Honors Research Project Thesis

Application of Reptilian Adult Neurogenesis in Mammalian Brains

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Expected Date of Graduation: May 2023

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2022-2023

Abstract

Adult neurogenesis, which is the development of new neurons in the brain, is a process that is only rarely seen in adult mammals but is commonly seen in a variety of adult reptiles typically after an injury. Reptiles and mammals have similar brains with several homologous areas, so the study of reptilian adult neurogenesis could lead to the discovery of mammalian adult neurogenesis, particularly in the cortex and other telencephalic divisions. Due to the many documented cases of reptilian adult neurogenesis, a thorough review of the literature is necessary to design a study that would involve the use of reptilian models to identify any gene(s) causing adult neurogenesis to occur and then identifying a homologous adaptation in mammalian models. From there, studying that adaptation to see what might turn on adult neurogenesis in mammals. Finally, this information could help develop new treatments for illnesses and injuries that would cause the loss of functioning brain tissue in mammals, such as Alzheimer's disease and rabies.

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Introduction

Neurogenesis is the regeneration of projecting neurons and microneurons in the brain (González-Granero et al., 2011). The most prominent time neurogenesis occurs is during development. The phenomena has been controversial in adult human studies, with older research claiming it as a fluke or nonexistent, but newer research citing it to be very real (Lucassen et al., 2019). However, it is commonly accepted that adult neurogenesis is, at best, extremely rare, only occurring in some animals in certain conditions (such as, when mice exercise). However, there are many cases of documented adult neurogenesis in various reptiles (González-Granero et al., 2011). Not only is this found in many species, but it is also found in many areas of the brain, as well (Lopez-García et al., 1990). With how common and accessible adult neurogenesis in reptilian species is, adult neurogenesis in humans can be further explored. The genetics, the conditions, and the types of cells can be explored, and perhaps reasons for why it would occur in reptiles and not humans. Further, this can be applied to situations of human or other mammalian brain damage or neurodegenerative diseases. This paper is meant to review the present literature and hypothesize how this might be possible in the future.

Methods

Methodology included an extensive and systematic search of the literature to find any recorded evidence of adult neurogenesis in mammals. Findings were controversial in human adult neurogenesis, so it was expanded to mammalian neurogenesis. There were some more results, but further research led to reptilian neurogenesis, which yielded the most evidence and the best results. Overall, the process was comprised of three steps: a) literature searching and screening; b) information extraction, analysis, and interpretation; and c) writing the literature review. The search began broadly with the concept of adult neurogenesis, and articles found

there led to the establishment of reptilian adult neurogenesis as the focal point for this project. Once the topic was decided, a broad search of reptilian neurogenesis was conducted. Several different papers were selected, reviewed, and annotated. Points of interest in each paper were noted, and then the publications that those points originated were located and reviewed in a similar process. This process was conducted for each section of this paper. Not all information analyzed could be included, so selection of data was determined by what data was most relevant to the topic and could contribute meaningfully to the topic, based upon personal opinion and vision.

Neurogenesis

Neurogenesis begins early in fetal development when the neuroepithelial cells in the neuroepithelium begin to travel up and down the apical-basal axis, which ultimately outlines the body plan of the organism (Götz & Huttner, 2005). These cells move and stay on their course because they are highly polarized and move away from their opposite pole due to transmembrane proteins like prominin-1 in the apical plasma of the neuroepithelial cells (Huttner & Brand, 1997; Wodarz & Huttner, 2003). At the other end of the pole that these cells are moving toward are receptors that ultimately connect the cells to the basal lamina through the use of adherens junctions and tight junctions, which are constantly reorganizing the cells into their proper locations and spurring development (Aaku-Saraste et al., 1996; Zhadanov et al., 1999; Manabe et al., 2002).

