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Neurogenesis in the Mammalian Central Nervous System

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ABSTRACT

Medical science have believed firmly for over a century that brain cells are incapable of recreating itself just like other cells of the mammalian body. That the adult brain is static in number developing as dendrites and synapses grow around a fixed number of neurons after birth. Over the past two decades, research have confirmed that adult neurogenesis, the process of generating new neurons which integrate into existing circuits after fetal and early postnatal development has ceased, actually occurs in the olfactory bulb and hippocampus of mammals and indeed man. In addition there is a high level of adult neurogenesis in the olfactory epithelium where olfactory receptor cells are constantly replaced. Furthermore, many vertebrates have neural regeneration capacities that involve neurogenesis (such as tail regeneration in salamanders). This scientific paradygm shift in our view of neurogenesis in the CNS is bound to aid the treatment of cirtain human disorders if advances in scientific research are able to tackle the unanswered questions. This paper reviews the status research so far and reflects on the current direction of adult neurogenesis in the mammalian central nervous system.

Key words: Neurogenesis, Mammals, Human, Brain

The subject of neurogenesis has gained considerable importance in recent years because of its immense potentials in changing an age long viewpoint on a classical biological milestone in the central nervous system. Weiss-man (2000) believes that it has opened up an intriguing new perspective on the treatment of damaged nervous system.

Neurogenesis which is the birth of new neuronal cells, was thought to occur only in developing organisms. Thus the knowledge from recent researches that neurogenesis does indeed continue into and throughout adult life in both vertebrates and invertebrates have curiously raised up topical issues for research.

Neurogenesis in the mammalian CNS - Early views

For more than a century now, neuroscience firmly believed that the mammalian brain cannot repair itself and that mammals are born with all the brain cells it would ever have. Literature is replete with the developmental anatomy of neurons in the central nervous system (CNS) which do not possess schwann cells that are capable of regenerating new neurons as in the peripheral nervous system (Basmajian 1980, Anibeze 2003).

Our current understanding of the human brain is that the adult brain's neuron is static in number. Unlike cells in most tissues, which are generated and replaced throughout life, most neurons of the human brain are not replaced if lost (Kornack and Rakic 1999). This observation is based on the experinments on macaque monkeys in 1960 by Dr Paoko Rakic which showed that brains develop as dendrites and synapses grow around a fixed number of neurons after birth (Blakeslees 2000). The fact that many people do not recover the ability to speak or walk after stroke or brain injury also seen to support this view.

Earlier, scientists have hinted on the possibility of neurogenesis in certain areas of the brain. However, over the past two decades, there have been confirmation that neurogenesis occurs in discrete areas of the adult brain and also that Neural Stem Cells (NSC) reside in the adult brain (Taupin 2002). This has overturned the long-held dogma that we are born with a certain number of cells and that the brain cannot generate new neurons to renew itself (Weissman 2000).

Neural Stem Cells (NSCs).

The evidence that neurogenesis occurs in the adult mammalian forebrain raised the question of the question of existence of NSCs in the adult mammalian brain. NSCs are the self renewing, multipotent cells that can generate the main phenotypes of the nervous system (Taupin 2000). Thus new neurons are generated throughout life from a population of dividing cells known as stem cells or progenitor cells. Aimone et al (2007) defined two criteria as typical in defining a stem cell. They include.

-The potential for self renewal, and
-The ability to give rise to multiple distinct cell types.

NSCs isolated from adult brain can differentiate into the three main lineage cell types of the nervous system namely: neurons, astrocytes and oligodendrocytes when culture *in vitro*. However, the evidence of multipotency of NSCs *in vivo* remain scanty (Aimone et al 2007).

The first cells from adult CNS characterized as capable of generating the three main phenotypes of the CNS *in vitro* were isolated from the mouse striatal tissue (Reynolds and Weiss 1992). These putative NSCs were called Neural Progenitor cells (NPCs) because their stem cell properties had yet to be demonstrated. The NPCs can give rise to neuronal and glial cells, astrocytes and oligodendrocytes *in vitro* (Frederiksen and Mckay 1988).

NPCs have since been isolated from diverse areas of the adult CNS. In the mouse brain (Richards et al 1992), in the subventricular zone (SVZ) of mouse (Lois and Alvarez-Buylla 1993), in the rat (Palmer et al 1995) and human (Kirschenbaum et al 1994, Pincus et al 1998, Kukekov et al 1999, Arsenijevic et al 2001). The demonstration that multipotent, self-renewing progenitor cells of neurons and glial cells can be cultured from NPCs from these adult brain regions shows that NPC cultures contain some NSCs.

Demonstrating that NPCs are multipotent relies on evidence that neurons, astrocytes and oligodendrocytes, the three main phenotypes of the CNS can be generated from single cells. The demonstration that NPCs can self-renew relies on showing that NPCs maintain their multipotentiality over time (Taupin and Gage 2002). Although these criteria are well accepted to show that a single cell is a NSC *in vitro*, they are not absolute.

