DOWNLOAD PDF ADULT NEUROGENESIS

Chapter 1 : Alcohol, Neural Stem Cells, and Adult Neurogenesis

Neurogenesis is the process by which neurons are generated from neural stem racedaydvl.compmental neurogenesis and adult neurogenesis differ markedly; this article is limited in scope to adult neurogenesis.

Adult Neurogenesis Neurogenesis occurs in two main areas in the adult brain: A chemical called BDNF also appears critical for the transformation into neurons. Most recently, T-cells have also been revealed as important for neurogenesis to occur. The extent and speed of neurogenesis can also be enhanced by various chemicals. Nerve growth factors appear to enhance the proliferation of precursor cells cells with the potential to become neurons , and the prion protein that, damaged, causes mad cow disease, appears in its normal state to speed the rate of neurogenesis. The integration of the new neuron into existing networks appears to need a brain chemical called GABA. Indications are that moderate alcohol may enhance neurogenesis, but excess alcohol certainly has a negative effect. Most illegal drugs have a negative effect, but there is some suggestion cannabinoids may enhance neurogenesis. Antidepressants also seem to have a positive effect, while stress and anxiety reduce neurogenesis. However, positive social experiences, such as being of high status, can increase neurogenesis. Physical activity, mental stimulation, and learning, have all been shown to have a positive effect on neurogenesis. Neurogenesis â€" the creation of new brain cells â€" occurs of course at a great rate in the very young. For a long time, it was not thought to occur in adult brains â€" once you were grown, it was thought, all you could do was watch your brain cells die! Adult neurogenesis the creation of new brain cells in adult brains was first discovered in , but only recently has it been accepted as a general phenomenon that occurs in many species, including humans Where does adult neurogenesis occur? It occurs, indeed, at a quite frantic rate â€" some new cells are born in the dentate gyrus every day in young adult rat brains â€" but under normal circumstances, at least half of those new cells will die within one or two months. The neurons produced in the SVZ are sent to the olfactory bulb, while those produced in the dentate gyrus are intended for the hippocampus. Adult neurogenesis might occur in other regions, but this is not yet well-established. However, recent research has found that small, non-pyramidal, inhibitory interneurons are being created in the cortex and striatum. These new interneurons appear to arise from a previously unknown class of local precursor cells. These interneurons make and secrete GABA see below for why GABA is important , and are thought to play a role in regulating larger types of neurons that make long-distance connections between brain regions. How does neurogenesis occur? New neurons are spawned from the division of neural precursor cells â€" cells that have the potential to become neurons or support cells. How do they decide whether to remain a stem cell, turn into a neuron , or a support cell an astrocyte or oligodendrocyte? Observation that neuroblasts traveled to the olfactory bulb from the SVZ through tubes formed by astrocytes has led to an interest in the role of those support cells. Adult astrocytes are only about half as effective as embryonic astrocytes in promoting neurogenesis. The latest research suggests that the astrocytes influence the decision through a protein that it secretes called Wnt3. When Wnt3 proteins were blocked in the brains of adult mice, neurogenesis decreased dramatically; when additional Wnt3 was introduced, neurogenesis increased. How are these new neurons then integrated into existing networks? Mouse experiments have found that the brain chemical called GABA is critical. Thus a constant flood of GABA is needed initially; the flood then shifts to a more targeted pulse that gives the new neuron specific connections that communicate using GABA; finally, the neuron receives connections that communicate via another chemical, glutamate. The neuron is now ready to function as an adult neuron, and will respond to glutamate and GABA as it should. However, it is clear that other brain chemicals are also involved. An important one is BDNF brain-derived neurotrophic factor , which seems to be needed during the proliferation of hippocampal precursor cells to trigger their transformation into neurons. Other growth factors have been found to stimulate proliferation of hippocampal progenitor cells: Recently it has been discovered that the normal form of the prion protein which, when malformed, causes mad cow disease, is also involved in neurogenesis. These proteins, in their normal form, are found throughout our bodies, and particularly in our brains. Now it seems that the more of these prion proteins that are available, the faster neural precursor cells turn into neurons. Among mice given environmental enrichment, only those with

healthy T-cells had their production of new neurons boosted. Factors that influence neurogenesis A number of factors have been found to affect the creation and survival of new neurons. For a start, damage to the brain from a variety of causes can provoke neurogenesis. Excess alcohol, however, has a detrimental effect on the formation of new neurons in the adult hippocampus. But although neurogenesis is inhibited during alcohol dependency, it does recover. A pronounced increase in new neuron formation in the hippocampus was found within four-to-five weeks of abstinence. This included a twofold burst in brain cell proliferation at day seven of abstinence. Most drugs of abuse such as nicotine, heroine, and cocaine suppress neurogenesis, but a new study suggests that cannabinoids also promote neurogenesis. The study involved a synthetic cannabinoid, which increased the proliferation of progenitor cells in the hippocampal dentate gyrus of mice, in a similar manner as some antidepressants have been shown to do. The cannabinoid also produced similar antidepressant effects. Further research is needed to confirm this early finding. A rat study has also found that stress in early life can permanently impair neurogenesis in the hippocampus. Also, a study into the brains of songbirds found that birds living in large groups have more new neurons and probably a better memory than those living alone. Learning that uses the hippocampus has also been shown to have a positive effect, although results here have been inconsistent. Inconsistent results from studies looking at neurogenesis are, it is suggested, largely because of a confusion between proliferation and survival. Neurogenesis is measured in terms of these two factors, which researchers often fail to distinguish between: But these are separate factors, that are independently affected by various factors. The inconsistency found in the effects of learning may also be partly explained by the complex nature of the effects. For example, during the later phase of learning, when performance is starting to plateau, neurons created during the late phase were more likely to survive, but neurons created during the early phase of more rapid learning disappeared. And finally, rodent studies suggest a calorie-restricted diet may also be of benefit. Now a mouse study using new techniques has revealed that dramatic restructuring occurs in the less-known, less-accessible inhibitory interneurons. Dendrites the branched projections of a nerve cell that conducts electrical stimulation to the cell body show sometimes dramatic growth, and this growth is tied to use, supporting the idea that the more we use our minds, the better they will be. Moderate ethanol consumption increases hippocampal cell proliferation and neurogenesis in the adult mouse. International Journal of Neuropsychopharmacology, 8 4 , Journal of Neuroscience, 25, New GABAergic interneurons in the adult neocortex and striatum are generated from different precursors. Journal of Cell Biology, , Differential effects of learning on neurogenesis: Molecular Psychiatry, 8, GABA regulates synaptic integration of newly generated neurons in the adult brain. Nature advance online publication; published online 11 December Hairston, I. Journal of Neurophysiology, 94 6 , Cannabinoids promote embryonic and adult hippocampus neurogenesis and produce anxiolytic- and antidepressant-like effects. Journal of Clinical Investigation, , Hippocampal brain-derived neurotrophic factor but not neurotrophin -3 increases more in mice selected for increased voluntary wheel running. Neuroscience, 1 , Stress in early life inhibits neurogenesis in adulthood. Trends in Neurosciences, 28 4 , The Journal of Neuroscience,24 30 , Dietary restriction increases the number of newly generated neural cells, and induces BDNF expression, in the dentate gyrus of rats. Journal of Molecular Neuroscience, 15 2 , Wnt signalling regulates adult hippocampal neurogenesis. Social change affects the survival of new neurons in the forebrain of adult songbirds. Behavioural Brain Research, 1 , Replaceable neurons and neurodegenerative disease share depressed UCHL1 levels. PNAS, 22 , Journal of Neuroscience, 24, Learning and adult neurogenesis: Survival with or without proliferation? Neurobiology of Learning and Memory, 81, Science, , Astroglia induce neurogenesis from adult neural stem cells. Prion protein PrPc positively regulates neural precursor proliferation during developmental and adult mammalian neurogenesis. FGF-2 regulates neurogenesis and degeneration in the dentate gyrus after traumatic brain injury in mice. Immune cells contribute to the maintenance of neurogenesis and spatial learning abilities in adulthood. Nature Neuroscience, 9,

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Adult neurogenesis, a process of generating functional neurons from adult neural precursors, occurs throughout life in restricted brain regions in mammals. The past decade has witnessed tremendous progress in addressing questions related to almost every aspect of adult neurogenesis in the mammalian brain.