From there, neurons are generated, and this action transforms the neuroepithelium from a pseudostratified, single-layer tissue to a multi-layered tissue that will mirror the development of the several layers of the brain (Aaku-Saraste et al., 1996; Aaku-Saraste et al., 1997). The top-most layer of the cells, which is now called the ventricular zone, downregulates epithelial

features like the tight junctions once more (Aaku-Saraste et al., 1996). This ultimately causes a delivery of more plasma-membrane proteins to the cells due to the increased polarity of the apical layer and the basal layer of the neuroepithelium (Aaku-Saraste et al., 1997). At the same time, the beginnings of astroglial cells, which are essential to creating radial glial cells that act as a scaffolding for developing neurons to continue the journey into their properly signaled place, start to appear (Kriegstein & Götz, 2003; Huttner & Brand, 1997; Campbell & Götz, 2002; Götz, 2003). This is considered to be the beginning of neurogenesis because from here, radial glial cells will finish forming and will direct neurons.

Radial glial cells are typically only seen during neurogenesis. They form the framework of the brain, and the developing neurons essentially climb up them and go to their designated location. Like other processes during fetal growth and development, there is a specific choreography these travelling neurons follow. In this way, the radial glial cells replace the neuroepithelial cells that only had slight influence in the movement of the neurons (Williams & Price, 1995; Malatesta et al., 2000; Götz & Huttner, 2005). Therefore, many of the neurons in the brain can be traced back to the radial glial cells. Many of the properties of the neuroepithelial cells are maintained in the radial glial cells to contribute to neuron movement, including the expression of filament proteins, the maintenance of the apical surface and the apical-basal polarity and prominin-1, and nuclear migration (Hartfuss et al., 2001; Chenn et al., 1998; Götz & Huttner,

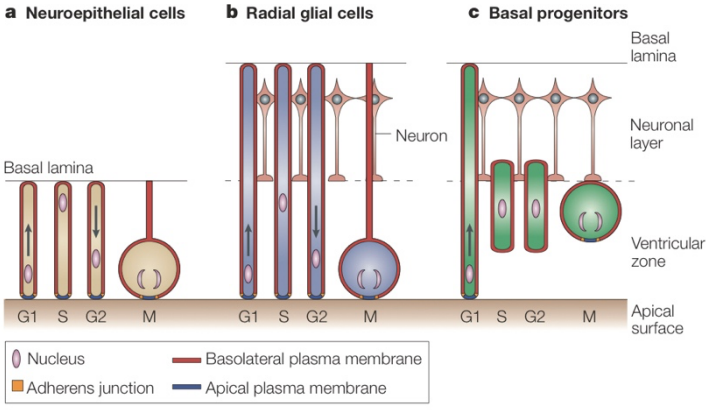

Figure 1: This figure depicts the movement of different types of initial neural cell migration (Götz & Huttner, 2005).

2005). All these traits are essential for the movement of the neurons, so that is why they are maintained. However, radial glial cells are a type of astroglial cell at their core and possess many glial cell properties that truly set them apart from neuroepithelial cells, with one of the more prominent differences being the presence of glycogen granules and the GLAST glutamate transporter (which also begins to appear during neurogenesis, seeing as glutamate is a prominent excitatory neurotransmitter in the central nervous system [CNS]) (Gadisseux & Evrard, 1985; Kriegstein & Götz, 2002). Although radial glial cells have the potential to form several neural cell types, including astrocytes, oligodendrocytes, and neurons, each radial glial cell specializes in one cell type. During neurogenesis, almost all radial glial cells will focus on the formation of neurons (McCarthy et al., 2001, Grove et al., 1993; Noctor et al., 2001; Götz et al., 2002; Williams & Price, 1995; Malatesta et al., 2000).

