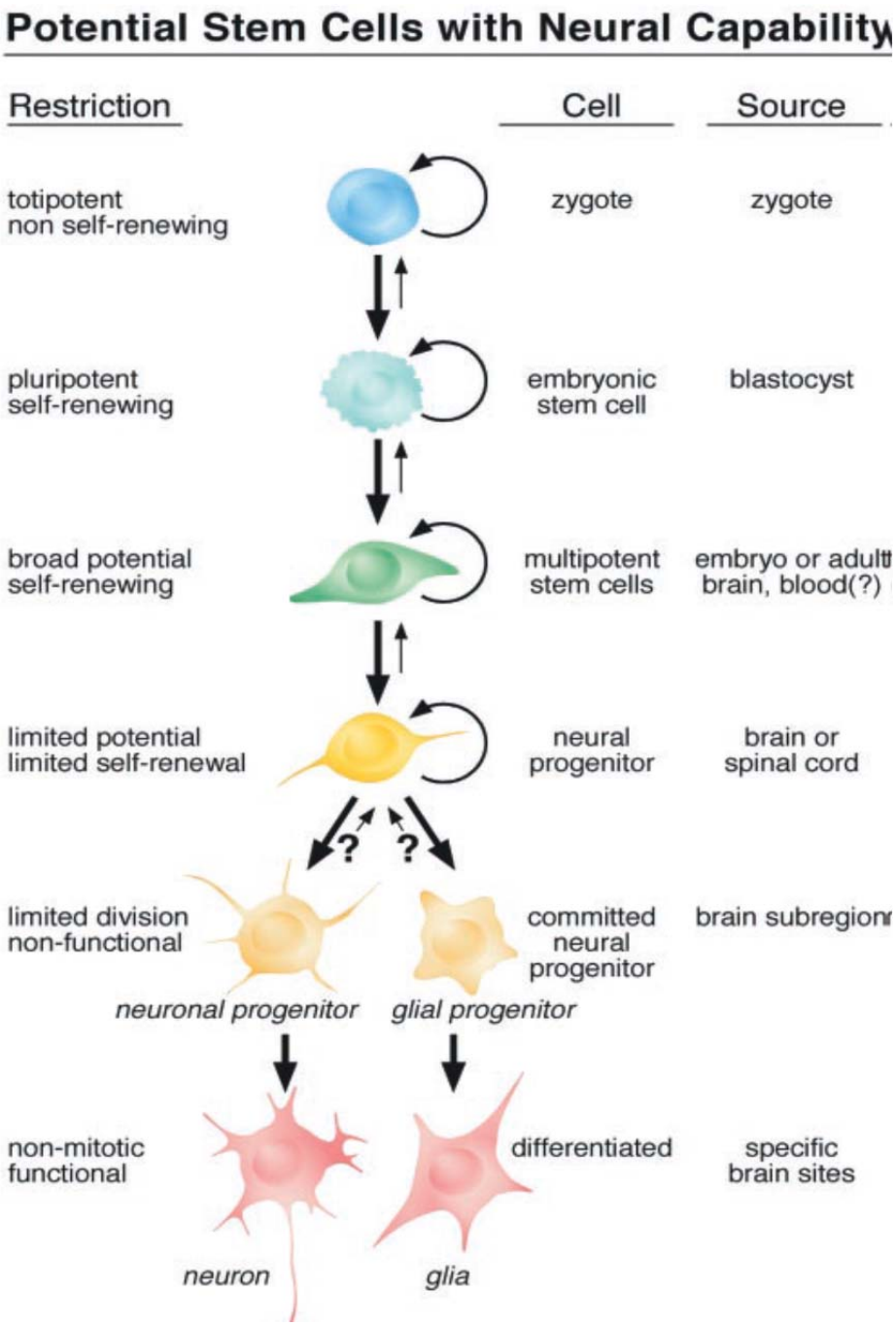


**FIG-2**

repeatedly passaged in the presence of high concentrations of basic fibroblast growth factor (FGF-2) do begin to generate neurons *in vitro* [25]. Stem cells in vitro. The standard method of isolating neural stem cells in vitro is to dissect out a region of the fetal or adult brain that has been demonstrated to contain dividing cells in vivo, for example, the subventricular zone (SVZ) or the hippocampus in the adult or a larger variety of structures in the developing brain. Usually, the tissue is disaggregated and then the dissociated cells are exposed to a high concentration of mitogens such as fibroblast growth factor–2 (FGF-2) [26] or epidermal growth factor (EGF) [27] in either a defined or supplemented medium on a matrix as a substrate for binding. After some proliferation, the cells are either induced to differentiate by withdrawing the mitogens or by exposing the cells to another factor that induces some of the cells to develop into different lineages. Cellular fates are analyzed by staining with antibodies directed against antigens specific for astrocytes, oligodendrocytes, and neurons. In some cases, cells are plated at low density and monitored to determine if a single cell can give rise to the three phenotypes [28]. Stem cell properties can be further demonstrated when cells are lineage tagged with a retrovirus in vitro, after which the clones of cells derived from the original tagged cell are proven to have been derived from a single cell by Southern analysis [29]. Whether stem cells from neural and other tissues are more defined by their tissue of origin or by their multipotentiality is at present unclear. However, neural stem cells can also be derived from more primitive cells that have the capacity

to generate neural stem cells and stem cells of other tissues (Fig. 1). Stem cells have varying repertoires. A totipotent stem cell can be implanted in the uterus of a living animal and give rise to a full organism, including the entire central and peripheral nervous systems.

Neural progeny of adult stem cells establish neuronal polarity with appropriate axon and dendrite formation, a key step in neuronal differentiation[30]. We visualized the distribution of the axonal growth-cone protein GAP-43 and the dendritic protein marker MAP-2ab [31]. In GFP+ neurons derived from our adult stem cells, as in primary neurons, MAP-2ab was present in the soma and in thick processes that emerged from the soma, whereas it was absent from the nucleus (**Fig. 1a**). GAP- 43 was mainly localized to fine processes (**Fig. 1a**). Overall, GFP+ neurons showed a single GAP-43+ axon and multiple MAP-2ab+ dendrites. Glutamate, the chief excitatory neurotransmitter in the CNS, and one of its receptor subunits (GluR1) were also detected in some GFP+/ MAP-2ab+ neurons (**Fig. 1b** and **c**). Within three weeks, some GFP+ cells acquired markers of more mature neurons, such as Ca2+/calmodulin-dependent protein kinase II (CaM kinase II, see **Fig. 1c**). Thus, neuronal progeny of adult neural stem cells in co-culture can establish appropriate neuronal polarity and express proteins that are normally found in mature neurons.

## CONCLUSION

Stem cells are the originator cells of any organism. They give rise to most of the other cells present in our body and has got various functions. Hippocampus consists of mainly grey matter and has a central role in memory processes which is essential for us.

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