Neurodegenerative Diseases & Preventatives

Vyapti Patel

Introduction

For decades, it has been said that the concept of neurogenesis – the process of generating new neurons- occurs during embryonic development only. Though recently through skepticism and experimentation, these doubts have been refuted. The first scientists to make the remarkable discovery were Joseph Altman and his colleagues back in the 1960s. They revealed that adult mammalian species are able to generate new neurons, and that neuron generation does not fully diminish with age. They first started off testing on adult lab rats and then came forth even more scientists who fueled this discovery even further through their own experimentations. This research has opened many doors within the scientific as well as medical community. Unfortunately, combined with the propagation of new neurons comes neurodegenerative diseases in which the opposite occurs, where there is a “gradual loss of different neuronal populations" (Winner, B., & Winkler, J. 1970). It has been shown that “millions of people worldwide” (Hollander et al.) suffer from neurodegenerative diseases as they age. With more pharmacology knowledge and the life expectancy of individuals increasing within the world, it is imperative to find a gateway to help individuals fight these neurodegenerative diseases before it becomes a norm with old-age. With the in-vivo testing methods and the application of already known knowledge with the combination of newly found knowledge on the inner workings of neurodegenerative disorders such as Alzeheimer’s disease as well as Parkinson’s disease, one can prompt prevalent clinical changes to help bring advancements towards a cure for these disorders.

Neurogen. / Neurodegen:

Neurogenesis is a concept that has been widely researched as of recently, especially through the use of adult rats and the inner workings of their hippocampal areas, as well as the olfactory region of their brain, where the creation of new neurons stem from. These new neurons that develop in these areas are what we call, stem cells. Stem cells are what prompted the discovery of adult neurogenesis; these cells are neurons that can ‘divide and differentiate into many types of cells’ (*What is neurogenesis?, 2021*). Their discovery in adult mice has been a realization to the scientific community that there is adult neurogenesis that exists and this may hold the key to fending off neurodegenerative diseases. More in depth mechanisms working in the ‘subgranular zone (SGZ) and subventricular zone (SVZ) of the adult brain’ provide more information on what is occurring within the brain to create new neurons. These sites are major for ‘Cell proliferation’ (Curtis et al. 2013), in which there is an increase in cell numbers due to the division of cells. Proliferating cells in these areas tend to migrate to regions that relate to learning and memory as well as in areas where neurogenesis still occurs in the adult brain, such as the olfactory bulb and in damaged areas due to ‘physical damage or disease’ (Curtis et al. 2013). The SGZ and the Granular Layer help formulate the Dentate Gyrus of the Hippocampus and this has shown that changes in the proliferation of cells in the SGZ can bring about change to an individual's memory and learning.

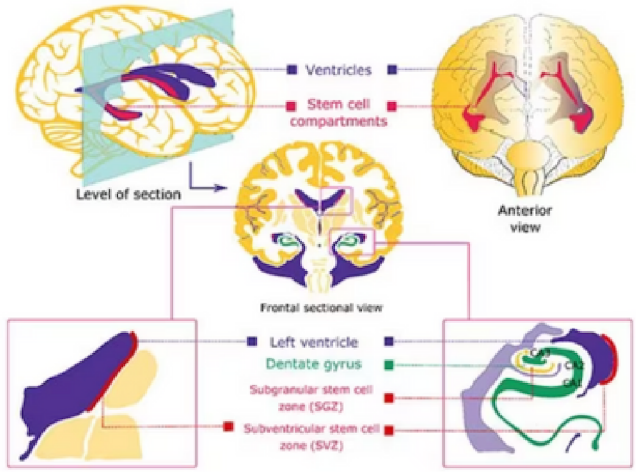

Figure 1. Important Regions Regarding Neurogenesis. In-depth view of where neural stem cells proliferate. (2023). Neural Stem Cell Culture Protocols. https://www.sigmaaldrich.com/US/en/tec hnical-documents/protocol/cell-culture-an d-cell-culture-analysis/stem-cell-culture/n eural-stem-cell-culture-protocols