Another cell type essential to neurogenesis is the basal progenitor (Haubensak et al., 2004). These cell types appear early in neurogenesis and can be distinguished from other neuroepithelial and radial glial cells due to the fact that their nuclei undergo mitosis on the basal side of the ventricular zone, as opposed to the apical side of the ventricular zone like the neuroepithelial and radial glial cells (Noctor et al., 2004; Haubensak et al., 2004). Although present early on, these cells do not significantly contribute to neurogenesis until later on, where they will take over from radial glial cells and begin to form the subventricular zone that exists in only certain regions of mammalian brains (Haubensak et al., 2004). Basal progenitors undergo symmetric cell division, which produces two identical neuronal daughter cells and increases the number of neurons that can be generated from a single basal progenitor (Smart et al., 1973).

Neurons are created from the type of division taking place. Asymmetric horizontal cleavage and asymmetric vertical cleavage, which are both cleavages that neuroepithelial and

radial glial cells undergo, give rise to new neurons (Huttner & Brand, 1997; Wodarz & Huttner, 2003). As previously mentioned, basal progenitor cells undergo symmetric division, producing two identical neuronal cells that have the potential to divide further into neurons. This is because, during asymmetric cleavage, all of the cell constituents that allow for continued proliferation are cut out from one of the daughter cells based upon the location of the cleavage (Chenn & McConnell, 1995). One cell will receive the basolateral plasma membrane, the adherens junction, and the apical plasma membrane, and the other will receive only the nucleus and end division there in order to become a neuron (Götz & Huttner, 2005). However, in symmetric division, both daughter cells each receive those constituents, so cell division will continue to take place until an asymmetric division occurs (Chenn & McConnell, 1995; Götz & Huttner, 2005).

Overall, neurogenesis is a complex process with various working parts to it that seem to become obsolete as the central nervous system finishes developing, and the structures take form. As previously discussed, most neurogenesis takes place mainly during early fetal development and can continue into perinatal development (Götz & Huttner, 2005). There is not a lot of evidence showing support for adult neurogenesis of the same caliber as early development in most organisms. However, data suggests that adult neurogenesis could take place in many reptiles for two reasons: either for a continuous addition of infinite neurons but not eliminating previous neurons, or to replace old

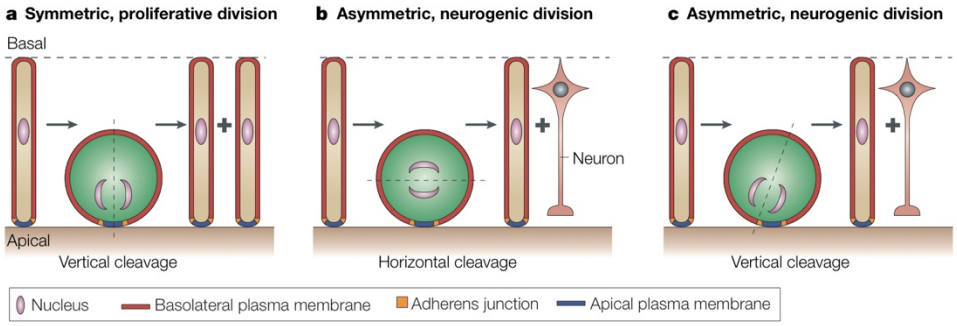

Figure 2: The three types of neural cell division. (a) results in two identical daughter cells that can still further divide, but (b) and (c) divide unevenly to create a new neuron that cannot divide further. What type of division takes place is dependent upon cell signaling (Götz & Huttner, 2005).

or damaged neurons without really increasing the number of neurons present significantly (Pérez-Cañellas et al., 1997).

Reptilian and Mammalian Brains

The reptilian brain is much less complex compared to a human or other mammalian brain. Despite this, there are many structural similarities that are present in most vertebrates (Naumann et al., 2015). Reptilian brains develop in three main sections: the forebrain, the midbrain, and the hindbrain (Starck, 1979). The forebrain is associated with most of the senses and motor skills; the midbrain is associated with visual processing and the endocrine system; and the hindbrain specializes in hearing, balance, and homeostatic maintenance (Starck, 1979). The cerebral hemisphere is formed by the pallium, but there is no cortical folding present (Wyneken, 2007).