Neural stem cells NSCs are the self-renewing, multipotent cells that generate the main phenotypes of the nervous system. Model organisms of neurogenesis[edit] Planarian [edit] Planarian are one of the earliest model organisms used to study regeneration with Pallas as the forefather of planarian studies. Planarian are a classical invertebrate model that in recent decades have been used to examine neurogenesis. The central nervous system of a planarian is simple, though fully formed with two lobes located in the head and two ventral nerve cords. This model reproduces asexually producing a complete and fully functioning nervous system after division allowing for consistent examination of neurogenesis. Axolotl [edit] The axolotl is less commonly used than other vertebrates, but is still a classical model for examining regeneration and neurogenesis. Though the axolotl has made its place in biomedical research in terms of limb regeneration, [15] [16] the model organism has displayed a robust ability to generate new neurons following damage. Zebrafish [edit] Zebrafish have long been a classical developmental model due to their transparency during organogenesis and have been utilized heavily in early development neurogenesis. The zebrafish displays a strong neurogenerative capacity capable of regenerating a variety of tissues and complete neuronal diversity with the exception of astrocytes , as they have yet to be identified within the zebrafish brain with continued neurogenesis through the life span. In recent decades the model has solidified its role in adult regeneration and neurogenesis following damage. The zebrafish is a rapidly developing organism that is relatively inexpensive to maintain, while providing the field ease of genetic manipulation and a complex nervous system. Chick [edit] Though avians have been used primarily to study early embryonic development, in recent decades the developing chick has played a critical role in the examination of neurogenesis and regeneration as the young chick is capable of neuronal-turnover at a young age, but loses the neurogenerative capacity into adulthood. Rodent [edit] Rodents, mice and rats, have been the most prominent model organism since the discovery of modern neurons by Santiago Ramon y Cajal. Rodents have a very similar architecture and a complex nervous system with very little regenerative capacity similar to that found in humans. For that reason, rodents have been heavily used in pre-clinical testing. Rodents display a wide range of neural circuits responsible for complex behaviors making them ideal for studies of dendritic pruning and axonal shearing. Tracking neurogenesis[edit] The creation of new functional brain cells can be measured in several ways, [27] summarized in the following sections. A nucleic acid analog is inserted into the genome of a neuron-generating cell such as a glial cell or neural stem cell. Fate determination via neuronal lineage markers[edit] DNA labeling can be used in conjunction with neuronal lineage markers to determine the fate of new functional brain cells. First, incorporated labeled nucleotides are used to detect the populations of newly divided daughter cells. Specific cell types are then determined with unique differences in their expression of proteins , which can be used as antigens in an immunoassay. Ki67 is the most commonly used antigen to detect cell proliferation. Some antigens can be used to measure specific stem cell stages. For example, stem cells requires the sox2 gene to maintain pluripotency and is used to detect enduring concentrations of stem cells in CNS tissue. The protein nestin is an intermediate filament , which is essential for the radial growth of axons , and is therefore used to detect the formation of new synapses. Cre-Lox recombination[edit] Some genetic tracing studies utilize cre-lox recombination to bind a promoter to a reporter gene , such as lacZ or GFP gene. Viral Vectors[edit] It has recently become more common to use recombinant viruses to insert the genetic information encoding specific markers usually protein fluorophores such as GFP that are only expressed in cells of a certain kind. The marker gene is inserted downstream of a promoter , leading to transcription of that marker only in cells containing the transcription factor s that bind to that promoter. For example, a recombinant plasmid may contain the promoter for doublecortin , a protein expressed predominantly by neurons , upstream of a sequence coding for GFP , thereby making infected cells

fluoresce green upon exposure to light in the blue to ultraviolet range [32] while leaving non doublecortin expressing cells unaffected, even if they contain the plasmid. By labeling a cell that gives rise to neurons, such as a neural stem cells or neural precursor cells, one can track the creation, proliferation, and even migration of newly created neurons. The insertion of genetic material via a viral vector tends to be sporadic and infrequent relative to the total number of cells in a given region of tissue , making quantification of cell division inaccurate. However, the above method can provide highly accurate data with respect to when a cell was born as well as full cellular morphologies. Pharmacological inhibition[edit] Pharmacological inhibition is widely used in various studies, as it provides many benefits. It is generally inexpensive as compared to other methods, such as irradiation, can be used on various species, and does not require any invasive procedures or surgeries for the subjects. To avoid these effects, more work must be done to determine optimal doses in order to minimize the effects on systems unrelated to neurogenesis. A common pharmacological inhibitor for adult neurogenesis is methylazoxymethanol acetate MAM , a chemotherapeutic agent. Other cell division inhibitors commonly used in studies are cytarabine and temozolomide. Pharmacogenetics[edit] Another method used to study the effects of adult neurogenesis is using pharmacogenetic models. These models provide different benefits from the pharmacological route, as it allows for more specificity by targeting specific precursors to neurogenesis and specific stem cell promoters. It also allows for temporal specificity with the interaction of certain drugs. This is beneficial in looking specifically at neurogenesis in adulthood, after normal development of other regions in the brain. The herpes simplex virus thymidine kinase HSV-TK has been used in studies in conjunction with antiviral drugs to inhibit adult neurogenesis. It works by targeting stem cells using glial fibrillary acidic proteins and nestin expression. These targeted stem cells undergo cell death instead of cell proliferation when exposed to antiviral drugs. Cre protein is also commonly used in targeting stem cells that will undergo gene changes upon treatment with tamoxifen. Irradiation[edit] Irradiation is a method that allows for very specific inhibition of adult neurogenesis. It can be targeted to the brain to avoid affecting other systems and having nonspecific effects. It can even be used to target specific brain regions, which is important in determining how adult neurogenesis in different areas of the brain affect behavior. However, irradiation is more expensive than the other methods and also requires large equipment with trained individuals. Inhibition of adult neurogenesis in the hippocampus[edit] Many studies have observed how inhibiting adult neurogenesis in other mammals, such as rats and mice, affect their behavior. Impaired fear conditioning has been seen in studies involving rats with a lack of adult neurogenesis in the hippocampus. A decreased ability in reducing interference could lead to greater difficulty in forming and retaining new memories. Correspondingly, this phenomenon might be the underlying cause of many of the symptoms of the disease. However, further research must be done in order to clearly demonstrate this relationship. It has been theorized that decreased hippocampal neurogenesis in individuals with major depressive disorder may be related to the high levels of stress hormones called glucocorticoids , which are also associated with the disorder. The hippocampus instructs the hypothalamic-pituitary-adrenal axis to produce less glucocorticoids when glucocorticoid levels are high. A malfunctioning hippocampus, therefore, might explain the chronically high glucocorticoid levels in individuals with major depressive disorder. However, some studies have indicated that hippocampal neurogenesis is not lower in individuals with major depressive disorder and that blood glucocorticoid levels do not change when hippocampal neurogenesis changes, so the associations are still uncertain. Stress and depression[edit] Many now believe stress to be the most significant factor for the onset of depression , aside from genetics. As discussed above, hippocampal cells are sensitive to stress which can lead to decreased neurogenesis. This area is being considered more frequently when examining the causes and treatments of depression. Studies have shown that removing the adrenal gland in rats caused increased neurogenesis in the dentate gyrus. In a normal brain, an increase in serotonin causes suppression of the corticotropin-releasing hormone CRH through connection to the hippocampus. It directly acts on the paraventricular nucleus to decrease CRH release and down regulate norepinephrine functioning in the locus coeruleus. This allows for the production of more brain cells, in particular at the 5-HT1a receptor in the dentate gyrus of the hippocampus which has been shown to improve symptoms of depression. It normally takes neurons approximately three to six weeks to mature, [68] which is approximately the same amount of