The human SGZ and SVZ are a bit different than those of rodents, sheep and or other animal models, as humans have “four distinct layers, an ependymal layer (EL) acting as a boundary with the lateral ventricle (layer I), a hypocellular gap region (layer II) where only sparsely scattered cells are seen, followed by an astrocytic layer (layer III) where type A, B and C cells are abundantly located and topographically organized in laminae from superficial to deep” (Curtis et al. 2013). These layers, specifically in healthy adult brain have a cell proliferation “rate of ≈50 PCNA(Proliferating cell nuclear antigen)-positive cells per mm, whereas in the SGZ there were only ≈0.2 PCNA-positive cells per mm” (Curtis et al. 2013), this indicates that any differentiation in this rate can determine whether neurogenesis is occurring at a normal rate or if it is gearing towards a neurodegenerative disease. By being able to examine this, preventative measures can be taken early in order to bring the rate back to its norm, as having a quantitative value can help professionals understand the concept more concretely.

Another factor playing a role in neurogenesis in the adult brain that leads up to neurodegenerative diseases would be the accumulation of the specific proteins termed as proteinopathies. Proteinopathies can originate in the Central Nervous System but are not subjected to just this area as this

can also occur within the peripheral cells, tissues and organs. In principle, these 'proteins change their conformation thereby gaining toxic activity or losing the normal function' (Bayer & T. A., 2013). They can also be characterized by a single aggregate, or by multiple and it is these multiple mixtures that make it hard to come to a 'definite diagnosis' and get 'therapy' for the Proteinopathies. Through understanding the inner workings behind Neurogenesis in the adult brain and its correlation to Neurodegenerative diseases, these advancements can bring about ways to eliminate specific occurrences from happening.

Parkinson's (PD)

Parkinson's Disorder occurs especially in the senior adult population. Parkinson's disease is estimated to affect 'nearly one million people in the United States' (Hollander et al.). The Basal Ganglia plays a huge role in the movements of an individual, and the Indirect and Direct pathways give the ability to do so. The direct pathway is more so related to Parkinson's Disease; as it is a 'positive pathway'(Latifa et al. 2021) allowing for movement to occur. A defect in the direct pathway is what 'inhibits movement' as this results in the Indirect pathway which is a 'negative pathway' to give off stronger signals resulting in the slowing down of movement or a complete stop in movement leading to Parkinson's Disease. These pathways also have excitatory neurons like Glumnate playing a role as well as inhibitory neurons like GABA, in order to balance out movement from the instructions of the release of the different Dopamine groups, but with a defect in one area, results in the abnormal functioning of the movement systems. There often are many pre-disease related symptoms that occur within the individuals such as, "depression, anxiety, cognitive, or olfactory dysfunction, symptoms linked to olfactory or hippocampal function" (Winner, B., & Winkler, J). The symptoms that occur during the stages of Parkinsons can range from Bradykinesia; slow movement, to Hypokinesia; decreased amplitude of movement in which there is an 'abnormally' slow muscle activity, to Akinesia; loss of the ability to move.

A neuropathological feature of Parkinson's is the build up of the clumped up form of the protein alpha-Synuclein, also known as Lewy Bodies (LB's). LB's "are insoluble, intraneuronal protein inclusions'' (Marotta et al, 2021). There appears to be an association between reduced cell proliferation in the Dentate Gyrus in Parkinsons but it is also found through experimentation and manipulation in Mice models that, "impairments of the local trophic support of newly generated DG neurons might play a role in the reduction of neurogenesis in the A53T α-syn transgenic model (Winner, B., & Winkler, J, 1970)". Many cell replacement therapies have undergone trial and error. One of them being, "human dopamine-producing fetal midbrain neurons into the striatum of PD patients was performed (Winner, B., & Winkler, J, 1970)". These transplants of the dopamine producing fetal neurons seemed to be a success in producing dopamine being functionally integrative, as it led to clinical improvement but led to a more severe side-effect of