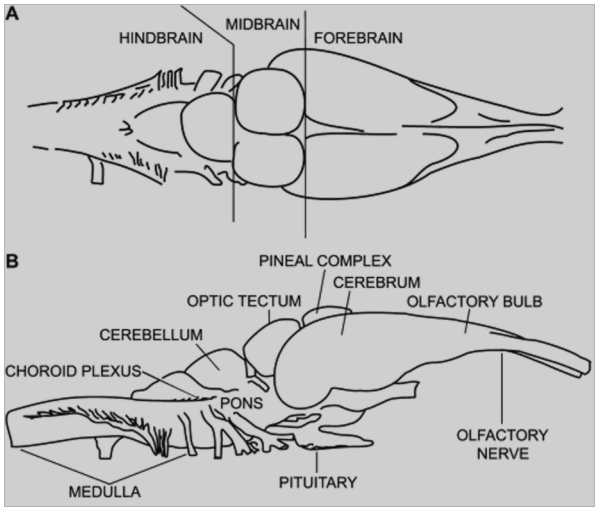

Figure 3: A basic reptilian brain, generalized from both lizards and turtles. (A) depicts a dorsal view. (B) depicts a lateral view (Wyneken, 2007).

Due to reptiles being ectothermic, the hallmark characteristic of reptilian brains is their ability to function in extreme temperatures and environmental conditions (Naumann et al., 2015). These adaptations are dependent upon the environment in which the reptile lives. Many turtles, such as *Chrysemys picta*, are adapted to low-oxygen conditions and can survive long periods of nearly freezing temperatures while hibernating in cold waters (Naumann et al., 2015). This tolerance is due to these reptiles' ability to reduce their rate of energy expenditure while shifting their metabolism to focus on anaerobic methods of ATP production, such as glycolysis, and using up any stored glycogen in the liver

and skeletal muscle tissue to facilitate anaerobic energy production (Naumann et al., 2015). This adaptation demonstrates the innate flexibility of the reptilian brain, which makes it ideal for researching developmental neurological processes. The wide variety of environments that reptiles inhabit, including deserts, jungles, and oceans, gives a wide variety of adaptations to be explored, as well.

In terms of structure, reptilian brains are general tubular and linear in shape, rather than very rounded like human brains are (Starck, 1979). The brain is surrounded by a tubular braincase that is held in place by several series of bones, besides the skull (Kardong, 1997). The amount of space between the brain and the braincase varies between species (Kardong, 1997). There seems to be no correlation between size of the reptilian species and amount of space present. Similar to mammals, there are a blood brain barrier and cerebral spinal fluid (CSF) present in reptiles (Cserr & Bundgaard, 1984). Their respective purposes are the same as in mammals and all vertebrates, and that is to protect the brain from foreign materials in the blood entering and causing damage and to lubricate the brain and drain debris from it.

Mammalian brains are characterized by a six-layered neocortex with a diversity of neural cell types, which can be attributed to tangential expansion of the subventricular zone creating many unique cell types and subtypes (Cheung et al., 2007). The reptilian three-layered cortex is comparable to mammalian layers I, V, and VI. Compared to reptilian brains, mammals have significantly more neurons (Cheung et al., 2007). The exact origin of the neocortex is still debated, but its genetic relation to the reptilian pallium and pallial divisions is still clear (Northcutt & Kaas, 1995; Naumann et al., 2015).

Cortical neurons are arranged in small columns perpendicular to the cortical surface (Cheung et al., 2007). Similar to reptiles, there is a wide variety of mammals with varying

cortical development due to different ecological niches and evolutionary needs. For example, rat olfactory bulbs are much larger compared to human olfactory bulbs because rats take in their environment through their sense of smell much more than humans would. In contrast, the human cerebral cortex is large, well-developed, and has many sulci and gyri (or folds in the brain) to increase surface area, allowing for high-level processing that is not found in the rat.