time it takes for SSRIs to take effect. This correlation strengthens the hypothesis that SSRIs act through neurogenesis to decrease the symptoms of depression. Some neuroscientists have expressed skepticism that neurogenesis is functionally significant, given that a tiny number of nascent neurons are actually integrated into existing neural circuitry. However, a recent study used the irradiation of nascent hippocampal neurons in rodents to demonstrate that neurogenesis is required for antidepressant efficacy. Under chronic stress conditions, the elevation of newborn neurons by antidepressants improves the hippocampal-dependent control on the stress response; without newborn neurons, antidepressants are unable to restore the regulation of the stress response and recovery becomes impossible. One study proposes that mood may be regulated, at a base level, by plasticity, and thus not chemistry. Accordingly, the effects of antidepressant treatment would only be secondary to change in plasticity. Effects of sleep reduction[edit] One study has linked lack of sleep to a reduction in rodent hippocampal neurogenesis. The proposed mechanism for the observed decrease was increased levels of glucocorticoids. It was shown that two weeks of sleep deprivation acted as a neurogenesis-inhibitor, which was reversed after return of normal sleep and even shifted to a temporary increase in normal cell proliferation. Nonetheless, normal levels of neurogenesis after chronic sleep deprivation return after 2 weeks, with a temporary increase of neurogenesis. The American Diabetes Association amongst many documents the pseudosenilia and agitation found during temporary hypoglycemic states. Much more clinical documentation is needed to competently demonstrate the link between decreased hematologic glucose and neuronal activity and mood. Transplantation of fetal dopaminergic precursor cells has paved the way for the possibility of a cell replacement therapy that could ameliorate clinical symptoms in affected patients. Due to the overwhelming number of traumatic brain injuries as a result of the War on Terror , tremendous amounts of research have been placed towards a better understanding of the pathophysiology of traumatic brain injuries as well as neuroprotective interventions and possible interventions prompting restorative neurogenesis. Hormonal interventions, such as progesterone, estrogen, and allopregnanolone have been examined heavily in recent decades as possible neuroprotective agents following traumatic brain injuries to reduce the inflammation response stunt neuronal death. Factors affecting[edit] Changes in old age[edit] Neurogenesis is substantially reduced in the hippocampus of aged animals, raising the possibility that it may be linked to age-related declines in hippocampal function. For example, the rate of neurogenesis in aged animals is predictive of memory. However, this is not the case, indicating that proliferation is balanced by cell death. Thus, it is not the addition of new neurons into the hippocampus that seems to be linked to hippocampal functions, but rather the rate of turnover of granule cells. In addition, IGF-1 alters c-fos expression in the hippocampus. When IGF-1 is blocked, exercise no longer induces neurogenesis. Yet, mice that did produce this hormone, along with exercise, exhibited an increase in newborn cells and their rate of survival. Effects of cannabinoids[edit] This section needs more medical references for verification or relies too heavily on primary sources. Please review the contents of the section and add the appropriate references if you can. Unsourced or poorly sourced material may be challenged and removed. November Some studies have shown that the stimulation of the cannabinoids results in the growth of new nerve cells in the hippocampus from both embryonic and adult stem cells. In a clinical study of rats at the University of Saskatchewan showed regeneration of nerve cells in the hippocampus. This is due to receptors in the system that can also influence the production of new neurons. Lack of synchronization corresponded with impaired performance in a standard test of memory. THC however impaired learning and had no effect on neurogenesis. Neurogenesis might play a role in its neuroprotective effects, but further research is required. Regulation[edit] Summary of the signalling pathways in the neural stem cell microenvironment. Many factors may affect the rate of hippocampal neurogenesis.

Chapter 3 : Adult neurogenesis - Wikipedia

Adult neurogenesis is the process of generating new neurons which integrate into existing circuits after fetal and early postnatal development has ceased. In most mammalian species, adult neurogenesis only appears to occur in the olfactory bulb and the hippocampus.

This article has been cited by other articles in PMC. Abstract New neurons are continuously generated in specific regions in the adult brain. Studies in rodents have demonstrated that adult-born neurons have specific functional features and mediate neural plasticity. Data on the extent and dynamics of adult neurogenesis in adult humans are starting to emerge, and there are clear similarities and differences compared to other mammals. Why do these differences arise? And what do they mean? Introduction For a long time, it was thought that the nervous system is fixed and incapable of regeneration. Although it is indeed true that most neurons in the brain are generated before birth and are never exchanged, it is now well established that new neurons are continuously generated by stem cells in at least two discrete regions in the brain throughout life in most mammals: At the end of last century, Eriksson, Gage, and colleagues established that new neurons are born in the adult human hippocampus [1]. Only recently, however, has it become possible to acquire quantitative data on the extent and dynamics of adult neurogenesis in humansâ€”by measuring the concentration of the radioactive carbon isotope 14C in genomic DNA. Nuclear bomb tests during the Cold War resulted in an enormous increase in atmospheric 14C, which thereafter has declined exponentially, mainly due to uptake by the biotope and diffusion from the atmosphere. The different 14C concentrations in the atmosphere at different times is reflected in the human body, and a cell that was born at a certain time will have a 14C concentration in its genomic DNA corresponding to the time when the cell was born [2]. Measuring 14C in genomic DNA allows retrospective birth dating of cells, and mathematical modeling of such data provides detailed information on the turnover dynamics of a cell population of interest [3]. This research has revealed both that there is more extensive neuronal turnover than many had predicted, and that there is a unique distribution of adult neurogenesis in the adult human brain compared to other mammals. And what are the roles of adult neurogenesis in humans? Adult Hippocampal Neurogenesis Is Conserved Among Mammals Carbon dating demonstrated that hippocampal neurons are generated at comparable rates in middle-aged humans and mice [4]. However, humans present a somewhat different pattern of adult hippocampal neurogenesis as compared to rodents Fig. Moreover, humans show a less pronounced age-dependent decline in hippocampal neurogenesis during adulthood compared to mice [4]. Adult-born hippocampal neurons are more likely to be lost than the neurons born during development in humans [4]. Whether this is also the case in other mammals has not been directly investigated, but data from mice is consistent with this notion [7].

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The willingness to accept adult neurogenesis was further enhanced by the convincing evidence that fetal tissue could be grafted in the adult intact brain. Even more convincing was the evidence that the damaged adult brain and spinal cord allowed these newly grafted cells to survive and differentiate (Bjorklund and Gage,).

The hippocampal formation HF , one of the main targets of these investigations, holds a neurogenic niche widely recognized among several mammalian species and whose existence in the human brain has sparked controversy and extensive debate. Many cellular features from this region emphasize that hippocampal neurogenesis suffers changes with normal aging and, among regulatory factors, physical exercise and chronic stress provoke opposite effects on cell proliferation, maturation and survival. Considering the numerous functions attributable to the HF, increasing or decreasing the integration of new neurons in the delicate neuronal network might be significant for modulation of cognition and emotion. The role that immature and mature adult-born neurons play in this circuitry is still mostly unknown but it could prove fundamental to understand hippocampal-dependent cognitive processes, the pathophysiology of depression, and the therapeutic effects of antidepressant medication in modulating behavior and mental health. Introduction Neurogenesis is the biological process through which new neurons are formed Altman and Das, Neural stem cells proliferate, migrate and differentiate during embryogenesis into mature neurons that will eventually form the central nervous system CNS; Angevine, The paradigm finally changed with cumulative evidence from the second half of the 20th century, which saw the birth of new methods and techniques that allowed the discovery of adult-born neurons in the brains of rodents Altman, , primates Gould et al. This raised relevant questions on the ultimate significance and impact of postdevelopmental neurogenesis, especially when only three distinct and specific neurogenic areas were mapped in the human brain Ernst and Frisen, Here, the discussion will be centered in the HF, as it remains the most likely neurogenic niche to play a significant role in brain function Spalding et al. Although beyond the scope of this review, the SVZ and the striatum could also display remarkable features and there is still much to be explored in these brain areas. Adult Hippocampal Neurogenesis in Humans The original study that established the presence of neurogenesis in the adult human brain used a thymidine analog incorporated into proliferating cells during DNA synthesis, bromodeoxyuridine BrdU , to demonstrate proliferation, differentiation, and survival of cells in the dentate gyrus DG , in the HF Eriksson et al. In the study, both the granular layer of the DG and the adjacent subgranular zone SGZ presented labeled cells, indicating the presence of recently-generated neurons Eriksson et al. This phenomenon was apparently restricted to the DG, as no other hippocampal region demonstrated such activity in man Eriksson et al. This occurs similarly to other mammals Kempermann, , making the SGZ widely recognized as neurogenic Altman and Das, and standing as the putative source of neural progenitors for the granular layer in primates Kohler et al. Using marmoset monkeys injected with BrdU Gould et al. After a 3-week post-BrdU injection period, most labeled cells were now located in the granular layer and exhibited mature phenotype. The same pattern of migration and differentiation is seen in rodents and indicates that neurogenesis per se is a property of the SGZ, not the granular layer Kohler et al. Extent of the Neurogenic Activity Recent data from human post-operative and post mortem samples of the HF suggest a very different scenario from the initial study. The direct conclusion for both findings was the virtual absence of neurogenesis in the adult human HF. However, these results not only disagree on the existence of a germinal SGZ in humans as they also conflict with positive reports of adult neurogenesis using the same endogenous markers Knoth et al. Nonetheless, inconsistency between studies could also arise from the methodology itself. Although BrdU staining for new neurons might be less sensitive than DCX and may produce false-positive results Sorrells et al. The apparent loss of neurons might instead reflect modification in marker expression. Additionally, the assumption that these markers are evolutionary conserved, and therefor identical in rodents and humans in representing the same cell types, is not yet entirely secure Knoth et al. Despite the inherent controversy of using indirect ways to study neurogenesis, more direct methods remain scarce. Neural precursors have been identified and directly isolated from the adult human HF and shown to mature as neurons in vitro Roy et al. However, this selective