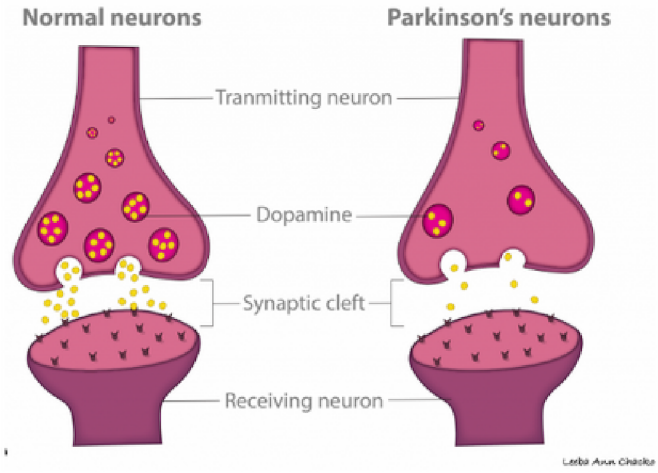

Figure 2. Normal Neurons vs. Parkinson's Neurons
Parkinson's Disease occurs due to the decrease in the release of Dopamine from the Dopaminergic neurons. (2011).
My hands are shaking, do I have parkinson's disease? from https://www.scirio.in/shaking-parkinsons-disease/

Alzheimer's (AD)

Alzheimers is a more severe case of dementia that many suffer from, specifically those in their late years. As many as 6.2 million Americans suffer from Alzheimer's Disease as discovered by a report from the Alzheimer's Disease Association. Alzheimers pertains to the diminishing of memory and its 'cognitive and functional deterioration'.This too pertains to the loss of neurons indicating that the diminishing effects of neurogenesis may be in play here. In addition to neuron loss, 'extracellular amyloid plaques and intracellular neurofibrillary tangles' (KATSNELSON et al., 2016) also pertains to the disease.

The amyloid hypothesis 'considers Aβ deposition' –a β-amyloid protein significance to Alzehimers disorder– to be a causative factor of Alzheimer's disease, this hypothesis describes the "sequence of AD etiology" (Bayer & T. A., 2013). The APP; a 'larger amyloid precursor protein' appeared to have an association with Alzehimers, and so in 1999 scientists had mice trials where they "immunized transgenic APP mice with pre-aggregated Aβ1-42, either before the onset of AD-type neuropathologies or after the onset of plaque deposition" (Bayer & T. A, 2013) this immunization shortly proved that this method was effective in reducing 'the extent and progression of these AD-like neuropathologies' implying that the 'immunization with pre-aggregated Aβ1-42' may help prevent and treat AD. In the short-term it was also shown that the vaccination protected 'transgenic mice from the learning and age-related memory deficits'; though when being tested on humans as a form of clinical trials, it was discovered that 'Six percent of AD subjects (18 of 300) developed serious brain inflammation resembling meningoencephalitis' (Bayer & T. A., 2013) and there was no prevention for progressive development of neurodegenerative diseases. Furthermore, the 'Aβ-mediated alters one of the GABAergic neurotransmission and brings an imbalance between hippocampal GABAergic and glutamatergic neurotransmission resulting in an impaired hippocampal neurogenesis' (Winner, B., & Winkler, J, 1970) in AD, which indicates the effect of storing memory within