Reptilian Adult Neurogenesis

Instances of adult neurogenesis in reptiles varies by species and which area of the brain neurogenesis occurs. Overall, it occurs in the telencephalon, particularly in the olfactory bulbs and cerebral cortex (plus all its divisions). This most typically happens after an injury, both chemical and physical. The injury turns on reactive neurogenesis, and neuroblasts migrate from proliferative zones to the site of injury to replace neurons and rebuild connections. (Seki et al., 2011). There are differences between species for the intensity of neurogenesis and where it will occur (Font et al., 2001). Neuroblasts that are created during neurogenesis are perpendicular to the ventricular surface while they travel radially. As they move, they express several neuronal migration markers, like collapsing response-mediated protein (CRMP-4) and polysialic neural cell adhesion molecule (PSA-NCAM) (Nacher et al., 2002; Ramirez-Castillejo et al., 2002).

Most adult neurogenesis in reptiles has been centered in the Squamata order, which is the largest order of reptiles and includes all reptiles with scales (Pérez-Cañellas et al., 1997). A study conducted by Pérez-Cañellas et al. in 1997 demonstrated that adult neurogenesis also takes place in turtles in the ventricular zone. Eventually, these newly proliferated neurons migrated from the ventricular zone to most telencephalic regions of the brain, such as the cerebral cortex, the striatum, and especially the olfactory bulbs The study found that both neurons and microneurons were created, and there is a strong possibility that glial cells were also produced from the

ventricular zone following experimental treatment. Within the turtle telencephalon, it was concluded that new neurons in the cerebral cortex migrated there radially, implying the function of radial glial cells very similar to mammalian brains. With these findings, the group concluded that further adult neurogenesis in turtles is likely.

In another study conducted by Pérez-Cañellas and García-Verdugo in 1996, they showed that lizards also consistently undergo adult neurogenesis. Similar to turtles, adult neurogenesis in lizards stems from the ventricular zone and radially migrate to various telencephalic regions. Both microneurons and large neurons were shown to be generated in lizard brains in this study. Additionally, since many areas of the telencephalon exhibited neurogenesis, it was also concluded that various types of neurons were created, specific for each region and its specialization (such as interneurons [smaller neurons in between larger neurons meant to further a signal] or projection neurons [very large neurons that stretch across large distances to further a signal]) (Birse et al., 1980; Bayer et al., 1982; Bayer, 1983).

Mammalian Adult Neurogenesis

Some evidence shows that general adult mammalian brain has some cells that demonstrate the potential for neurogenesis (Doetsch et al., 1999; Bedard & Parent, 2004; Sanai et al., 2004). However, these cells are very few and are only limited to certain areas of the telencephalon and are not very significant (Bedard & Parent, 2004; Alvarez-Buylla et al., 2001; Garcia et al., 2004). The reason behind these particular cells is due to nearby astrocytes that show lifelong capability for neurogenesis, they are just simply not functional (Doetsch et al., 1999; Seri et al., 2001). Again, this is extremely rare, and the findings cannot be extended to most astrocytes found in the mammalian brain. Typically, it has been found that astrocytes with direct contact to the ventricle from which neurogenesis first began have this potential (Doetsch et

al., 1999; Doetsch et al., 2002). Most astrocytes in the brain do not contact the VZ and instead surround blood vessels.