extraction lacks quantitative analysis, therefore leaving doubts on the extent of cell production Eriksson et al. Thus, even when successful, direct approaches normally yield limited results and require complementary studies. For instance, some reports focusing on neuroblast counts have revealed small numbers of cells after the first postnatal year Knoth et al. On the other hand, carbon assessment, which allowed retrospective birth dating of neurons through quantification of the isotope concentration in genomic DNA, demonstrated that even small numbers of neuronal precursors were sufficient to give rise to significant amounts of newly generated neurons Spalding et al. In contrast, neurogenesis in rodents, although prominent among mammals Amrein et al. Neurogenesis Throughout Age These numbers demonstrate a remarkable extent of human neuron production, but turnover dynamics must be analyzed together with age-dependent changes for a complete understanding of hippocampal neurogenesis Bergmann et al. In fact, in the early post-natal period, there is a general consensus that a dramatic and exponential decline in the population of cells with neuroblast markers occurs, comparatively to numbers seen during fetal development Knoth et al. Afterwards, hippocampal dynamics are disputed. As previously mentioned, some studies showed that DCX-positive neuroblasts may become undetectable after infancy, suggesting that neurogenesis ceases in the adult HF Dennis et al. Others found that neurogenesis occurs during adulthood and that the number of DCX-positive cells and the neuronal turnover rates from the self-renewing fraction of HF neurons present an insidious parallel decline along basal values Knoth et al. Finally, the most optimistic results were rather surprising, partially contradicting previous data from humans and consistent data from rodents and primates. This suggests that a finite pool of early progenitors does not compromise the proliferative potential of this cell lineage as a whole, which may be supported in older age by late progenitors Boldrini et al. Unfortunately, this study failed to analyze such cell markers in hippocampal samples from donors younger than 14 years of age, preventing a complete analysis for the total human age spectrum. Cell Count and HF Volume Dynamics Neuroblast numbers and neuronal exchange rates could be associated with variations in the neuron count and HF volume, since the production of new cells could ultimately affect the number of neurons and the dimensions of this specific CNS region at each time point in human life. Indeed, there is evidence of a net loss of neurons in the whole HF with age, although stereological investigations have established that not all hippocampal subdivisions are equally affected West, ; West et al. Neuroblasts occur in the DG and, interestingly, this region seems to be the least affected by the decrease in neuronal numbers Bergmann et al. In fact, there might not be any actual change in the number of mature granule neurons in the DG Boldrini et al. Curiously, there was also no age-related change in the volume of the DG in this study Boldrini et al. However, others have shown that, in spite of its neurogenic potential, the human DG still presents a net loss of granule cells in adult life Spalding et al. The impact of adult neurogenesis on the total number of neurons in humans widely contrasts with the situation of rodents, where neurogenesis is additive and leads to an increase in granular layer volume and in the number of granule cells with age Bayer, Nevertheless, the correlation between neurogenesis and hippocampal volume in humans is not yet entirely clarified. Apart from these results, an increase is expected in the proportion of renewing neurons in the HF due to neurogenesis, since non-renewing cells die without being replaced Spalding et al. The HF can be seen as a dynamic structure that permanently loses cells initially formed during development, with significant replacement in the DG with subgranular neuroblasts during adult life. Further complexity in hippocampal cell dynamics is added by the fact that adult-generated cells are also lost during adulthood. In fact, within the renewing neuron population, younger cells were found to survive less than cells originated during development Spalding et al. Unlike neurons from other hippocampal regions, which originated from development and are as old as the individual itself, the DG is composed of neurons generated at different time points throughout life, creating a complex mosaic where cell turnover is accompanied by a preferential loss of adult-generated neurons. This deepens the complexity of the HF neuron regulation and may possess relevance for the functional purposes of adult neurogenesis Spalding et al. Regulatory Mechanisms for Adult Hippocampal Neurogenesis Cell proliferation, neuronal differentiation and cell survival Christie and Cameron, are responsible for the division of progenitor cells, selection of a neuronal fate rather than a glial one and incorporation and maintenance of new neurons into their final circuits, respectively. This explains the basis of the cytological organization seen in neuronal

tissue Kempermann, ; Aimone et al. These factors can depend on human behavior or the surrounding environment and, since they can actively up-regulate or down-regulate the formation of new neurons during adulthood, they are critical to understanding the relevance of adult neurogenesis on a functional basis Kempermann, , either behaviorally, cognitively or clinically. Here, age, physical exercise and chronic stress will be addressed in more detail although several other factors should deserve similar attention, like diet Cardoso et al. Age As stated, there is a substantial decline in neuroblasts in the DG from infancy to adulthood Knoth et al. More studies are necessary to understand whether this decrease actually reaches zero Dennis et al. It is essential to comprehend the mechanisms behind these unclear age-related changes, and understanding senescence at a neuroanatomical level could be necessary to distinguish physiological from pathological aging and the associated cognitive impairment Capilla-Gonzalez et al. For example, adding to the increased production of inflammatory factors, senescence of the cellular neurogenic niche may lead to a decrease in neurotrophic factors levels, turning the milieu less suitable for precursor cell activity Lucin and Wyss-Coray, ; Aimone et al. Restoration of FGF-2 and IGF-1 levels by intracerebroventricular infusion significantly promoted neurogenesis in adult rats Lichtenwalner et al. Although levels of hippocampal BDNF remain stable with age in rodents, serum BDNF is diminished in human adults and could mediate the age-related decline in hippocampal volume Erickson et al. Physical Exercise The neurogenic capacity of an adult brain can be enhanced, and the first evidence originated from a study where mice were housed in artificially enriched environments Kempermann et al. By isolating the environmental variables, voluntary exercise was shown to be the primary condition behind the increased newborn neuron survival and upregulation in hippocampal neurogenesis van Praag et al. It was shown that running increased cell division and enhanced survival and maturation of new cells on the HF van Praag et al. Additionally, physical exercise was associated to DG plasticity, with a rise in long-term potentiation LTP; van Praag et al. Interestingly, LTP is more easily induced in younger neurons, due to different active and passive membrane properties Schmidt-Hieber et al. These neuroplastic changes may present relevant implications, as exercise is known to facilitate learning and memory and to decrease depressive symptoms, which are linked to cognitive decline Cotman et al. A neuroprotective effect of physical exercise has been considered to fight brain atrophy and could protect against age- and disease-related mental decline Cotman et al. This volume gain after physical exercise is apparently selective to the HF, which suggests that neurogenic cell proliferation could be at least partly responsible Pajonk et al. In mice, a strong correlation was found between the number of DCX-positive cells and the gray matter volume of the DG Biedermann et al. Additionally, HF focal irradiation, which can nearly abolish neurogenesis, is sufficient to block the effects of running on hippocampal morphology Fuss et al. Neurogenesis-related plasticity seems to play a role in exercise-induced volume changes, but other biological mechanisms could help explain such changes in the CNS Ho et al. Many cellular and molecular mechanisms could influence the positive effects of exercise in neurogenesis Figure 1. Ablation of the gene encoding TrkB in precursor cells blocks the exercise-induced potentiation of neurogenesis Li et al. Serum IGF-1 uptake by hippocampal neurons increases in response to exercise in rats, and administration of a blocking IGF-1 antiserum impaired exercise-induced stimulation of neurogenesis Carro et al. Consequently, peripheral IGF-1 may stimulate neurotrophic molecular cascades and influence synaptic plasticity Vivar et al. Possible mechanisms for exercise-induced effects on hippocampal neurogenesis. Physical exercise may be a rewarding or a stressful activity and can influence neurogenesis on the basis of a neuroendocrine balance. A predominant activation of the hypothalamic-pituitary-adrenocortical HPA axis, with a consequent increase in blood glucocorticoids Droste et al. When the hedonic component of a physical activity is more significant than the stress response, it may increase the levels of growth factors BDNF, fibroblast growth factor-2 FGF-2 , insulin-like growth factor-1 IGF-1 and vascular endothelial growth factor VEGF and neurotransmitters serotonin 5-HT in the hippocampal formation HF enough to promote neurogenesis Gomez-Merino et al. This regulatory influence of physical exercise could also be achieved through the blood. Exercise and the accompanying increase in cerebral blood flow and blood-brain barrier permeability may enhance the transportation of circulating factors into the brain Sharma et al. Newborn hippocampal cells appear to be closely associated with blood vessels, forming angiogenic niches Palmer et al. Interestingly, this