Taken together, these studies have confirmed the existence of NSCs in the adult CNS and shows that NSCs like NPCs can be isolated from the neurogenic and non-neurogenic areas. Based on the in vitro works done by various scientists using neurosphere assay (Reynolds and Weiss 1992, Zigora et al 2002, Taupin and Gage 2002, Taupin et al 2000, Campos et al 2004, Lobo et al 2003), it can be hypothesized that neurogenesis in the adult brain originates from neural stem cells. However the origin and identity of NSCs in the adult brain remain a subject for proper identification.

Adult Mammalian Neurogenesis

The first study to investigate age changes in the number of Dorsal Root (DRG) neurons in mammals (rat) was publi Hatai (1902). Though this author concluded total number of DRG neurons rer approximately constant with age, data rep his paper (that were obtained from four only) showed a clear increase in cell count fr month to five months old rats (Geuna et al From then on, there has been an avalanche for and against the existence of an age increase in the number of mammalian neurons.

From the 1950s-1980s several studi demonstrated an age related increase in neurons in mammals. Sosa and de Zorrila reported increase in DRG neurons in rabbits; et al (1985) reported same in the cat while observation were found in the rat (Cavanaug Devor and Govrin-Lipman 1985, Devor et al In contrast with these results, coggeshall a workers using a modern design-based c method provided data in favour of the abs neurogenesis in rat DRG, (La forte et al 1991, et al 1994) ascribing previous contrasting re the employment of biased counting m However, evidence supporting the existence related increase in DRG neurons have provided more recently by Cecchini et al (Ciaroni et al (2000).

Despite the foregoing, Geuna et al posited that the great scientific relevance existence of neurogenesis in DRG of mammals and the controversies have surpr not stimulated enough scientific inquest witl scientific community. They attributed the sci calm surrounding the issue to the impossibi properly understanding and explainin occurrence of relevant neurogenesis in adult in the context of scientific milieu that res adult neurogenesis in mammals to a few par situations. However, it in hoped that more scientific advances in stem cell biology tech (Momma et al 2000, Weiss 2000, Weissman will open new ways for understandin interpreting the age-related increase in neurons in mammals, if this occurrence confirmed by further experimental evidence.

In most mammalian species confirme neurogenesis appear to occur in the olfactor and hippocampus. The first evidence

neurogenesis occurs in certain regions of the adult mammalian brain came from (3H)-thymidine labeling studies conducted by Altman and Das (1965). New methods of study using retroviral virus and bromodioxyuridine confirmed that neurogenesis does actually occur in the mammalian brain (Corotto et al 1993, Luskin 1993, Seki and Arai 1993). Two neurogenetic areas were identified namely, the olfactory bulb (OB) and the dentate gyrus (DG) of the hippocampus.

Many studies have reported neurogenesis in different mammalian species. Altman (1969) Bayer (1983) showed the occurrence of neurogenesis in the OB of adult rodents. Similar studies confirmed the existence of neurogenesis in non-human primates (Kornack and Rakic 2001). Eriksson et al (1998) reported the occurrence in humans.

Generally, there is agreement among scientists that the two neurogenetic regions in the adult brain where under physiological conditions NSCs give rise to new neurons are:

- The subventricular zone of the lateral ventricles (SVZ) where NSCs generate cells that migrate into the olfactory bulb, and
- The subgranular zone (SGZ) of the dentate gyrus (DG) where new granule cells become integrated into local neuronal network.

Neurogenesis in Human Brain

Evidence has accumulated that neurogenesis occurs in the adult brain of many mammals Eriksson et al (1998) reported the occurrence of neurogenesis in the adult human brain. Human brain tissue was obtained postmortem from patients who had been treated with a radioactive marker that labels the DNA of dividing cells. New neurons identified by these markers, were found in the dentate gyrus of these patients. The result indicates that the human hippocampus retains its ability to generate neurons throughout life.

Gould et al (1999) reported similar result in macaque monkeys which are phylogenetically close to humans. Both species being old world primates and have similar hippocampal structure and function. Further studies on macaque monkeys reported that new neurons are added to three neocortical association areas that are important in cognitive function-the prefrontal, inferior temporal and posterior parietal cortex. No new neurons were detected in the striate cortex (a primary sensory areas that processes visual information from the eyes). The new neurons appear to originate in the SVZ zone where the stem cells are located and migrate through the while matter to the neocortex. The researchers hypothesized that the presence of new neurons in brain areas involving learning and memory supports earlier suggestions that adult-generated neurons may play a role in these functions.

CONCLUSION

These data, taken together, confirm the existence of neurogenesis in the adult mammalian CNS. The two zones of the SVZ and DG have been identified as possessing the stem cells that give rise to new neurons even in adult. The researches on the age related changes in the number of DRG neurons in mammals appear to remain inconclusive.

Although these research insights have been made which has necessitated a scientific paradygm shift in our view of the cells in the CNS, there is no doubt that so many issues still remain unanswered. For instance the identification of cellular origins of NSC and the functions of newly generated neural cells in the adult CNS remain vague. Thus the key question will remain for now: what do these new neurons do once they survive and become part of the working brain? Do they merely replace old neurons or do they entirely form new circuits? Are they responsible for new memories?

These findings may have critical roles in new therapies for repairing aged or damaged brain. The treatment of human brain disorders that involve the hippocampus, including epilepsy and schizophrenia may be aided by the ongoing neurogenesis in the DG of affected patients.

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