There is very conflicting evidence of adult neurogenesis taking place in the human hippocampus. Neurogenesis in the adult human hippocampus is very rare or almost never observed (Sorrells et al., 2018). When it has been documented to occur, it is in regions that already have extreme neuroplasticity, such as in the hippocampus or olfactory bulbs (Bayer, 1983; Bayer et al., 1982; Kaplan & Hinds, 1977). There are some documented cases of mammalian neurogenesis. Granule cells in the adult dentate gyrus, which is part of the hippocampus, has been shown to occur in many species. However, there is no evidence for substantial adult neurogenesis in this area or in other areas of the brain, enough that could truly make a difference in the neural functions of mammals. The first documented case of human adult neurogenesis was upon postmortem hippocampal cells through the use of bromodeoxyuridine pulse-chain experiments conducted by Eriksson et al. in 1998 (Eriksson et al., 1998). Several studies using various methods to recreate adult neurogenesis was followed by this, including the use of carbon 14 (^{14}C) dating, but another paper published by Sorrells et al. found very little hippocampal neurogenesis in children and basically undetectable neurogenesis in the adult hippocampus (Sorrells et al., 2018). However, right after this study came out, another study was conducted by Boldrini et al. that stated the exact opposite of Sorrells et al., creating even more controversy regarding adult neurogenesis (Boldrini et al., 2018). All in all, there is a lot of controversy surrounding the concept of adult neurogenesis, especially in humans. Even so, most of the evidence found has been in the hippocampus, which has more neuroplasticity (ability to reorganize and form new connections) than other areas of the brain simply due to its memory

formation and learning functionality. There is almost nothing to be found regarding adult neurogenesis in the mammalian neocortex, human cerebral cortex or other areas of the brain.

Some mammalian gene sequencing to identify neurogenesis genes has been performed to some degree and found an expression of doublecortin (DCX) to be a marker of neuroblasts and immature neurons, the building blocks of the central nervous system. However, other studies have been unable to locate this gene expression in adults. At the same time, different studies identified adult cells expressing DCX, but in a much smaller quantity compared to young, developing individuals. Some have found that granule cells (the smallest and most numerous neuron type) can be recreated in the dentate gyrus in the hippocampus, but other studies did not find evidence of this either. Overall, these findings have made the results more controversial as each one is published, making the question of adult mammalian neurogenesis difficult to answer (Franjic et al., 2022).

Comparative Between the Two

Naumann et al. published a comparison between mammalian brains and reptile brains in 2015 that showcased many of the similarities and differences between the two. Although reptilian brains lack several features that mammalian brains possess, like a cerebral cortex, there are homologies present in reptiles that make comparison more accurate. This is shown when looking at gene expression found in all vertebrates. The cerebral cortex originates from the pallium, which is a section of the brain originating from the telencephalon (Naumann et al., 2015). The division of the telencephalon is induced by several transcription factors (Pax6, Emx1, and Tbr1), which are also found in all vertebrates (Naumann et al., 2015). Therefore, the pallium subdivisions that eventually give rise to the cerebral cortex are present in all vertebrates, it is just

a further division of the dorsal subdivision of the pallium that differentiates further to form the cerebral cortex that sets mammals apart from other vertebrates (Naumann et al., 2015).

Other areas of the reptilian brain can be compared to their homologous areas on the mammalian brain. The telencephalon has several areas of focus, including integrating and storing higher information and motor control, meaning it serves the same functions that the mammalian cerebral cortex and basal ganglia do, respectively (Naumann et al., 2015). Additionally, the reptilian "cerebral cortex" is also structured in three distinct layers, very similar to the mammalian allocortex (Naumann et al., 2015). Therefore, it is not much of a jump to compare reptiles to humans, who seemingly have very different brain structures.

Not only can neural structures be compared between mammals and reptiles, but cell types can also be compared. It can be argued that cell type similarities might be more important than structural similarities when tackling the question of adult neurogenesis because neurogenesis is dependent on the type of cell present since neurons originate from other neural cells. While location does play a factor in adult neurogenesis, comparing similar cell types might lead to more evidence in support of applying reptilian adult neurogenesis to human adult neurogenesis. Mammals and reptiles are shown to share complementing cortical cell types, specifically excitatory glutamatergic neurons and inhibitory GABAergic interneurons (Naumann et al., 2015). These cell types also share the same origin between mammals and reptiles (Naumann et al., 2015).