microenvironment seems to be regulated by the circulating neurotrophic factors FGF-2 Eppley et al. VEGF may present a double action in this context, directly stimulating neural progenitor cells Jin et al. Other evidence for this neurogenesis-angiogenesis correlation exists. Although there are contradicting results Biedermann et al. Physical activity selectively increases DG blood volume, both in mice and humans, and changes in this parameter correlated with post mortem evaluation of neurogenesis in rodents Pereira et al. Indeed, the proliferation of neural progenitor cells may be dependent on the vasculature Van der Borght et al. Finally, other mechanisms, independent of the hippocampal vascular system, may additionally regulate the effects of exercise. For example, serotoninergic inputs may lead to an increased proliferation of granule cells and, during physical exercise, extracellular levels of this monoamine in the rat ventral HF are increased Gomez-Merino et al. In mice lacking brain serotonin 5-hydroxytryptamine, 5-HT , activity-induced hippocampal proliferation was impaired Klempin et al. The importance of 5-HT in adult neurogenesis goes far beyond physical activity since it might be fundamental to understand the pathophysiology of depression and its connection to environmental triggers and treatments Mahar et al. Chronic Stress Stress is one of the most studied modulators of neurogenesis in the mature brain. Expectedly, understanding mechanisms behind stress and its influence on the HF could be fundamental to study mental disorders. The biological stress system is an adaptive mechanism that focuses the individual on detected environmental threats, either of psychological, physical or biological nature, and then attempts to regain homeostasis through neuroendocrine pathways Lucassen et al. While acute stress is the consequence of a single stressful event, and can display physiological adaptive advantages, chronic stress is caused by multiple stressful events over a period of time Aimone et al.

Chapter 5 : Is Human Adult Neurogenesis Dead? And Does It Matter? - Neuroskeptic

of 60 results for "adult neurogenesis" Adult Neurogenesis: Stem Cells and Neuronal Development in the Adult Brain Nov 28, by Gerd Kempermann. Hardcover.

Neural Stem Cells Figure 2: Two criteria are typically used to define a cell as a stem cell: The evidence for multipotency of NPCs in vivo remains scant. There are two neurogenic regions in the adult brain where under physiological conditions NPCs give rise to new neurons: For those two regions several types of dividing progenitors were identified. Although they reside in the SGZ, they extend processes up into the molecular layer. Type-1 and B cells are relatively quiescent. NPCs are not limited to neurogenic regions of the brain, rather their proliferation can be observed in most CNS regions, especially after injury. However, in these other regions it appears that neurogenesis is actively repressed by the local environment - NPCs from non-neurogenic regions have been observed to give rise to neurons when transplanted into the hippocampus. Some evidence indicates that this effect is mediated by the local astrocyte populations. NPCs have historically been labeled in the brain by the addition of a proliferation marker, such as 3H-thymadine or bromodeoxyuridine BrdU; Figure 2 , bottom. Immunohistochemistry for BrdU can be combined with the detection of mature markers to identify the phenotype of the newborn cells. BrdU labeling has been used to definitively show that new neurons are incorporated into the dentate gyrus and olfactory bulb of the adult human brain Eriksson et al. Maturation of New Neurons Adult neurogenesis is unique from developmental neurogenesis because the new neurons must integrate into an established, functioning network. Much of the present knowledge about neuronal development in adult neurogenesis has been reviewed by Kempermann et al. Maturation of new neurons in the adult dentate gyrus The process of adult hippocampal neurogenesis is entirely confined to the dentate gyrus. The speed of maturation is likely experience dependent, and varies between neurons. Approximate duration of a number of distinct post-mitotic developmental phases of newborn granule cells are listed here. Figure 3 shows a scematic of the anatomical phases of granule cell growth. Less than 1 week old Immature neurons have neurite outgrowth, but often not polarized towards molecular layer. Few or no synapses, but sensitive to locally diffuse GABA, which is depolarizing. Synaptic GABA inputs can be observed, which is still excitatory. Glutamatergic inputs are not present. Immature action potentials can be observed when cells are directly stimulated. Spine formation onset and axon outgrowth: By about 16 days neurons begin to develop spines in the molecular layer. GABA transitions to inhibitory around this time. By 17 days, new axons mossy fibers can be observed forming functional connections onto downstream hilar neurons and CA3 pyramidal cells. Mossy fibers continue to mature, with boutons on CA3 neurons growing considerably by 28 days. Neurons still have unique physiological properties, including increased LTP, and different resistance, capacitance and resting potentials. Newborn neurons eventually become physiologically indistinguishable from fully mature neurons. Recent work using immediate early genes such as c-fos, Zif, and Arc as putative markers of neuronal activity have shown that water maze training Kee et al. Maturation of new neurons in the adult olfactory bulb In contrast to adult neurogenesis in the dentate gyrus, cells that were born in the SVZ migrate a long distance into their target area, the olfactory bulb. This long migration gives olfactory neurogenesis a different timescale from DG neurogenesis. After the newborn neurons reach the middle of the OB they detach from the chains and migrate radially. Newborn granule cells can be distinguished into cells with dendrites that do not extend beyond the mitral cell layer and other cells that possess non-spiny dendrites reaching into the external plexiform layer. Neuronal selection and survival One critical aspect of adult neurogenesis is the selection process. While large numbers of new neurons are born to the OB and DG, only a fraction of these cells survive. In the dentate gyrus, approximately half of the newborn neurons die within 2 weeks of birth, but this number is heavily regulated by various factors. In contrast to newborn DG neurons the selection process in the OB appears to be later in the development process, when young neurons with extended dendrites already covered with spines are susceptible to cell death. Numerous drugs and behaviors have since been shown to affect the levels of new neurons in the brain. Modulation of neurogenesis typically occurs in one of two ways in vivo â€” either the