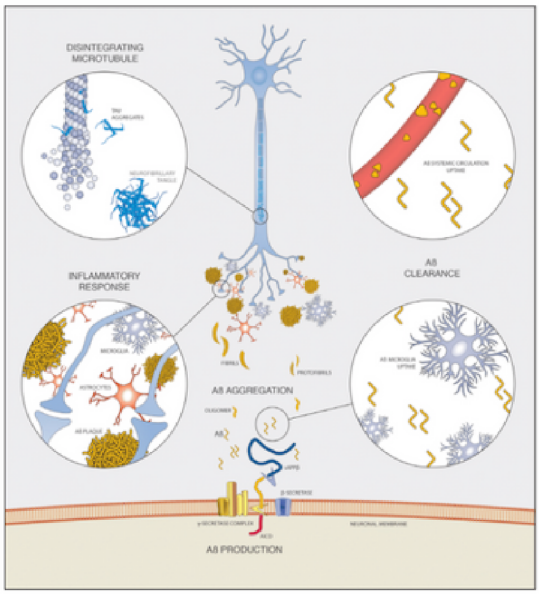

Figure 3. Amyloid-B (AB) cascade hypothesis
The disposition of the amyloid-B peptide and the accumulation of it in the brain is a preliminary step towards the process of the Alzheimer's Disease. (2019). Amyloid-3 immunotherapy for alzheimer disease: Is it now a long shot? doi: 10.1002/ana.25410.Epub

older individuals. As the Hippocampus is one of the places where Neurogenesis still appears to occur even with old age, this blockage is a big factor indicating the progression of AD.

Another major reasoning behind the development of Alzheimer's Disease would be 'presence of inclusions within neurons that are composed of fibrils' which are curated from the 'microtubule-stabilizing protein tau'. The misfolding of the oligomeric and post-translational alterations of the tau molecules is said to partake in the neuron loss and 'cognitive impairments in AD'. Tau is said to be a toxic factor as there is evidence pertaining to the fact that tau oligomers can motivate ' neurodegeneration and memory impairment in the absence of Aβ' (Bayer & T. A., 2013). The exposure that scientists have gotten from the inner mechanisms of these individual proteins that pertain to Alzheimer's Disease can allow us to narrow in on the specifics. So when trying to find a cure, we know the contribution of certain proteins to Alzheimer's disorder allowing us to design a method to turn on or off specific proteins and their functioning.

Preventatives

Many preventative measures have been explored and many have failed as the side effects were too detrimental on their subject of testing, which included mice. By testing on mammals that resemble the behavior and certain organ systems similar to humans, scientists, through trial and error, obtain more knowledge upon these diseases allowing for them to bring advancements towards change. Other than the inner workings of proteins and specific factors within the nervous system, there appears to be a positive association between environmental enrichment as well as physical exercise to neurogenesis. Through testing different stimuli pertaining to these areas of living they appear to have 'positive effects on survival, cognitive performance, as well as reduction of neuronal intranuclear inclusion load'.

Though none of them were able to reduce the effects of neurogenesis, it was shown that environmental enrichment played a role in increasing 'levels of hippocampal neurogenesis to some extent'. Through the experimentation of mice put on trials where mice were placed in an enriched environment which sped up their social interaction and the availability of the 'wheel for exercise' (van Praag et al., 2005) appeared to have inflated the hippocampal neurogenesis versus those mice kept in cages deprived of such enrichment. The voluntary running on a wheel and the physical activity exercised by the mice, has also led to an '[increase] cell proliferation, cell survival and net neurogenesis' (van Praag et al. 1999) even if these mice were not necessarily placed in an enriched environment. If one cannot get rid of neurodegenerative diseases, one can bring upon an opposition that counters the loss of neural cells, through proliferation of these cells.