modulator changes the levels of proliferation of NPCs, or the effect is on the survival of the new neurons. The most studied modulators have been summarized in the following tables. See Ming and Song and Abrous et al. In each of these cases, it remains unclear whether perturbed neurogenesis is a symptom of the disorder or has a causal role. Aging also has a robust effect on neurogenesis, with levels of new neurons decreasing in later stages of life. The marked decrease occurs fairly early and neurogenesis is maintained at a very low level for most of the life span. Nonetheless, because neurons are integrating into regions of relatively well described circuitry and function, several behavioral and computational ideas have been explored. These have included x-ray irradiation, anti-proliferative drugs MAM and molecular knock-downs. A range of hippocampus-dependent behaviors have been tested with mixed results see Deng et al. Trace eyeblink conditioning was shown to be affected in MAM experiments, and contextual fear conditioning was impaired following irradiation and genetic ablation of adult neurogenesis. Morris Water Maze MWM testing has shown inconsistent results in several paradigms, with some experimenters seeing deficits in short-term retention, others in long-term retention, and others no discernable differences at all. Furthermore, set of behavioral studies have demonstrated that neurogenesis may have a role in the pattern separation function of the dentate gyrus Clelland et al. Finally, a recent study has suggested that new neurons may be important in memory consolidation Kitamura et al. In addition to its presumed role in memory, the correlation of neurogenesis levels to stress has suggested a role in anxiety-related behaviors. For example, fluoxetine the active compound in Prozac is not effective as an anti-depressant in mice without adult neurogenesis due to irradiation. Olfactory bulb-dependent behavioral tasks The function of the olfactory pathway can be tested with a variety of behavioral tasks that test odor discrimination or odor learning. Using transgenic mice with reduced OB neurogenesis it could be shown that new OB neurons appear to be critically involved in odor discrimination. At the same time odor discrimination learning itself increases the survival of newborn OB neurons. The same effect on survival has been found using odor enrichment resulting in improved odor memory. Computational impact of new neurons Because the dentate gyrus is the entry structure to the hippocampus, which has a substantial history of neural network modeling, several non-exclusive computational functions have been suggested for neurogenesis. These have arisen from both theoretical and computational modeling ventures. For a more detailed review of the theoretical functions of adult neurogenesis, see Aimone, Deng, and Gage; Becker predicts that the increase in possible sparse codes due to new neurons increases the quality of memory formation in downstream hippocampal regions. Reduction of interference between new and older memories â€" Wiskott and colleagues propose that the presence of new neurons helps the dentate gyrus network respond to changing inputs. Encoding time in memories â€" Aimone et al. Olfactory bulb neurogenesis has not been as extensively studied computationally, possibly because the olfactory bulb circuit does not have the history of modeling that the hippocampus has. Adult Neurogenesis in other Species Higher levels of adult neurogenesis are observed in many non-mammalian species, many of which retain regenerative neurogenesis capabilities throughout life. Neurogenesis in the course of normal adult function has been best described in birds and fish. Birdsong system Adult neurogenesis in birds has been most heavily characterized in the higher vocal center HVC area of the birdsong system, although it has been observed in other regions, including the avian hippocampus. Bird song neurogenesis is sometimes characterized by very high levels of seasonal variation â€" with more neurons appearing in months which have higher levels of song learning. For example, in the canary brain, there is a high level of seasonal cell death of RA projecting HVC neurons in males - in low-neurogenesis, non-learning periods, the HVC is a fraction of the size of learning seasons. Many of the underlying regulators of this process have been elucidated, including seasonal variations in testosterone. The specific role of new neurons in bird song learning still unclear, but it is interesting to note that the neurogenic cells in HVC have been implicated in sparse coding, just as dentate gyrus cells in the mammalian hippocampus. Adult neurogenesis in Fish Fish have many proliferative zones throughout the brain, which are thought to be able to provide neurons to almost any region of the brain Zupanc, Consistent with other vertebrates, the olfactory bulb and dorsal telencephalon the fish equivalent of the hippocampus have robust neurogenesis, though most of the new neurons are found in the cerebellum. Because of this widespread proliferation, the overall rate of neurogenesis appears several orders of magnitude higher in fish than in

rodents â€” with an estimate over about 0. References Below we include references from classic papers, key reviews summarizing the field,and recent studies which have not been reviewed elsewhere in detail such as the computational modeling work. Altman J and Das GC - "Autoradiographic and histological evidence of postnatal hippocampal neurogenesis in rats" Journal of Comparative Neurology; 3: Scholarpedia , 2 Eugene Roberts Gamma-aminobutyric acid. Recommended reading "Adult Neurogenesis" eds.

Chapter 6 : Adult Neurogenesis | BioEd Online

Researchers showed that neurogenesis does occur in the brains of various adult animals, and eventually found signs of newly formed neurons in the adult human brain. Hundreds of these cells are.

This is as differentiated from "neurogenesis" typically used to describe the processes of neuronal generation that occur during the prenatal embryonic and fetal period extending in to the early years of postnatal life. Some scientists back then disputed this as fact but had no means of disproving the widely accepted notion, the non-availability of advanced equipment back then and less advanced scientific investigation and laboratoty techniques meant this notion would go unchallenged for a very long time. This generated a lot of interest and a shift of focus was made to the mammalian species which were considered to be more advanced species and closer to the human being. In a scientist by the name of Peter Ericksson and his team were the first to conclusively demonstrate that adult generated neurons could be identified in the human brain as well [3]. Two areas have been consistently identified across all species studied to date, which are the subgranular zone of the hippocampus hippocampus is responsible for spatial memory and the subventricular zone of the lateral ventricles the area from which neurons migrate to form the cerebral hemispheres and cerebral cortex in the embryonic and fetal periods [4]. Adult neurogenesis and neurological disease Immense interest has been generated around this area, now that adult neurogenesis is known to be a fact, focus has shifted towards determining the factors that affect adult neurogenesis increase or decrease it rate of occurrence and the functions of these adult generated neurons. Interstingly it has been shown that such factors as physical exercise, living in an environmentally enriched area and mentally challenging tasks among other things improve the rate of production of new neurons in the adult hippocampus as well as increase the longevity of these newly generated neurons [5] [6]. In the same vein, scientists have managed to demonstrate that laboratory animals in which the rates of neurogenesis had been increased by such means as physical exercise performed better at tasks such as learning a new skill or spatial navigation in a novel new environment [7]. Promote a healthy lifestyle - eat healthy, avoid the use of drugs. Adult neurogenesis produces a large pool of new granule cells in the dentate gyrus. Journal of Comparative Neurology. Neurogenesis in the adult brain: Neurogenesis in the adult human hippocampus. Adult neurogenesis in the mammalian brain: Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. European Journal of Neuroscience. Paradoxical effects of learning the Morris water maze on adult hippocampal neurogenesis in mice may be explained by a combination of stress and physical activity. Genes, Brain and Behavior. Proceedings of the National Academy of Sciences. Retrieved from " https: Physiopedia is not a substitute for professional advice or expert medical services from a qualified healthcare provider.

Chapter 7 : Adult Neurogenesis in Humans- Common and Unique Traits in Mammals

This up-to-date resource provides comprehensive coverage of the rapidly evolving topic of adult neurogenesis. It has become an essential reference resource for everybody interested in adult neurogenesis and stem cell biology of the adult brain.

Is Human Adult Neurogenesis Dead? And Does It Matter? By Neuroskeptic March 14, 3: The idea that neurogenesis exists in the adult human hippocampus has generated a huge amount of excitement and stimulated much research. But a new study, published in Nature , has just poured cold water on the whole idea. Sorrells and colleagues report that neurogenesis ends in humans some time in childhood. In rodents, adult neurogenesis takes place in a region called the subgranular zone SGZ , located in the dentate gyrus of the hippocampus. Strikingly, Sorrells et al. This result challenges previous studies, using other methods, that did report adult neurogenesis in the human hippocampus. However, the new study is consistent with another no-neurogenesis finding from a couple of years ago. For more on the methodology of these neurogenesis studies, see this excellent post by Jason Snyder. Overall, it seems to me that the evidence against adult neurogenesis is becoming pretty convincing. So what does this all mean? Interestingly, a lack of neurogenesis in the hippocampus has been suggested for aquatic mammals dolphins, porpoises and whales 5 , species known for their large brains, longevity and complex behaviour. This hypothesis seems pretty wild to me. From memory to depression, hundreds of papers have been published on the possible function of the phenomenon. Most of the claimed functions are based on rodent studies, and while it may be that in rodents, neurogenesis helps to say prevent depression , it looks like the same is not true of humans. Our brains are still plastic , thanks to the fact that even old neurons are able to change and develop new connections. Any attempt to partition functionality creates its own partitions, which vanish when the observer withdraws. May I have my massive grant funding now? We all censor different unlucky elevator buttons. They said the end was near. An unprotruding septum, And aura of understanding, a persevering grin, Cover up how its bane in part an appeal did not comprehend Which now is dead, eroded from these lively things, The heart that respected it, and the hand that fed; And on the land lichens grow a sequence of letters: This fountain of youth is surrounded by evergreen life. And far away The branches crowd the vines. Since one main criticism was that it was more likely BDNF increases were a sign of neuron damage. And who would even want to take choline to mitigate this effect knowing that choline produces negative affect in humans as well as experimental mammels? The studies thus far â€” many, admittedly, taking an indirect approach of various happenings downstream, which hypothetically promote neurogenesis â€” exploring psychopharmacological models of antidepressant efficacy as another commenter already pointed out must mean something. At the same time, direct provision of BDNF a presumably important agent vis-a-vis antidepressants to the CNS has not itself been effective in resolving conditions for which these BDNF-provoking agents are utilized to treat. Perhaps neither view is completely wrong â€” even if both are, when construed in their strongest forms, incompatible. If the effect of antidepressants, not so much as promoting neurogenesis, but rather prove to protect neurons from destructive stress while promoting ameliorating neuronal rewiring, is it any less true that, as we say now, antdepressants can indeed help patients who are depressed? I think this would include myelin.. I thought it was horrible. There was no proof that any putative drug-induced neurogenesis was helpful. I hold a low opinion of any scientist who would proclaim such an effect beneficial without knowing whether it was or was not. Neurogenesis seems like a great first step on the way to neoplasm. One day, , new neurons appear and say they want to help you. Whatever are you going to do with them? You have your connections all connected up and humming along. Will the new nerves form a suburb on your outskirts? Or will they be more like urban infill, nestling into gaps between existing neurons, glibly gumming up the works while doing nothing more useful than sending headshots to Lundbeck, hoping to star in its next misleading Vortioxetine marketing campaign? Will RetractionWatch have to double their rack space?

Chapter 8 : Human Adult Neurogenesis Revealed | The Scientist MagazineÂ®

The first direct evidence for adult neurogenesis in humans came in , but the method usedâ€"injecting a chemical label that permanently integrates into the DNA of dividing brain cellsâ€"is no longer available to researchers due to safety concerns, so the results were never replicated.

Recent research demonstrates that neural stem cells divide throughout life and give rise to new neurons, a process known as neurogenesis. This article addresses two principal questions concerning alcohol and adult neurogenesis: To what extent are neurogenesis in the adult brain and the risk for alcoholism governed by similar factors? And, to what extent and through what mechanisms do alcohol use and alcoholism affect adult neurogenesis? This article also discusses genetic and environmental influences on risk for alcoholism and on regulation of neurogenesis; the possibility that modulation of neurogenesis contributes to alcoholic pathology; and the evidence that alcohol disrupts neurogenesis in the adult brain, and the neurochemical processes by which this may occur. The theoretical understanding of plastic processes such as learning, memory, mood, and other features of adult behavior is entrenched in this concept of a fixed number of neurons in the adult brain. As a result, research on brain plasticity has long focused on alterations in neurotransmitter receptors, numbers of synapses, structure of synapses, and transmitter release mechanisms. The basis of these networks is communication from cell to cell by chemical messengers called neurotransmitters. Released at narrow gaps, or synapses, between cells, neurotransmitters cross the synapses and activate proteins called receptors. Activated receptors, in turn, induce cascades of molecular interactions within the receiving cell [and, via feedback mechanisms, to the signaling cell as well], resulting in shortâ€" and longâ€"term functional changes within the brain. The seminal discoveries on the formation of new neurons i. Until recently, dogma and insufficient technology prevented acceptance of these findings as an additional process influencing brain plasticity. This area remains controversial, with researchers currently debating how extensive neurogenesis is in the adult brain Rakic Recent research clearly establishes that neural stem cells NSCs divide throughout life and give rise to new neurons in at least two regions of the adult brain: The function of adult NSCs is not known, but they are associated with complicated brain functions such as learning, mood, and association of sensory information. The discovery of NSCs and adult neurogenesis provides a new theoretical framework for understanding processes regulating brain plasticity Gage Types of Stem Cells Stem cells are cells that can divide indefinitely, renew themselves, and give rise to a variety of cell types. There are several different types of stem cells. Totipotent stem cells i. Pluripotent stem cells another type of embryonic stem cell are capable of giving rise to every cell type except the trophoblasts of the placenta. Multipotent stem cells, including neural stem cells NSCs , are more restricted in the types of cells they are capable of producing or becoming. A totipotent embryonic stem cell may first become a pluripotent stem cell and then eventually a multipotent stem cell through a series of events called fate restrictions, which limit the types of differentiated cell it can become. Neural Stem Cells A variety of adult neural cell populations have been identified as stem cells, although the exact characterization and definitions of these populations are evolving. It is generally accepted that NSCs selfâ€"renew and are potentially multipotent in that, under the right conditions, they can produce other cell types and give rise to several types of cells in the central nervous system, including neurons and other brain cells. In this report NSC is used in a general way to refer to adult brain cells that divide to form differentiated nervous system cells Nowakowski and Hayes The role of stem cells in central nervous system development is well described Kennea and Mehmet , but their existence in the adult brain was confirmed only recently Gage In vitro studies have been able to culture NSCs from many regions of brain. Furthermore, brain insult studies have suggested that NSCs are present in all brain regions but normally are suppressed from dividing. Under normal conditions, however, continuous neurogenesis occurs primarily in two discrete brain regions, each of which contains NSCs. It is well accepted that NSCs underlie adult neurogenesis in the subventricular zone SVZ of the anterior lateral ventricles and the dentate gyrus of the hippocampus see the figure in this sidebar. Sites of adult neurogenesis rodent studies compared with appropriate human brain regions. Neurogenesis has been confirmed in two regions of the adult brain: In the SVZ, progenitor cells migrate to the olfactory bulb,

where they differentiate into neurons. In the dentate gyrus, cells divide along the subgranular zone also see the figure in the sidebar, below and migrate into the granule cell layer before terminally differentiating into granule cells. Neurogenesis in the SVZ occurs when cells divide along the SVZ, then migrate to the olfactory bulb, which is involved in the sense of smell Alvarezâ€"Buylla and Temple Hippocampal NSCs also originate in the walls of the lateral ventricles during embryonic development but migrate out to begin forming the hippocampus. Granule cells within the dentate gyrus of the hippocampus do not begin forming until midâ€"gestation, peaking during the third trimester in humans, or its equivalent in other organisms Bayer Granule cell neurogenesis continues through adulthood, declining with age in rats and in humans Altman and Das ; Gage In the dentate gyrus of the hippocampus, hundreds of thousands of new granule cellsâ€"up to 6 percent of the total adult populationâ€"are formed each month, though equivalent cell death has not been observed with current techniques Cameron and McKay New cells in the dentate gyrus divide along the subgranular zone during early development, migrate into the granule cell layer, and become neurons in shape morphology and gene expression phenotype. These new cells express neuronal markers, show electrophysiological characteristics of neurons, and make appropriate connections to carry information to and from other parts of the brain Gross Several findings suggest that NSCs are important to adult brain plasticity. First, thousands of new brain cells are formed daily, and most of them are integrated as new functional neurons Cameron and McKay Second, this process occurs across many species, including humans Gould Third, environment, genetics, and drugs alter neurogenesis in a manner that is consistent with NSCs having an impact on plastic processes such as learning and mood Duman et al. Finally, newborn neurons alter brain structure and circuitry, a process historically thought to occur only in the developing brain or through growth of existing adult neurons. Autoradiographic and histological evidence of postnatal hippocampal neurogenesis in rats. Journal of Comparative Neurology 3: Stem cells in the developing and adult nervous system. Journal of Neurobiology 36 2: Development of the hippocampal region in the rat. Neurogenesis examined with 3Hâ€"thymidine autoradiography. Journal of Comparative Neurology Adult neurogenesis produces a large pool of new granule cells in the dentate gyrus. Journal of Comparative Neurology 4: Regulation of adult neurogenesis by psychotropic drugs and stress. Journal of Pharmacology and Experimental Therapeutics 2: Mammalian neural stem cells. Serotonin and hippocampal neurogenesis. Neurogenesis in the adult brain: Death of a dogma. Nature Reviews Neuroscience 1 1: Journal of Pathology 4: The promises and pitfalls. First, to what extent are neurogenesis in the adult brain and the risk for alcoholism governed by similar genetic and environmental factors? Second, do alcohol use and alcoholism affect adult neurogenesis, and if so, what are the mechanisms underlying those effects? Can stem cells be used to repair brain damage caused by alcohol? The question of brain repair by stem cells is a hot topic; the research discussed here provides the scientific foundation for research into this question. In addition, great therapeutic potential lies in the pharmacological or behavioral regulation of these endogenous stem cells. Altering endogenous stem cells by behavior or drugs is noninvasive and is a growing area of research. Indeed, many of the environmental factors that regulate adult neurogenesis also are affected in people with chronic alcoholism. Thus, the regulation of NSCs is similar to some aspects of alcohol abuse and alcoholism. Alcoholism is a progressive disease associated with maladaptive changes in behavior that are mediated by environmental and genetic factors, as well as by physiological changes that take place in the brain as a result of exposure to alcohol. Interestingly, genetics and specific environmental factors play an important role in regulating neurogenesis, and these same environmental factors discussed below are key factors in the risk of developing alcoholism. Given the overlapping genetic and environmental factors that appear to be involved in both adult neurogenesis and alcoholism, we argue that understanding the commonalities between these two plastic processes may provide new clues to the treatment and prevention of chronic alcoholism. Genetic Regulation Animal genetic studies; classic twin, family, and adoption studies; and systematic searches of the entire human genetic makeup i. Furthermore, animal studies clearly have indicated that genetic factors influence many responses to alcohol use, including sensitivity to alcohol intoxication, alcohol withdrawal seizures, and preference for drinking alcohol over water Crabbe Likewise, genetics influences the three main components of neurogenesis: NSC proliferation, cell survival, and cell differentiation into neurons and other types of brain cells. For example, in