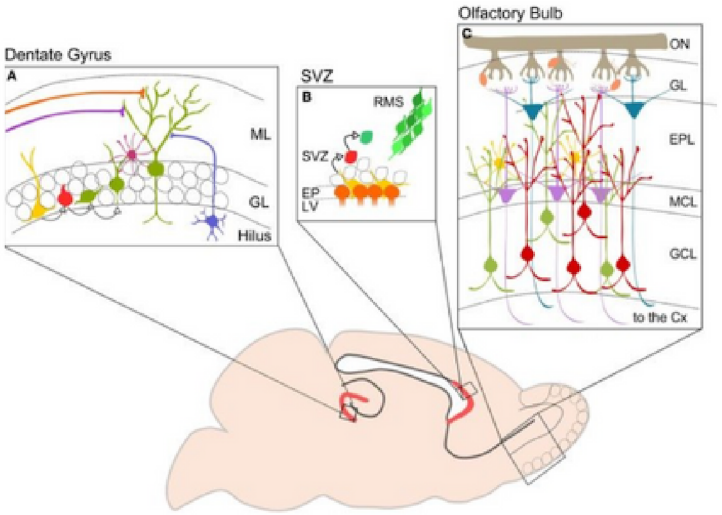

Figure. 4 Neurogenesis in the Adult Mouse brain.
The different processes of the occurrence of Neurogenesis in the neurodegenerative sites, Dentate Gyrus of the Hippocampus, as well as the SVZ and the Olfactory Bulb. (2014). Regulation of adult neurogenesis by GABAergic transmission: signaling beyond GABAA-receptors. Frontiers in cellular neuroscience. 8.166.10.3389/fncel.2014.00166

Antipsychotic drugs appear to also have an effect on neurogenesis within the hippocampus, although it appears to depend on the pharmacology behind it and there is not much evidence pertaining to it. It appears the best approach to combat neurodegenerative diseases consists of treatment for proteinopathies. Multiple vaccines and trials have been conducted, although all appear to have some sort of side effect on other areas of the brain and body that results from the treatment, most common ones to consider would be clinical side effects. Though there appears to be a similarity in what is being the main target when it comes to combating these diseases, new vaccines that were taken on trial initiate to avoid harmful T cell responses, while removing 'harmful Aβ peptides', and targeting plaques. It is discovered that, "Aβ immunization with AN1792 can initiate plaque removal" (Bayer & T. A., 2013) on AD patients, but in order to fully put this to the test, the Neuropathology team of Delphine Boche and James A.R. Nicoll initiated a follow up on the AD patients from the Elan Abeta immunization trial, who were given the vaccination. What they determined from the trial was that the

Aβ load was lowered as well as evidence of 'plaque removal' and 'reduced tau load in neuronal processes, but not in cell bodies' (Bayer & T. A., 2013). The main goal appears to be targeting 'Aβ-amyloid plaques' and there have been multiple vaccines that intended to do so, but they did not get too far in their phases of trial on human trials. In phase II of the vaccine bapineuzumab study, the human participants developed 'vasogenic cerebral edema' (LIEBESKIND & D. A. V. I. D. S., 2002) which is brain swelling that can result in the disruption of the blood brain barrier. Another drug such as the Solanezumab has been tested on participants as well, but it does not show much promise in the upper level phases such as phase III and appears not be very helpful in those individuals suffering from a more intensive case of Alzheimer's Disorder.

However, those struggling from mild levels have shown a bit of an improvement. This form of treatment is known as a humanized monoclonal antibody, which aims to target and neutralize soluble Aβ peptides. As mentioned previously this was not a successful attempt but the evidence that was found through these trials was that, "statistically significant slowing of cognitive decline" (Bayer & T. A., 2013) Preventative measures can be understood and taken early on as a means to prevent neurodegenerative diseases from occurring in the future. There appears to be an increase in the development of neurodegenerative diseases within aging adults and through understanding the ways one can prevent such diseases can gradually decrease the development of neurodegenerative diseases.

Conclusion

This newfound discovery of neurogenesis within the adult brain has opened up many doors to understanding the specifics of neurodegenerative disorders and ways to combat them. Through trial and error within experimentation in the scientific community as well as environmental enrichment from one's life, newfound knowledge on neurodegenerative disorders and their inner mechanisms is being obtained. This can ultimately help identify a cure or close-to a cure that can help eradicate humanity from advancing towards such diseases and get rid of the notion of this becoming a norm with old-age.

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