the dentate gyrus of the hippocampus, these components differ for each of the commonly used strains of mice: The formation of fewer neurons results in significantly less hippocampal neurogenesis than in other strains. The volume of the brain cell layer of which these newborn cells eventually become a part i. Thus, genetic differences make significant contributions to neurogenesis the new mechanism of brain plasticity , which results in differences in brain structure between animals. The fact that mice share over 80 percent of their genes with humans leads researchers to question whether genetic differences in humans also may underlie differences in brain plasticity or brain structure among individuals. Further studies will need to address the genetic components of adult neurogenesis in models of chronic alcoholism. Environmental Regulation Adult neurogenes also is regulated by environmental factors. Research indicates that animals placed in an enriched environment in particular, one that promotes physical activity and learning show a significant increase in neurogenesis compared with animals in normal housing conditions Gage ; Gould For example, running and hippocampalâ€"dependent learning such as spatial learning, or learning how to find something in an area increase NSC survival and differentiation. Furthermore, inhibiting neurogenesis with a drug that prevents cell division disrupts associative learning. Interestingly, this disruption only is observed 1 to 2 weeks after administering the drug, when newborn cellsâ€"now functional neuronsâ€"would be expected to begin contributing to learning Gould and Gross Thus genetic factors and environmental factors overlap in this new mechanism of brain plasticity. An important environmental factor is stress. Stress reduces neurogenesis and also is known to precipitate depression and increase drinking. The fact that the number of BrdUâ€"positive cells was decreased 5 hours after acute alcohol exposure is consistent with the idea that alcohol inhibits the number of cells entering Sâ€"phase, or NSC proliferation. Those cells exiting the 25â€"hour cell cycle either die or migrate and differentiate into neurons and other brain cells, including glia and oligodendrocytes. As differentiation takes approximately 2 to 4 weeks, any functional effect of reduced proliferation would not be observed until weeks later. Thus, there is a time lag between alcohol consumption and its effects on hippocampal circuitry. As a single dose of alcohol decreases proliferation by 40 percent, this suggests that any observable effects on hippocampal integrity and function would be delayed. The effect of alcohol on neurogenesis.

Chapter 9 : Neurogenesis - Wikipedia

Neurogenesis occurs during embryonic development, and also in parts of the adult brain following birth.. This process, known as adult neurogenesis, was first recognised in the s, although it took until the s for the field as a whole to accept that neurogenesis in adult animals could play a substantial role in brain function.

Photo courtesy of Wikimedia Commons The last decade of the 20th century, proclaimed the "Decade of the Brain," yielded tremendous advances in the field of neuroscience. For at least a century before the discovery of neurogenesis the birth of new neurons in the adult human brain, a prevailing belief in the field of neuroscience was that the brain of virtually all mammals not just humans remained structurally constant throughout life and was incapable of producing new neurons. There were a number of reasons for this belief, including the observation that the mammalian brain and spinal cord have limited capacity for self-repair following injury. In addition, detailed studies of the elaborate architecture of the adult brain indicated that it remained constant in appearance, with an unchanging number of neurons, and that no mitotic dividing neurons were present. Indeed, the human brain is enormously complex; it is composed of an estimated billion neurons that make an estimated trillion connections, so it is very difficult to imagine how new neurons could develop and integrate successfully into the mature brain structure. The belief in the constant nature of the brain and spinal cord carried profound implications, namely, that recovery from traumatic injuries such as stroke or spinal cord injury was impossible. Beginning in the s, studies emerged that contradicted the long-standing dogma of the adult mammalian brain as a static organ. However, the prevailing belief in the stability of the adult brain was upheld for roughly 40 years after these initial reports. During that time, increasingly sensitive techniques were developed to detect cell division. In addition, technological advances enabled scientists to identify the types of new cells produced in the brain. Spurred by these developments, evidence accumulated in support of adult neurogenesis, including the publication of a seminal paper describing the birth of new neurons in the adult human brain. Today, the concept of adult neurogenesis is widely accepted by the scientific community. We now know that while most cells in the brain are born during embryonic and early postnatal development, new neurons are generated throughout life and are added to at least two areas of the brain: These newly generated neurons arise from populations of cells known collectively as "neural precursors," which can differentiate into the various types of cells that make up the nervous system. New neurons are born in two regions of the adult brain: New hippocampal neurons are generated by neural precursors located in the hippocampus, in a region known as the subgranular zone. In contrast, new olfactory neurons arise from neural precursors located outside of the olfactory system, in a region known as the subventricular zone of the lateral ventricle. These cells migrate to the olfactory bulb through a tract known as the rostral migratory stream. Over the past decade, adult neurogenesis has become one of the most exciting and rapidly evolving areas of research in the field of neuroscience. While many answers remain unknown, new insights are emerging at a stunning rate. Indeed, experimental studies suggest that new neurons are not only generated throughout life, they also integrate into the circuitry of the brain and actively participate in its functions. The hippocampus is known to play a critical role in learning and memory and many scientists have hypothesized that newly generated neurons within the hippocampus contribute to these processes. Although currently limited, there is support for this hypothesis. It appears, for instance, that conditions that impair adult neurogenesis, such as stress5, also impair learning. In contrast, conditions that promote the generation of new neurons, such as physical exercise, often are associated with improved memory and learning of tasks that rely on the hippocampus. Studies also have shown that learning promotes the survival of new neurons. In fact, better learners seem to retain more new neurons, especially when trained on difficult tasks. These findings suggest an intriguing link between neurogenesis and learning. Some evidence suggests that neurogenesis is not only correlated with learning and memory, but actually may be required for some forms of learning. This finding suggests that new neurons could be required for the acquisition and retention of new memories. Unfortunately, the methods used in this study, and all other methods currently available to selectively diminish neurogenesis, are likely to have additional affects on brain function, making results less than conclusive. Nevertheless, these

studies provide initial support for the hypothesis that newly generated neurons participate in at least some forms of hippocampal learning and memory. Hippocampal neurogenesis also may play a role in various neurological disorders and diseases, including epilepsy and depression. Studies have shown that many of the therapies and medications used successfully to treat individuals suffering from depression can cause an increase in the production of new hippocampal neurons. Others have demonstrated that the beneficial effects of some antidepressants are blocked when neurogenesis is prevented These and other observations suggest that diminished neurogenesis could be an underlying cause of depression. If this hypothesis proves correct, people suffering from depression could potentially be helped through treatments that increase the production of new neurons in the hippocampus. In contrast, by using animals to study temporal lobe epilepsy, scientists have shown that neurogenesis increases in response to seizure activity. However, in this case, the production of new neurons is not beneficial because those neurons develop, migrate and integrate inappropriately, and actually seem to contribute to recurrent seizures. Although the functional significance of abnormal neurogenesis in these and other medical conditions is not yet understood, it is an area of intense research that may one day yield new treatments for these disorders. The discovery of adult neurogenesis has also uncovered the exciting potential for novel approaches to repair the injured brain and spinal cord. Some animals, such as lizards and goldfish, can regenerate entire segments of their injured nervous systems. While the human brain clearly does not have this capacity, it does appear to have greater regenerative ability than was previously believed. In fact, many studies have shown that neurogenesis is stimulated in the mammalian brain in response to injury and disease4. For example, experiments in rodents have demonstrated that new cells are generated in response to brain injury caused by a stroke. Those new cells can migrate to the site of the injury in the cerebral cortex where neurogenesis does not normally occur and differentiate into mature neurons that form connections with neighboring cells. Naturally, this will not be an easy undertaking. It will require an understanding of how to stimulate the generation of new cells, direct their migration to areas that require repair, and control their differentiation into the appropriate kind of neuron. It also may be necessary to manipulate the natural environment of the adult brain to make it more conducive to regeneration. In addition, problems may arise if new neurons do not integrate properly into the existing network of nerve cells. The discovery of life-long neurogenesis in humans has redefined our understanding of the brain and spinal cord. Although still in its infancy, the study of neurogenesis already has provided insights into the mechanisms of learning and memory, epilepsy, depression, and other disorders and diseases of the nervous system. It also has inspired hope that new strategies will be developed to treat injuries and diseases of the brain and spinal cord. While much progress was made over the past decade, many questions remain unanswered, ensuring that the investigation of neurogenesis in the adult mammalian brain will remain an exciting and intense area of research well into the future.