Seeing as reptilian adult neurogenesis has been shown to occur in the reptilian telencephalon, and many characteristics of the reptilian telencephalon are, as a whole, shared with the mammalian cerebral cortex, it is not far off to compare reptilian adult neurogenesis in the telencephalon to human adult neurogenesis in the cerebral cortex. Although adult

neurogenesis has not been observed in the human cerebral cortex quite yet, studying and comparing the similar cells in both reptiles and humans might elucidate further connections between the two and unlock doors to discovering human adult neurogenesis in the cerebral cortex.

In that vein, amphibians and fish are unusable in these studies because, although being vertebrates and exhibiting occasions of neurogenesis, there are not enough similar structures between amphibian and fish brains and mammalian brains, the starkest difference being the lack of a proto-cerebral cortex with distinct layers like what reptiles have (Pérez-Cañellas et al., 1997; Naumann et al., 2015; Wyneken, 2007). Therefore, since several reptile species have been shown to exhibit adult neurogenesis and have clear homologous structures to mammalian brains, they would be more useful and more applicable.

Future Research

Research would first begin in applicable reptilian models, such as lizards or turtles. The focus would be on telencephalic or cerebral cortex adult neurogenesis, so lizards such as the Moorish gecko (*Tarentola mauritanica*) can be utilized for this phase of the study, similar to what Pérez-Cañellas and García-Verdugo used in their 1996 study focusing on adult neurogenesis in the lizard telencephalon (Pérez-Cañellas & García-Verdugo, 1996). Ideally, it would start with an *in vitro* primary cell culture or immortalized cell line to begin studying and searching for a gene or trigger to cause adult neurogenesis. Once this is established, the study can move onto mammalian *in vitro* cell studies, such as neural cells taken from a rat or mouse. Since mammalian brains and reptilian brains are shown to have many homologous structures regarding the telencephalon and cerebral cortex, so there is a decent probability that they share a gene that would activate radial glial cells and promote adult neurogenesis. A reason this gene might not

function in the mammalian cerebral cortex could be because other signals keeping the brain functioning or keeping its structure might interfere with the necessary plasticity for adult neurogenesis. Mammalian brains are more developed than reptilian brains, so it might not have been evolutionarily useful for possible to maintain the capacity for adult neurogenesis as higher learning and reasoning were developed in the mammalian neocortex.

However, if this gene can be isolated and reliably activated, the research could then move onto *in vivo* mammalian systems rather than cells. If this is successful, then this research could be used to develop medications or treatments for disorders or diseases that cause brain tissue to degenerate or inflame, such as Alzheimer's disease in humans and rabies. With neurogenesis and the creation of new neurons comes the creation of glial cells and microglial cells as well that are capable of fighting off infection or clearing away debris in the brain, nervous system, and other tissues also.

A prominent challenge with research into treatments meant to trigger adult neurogenesis in the brain is crossing the blood-brain barrier (BBB). The BBB is present in all vertebrates (Abbott, 2005). It is created by endothelial cells from the walls of capillaries directly surrounding the CNS and forming an extremely tight junction system (Nag & Begley, 2005). It does allow for some molecular exchange between the cardiovascular system and the nervous system, with metabolites like glucose and oxygen being able to pass through to the CNS, but it is otherwise extremely exclusive. The CNS is therefore immunologically privileged, which is part of the difficulty with treating neural diseases and disorders. While the brain does have its own form of immune support in the form of microglia cells, which act as macrophages in the brain, it is often not strong enough to stave off tumors or other harmful foreign materials that might be present, let alone healing or regenerating damaged or dead neurons. Despite the exclusivity of the BBB, it

is still the preferred route for drug dispersion since it is so close to the individual neurons that it will spread throughout the brain quickly and efficiently. Medications that target the BBB usually act extremely quickly in the brain due to the proximity of the BBB to the brain, and they spread very quickly to neighboring neurons. Another challenge to overcome with this pathway is keeping the medication specific to the desired target of the brain. This can be accomplished with receptors specialized to certain cells or genome expressions in the desired area so that there is not uncontrollable mass neurogenesis.

In addition to the BBB, the brain is also protected by the blood-CSF barrier (BCSFB) and the arachnoid barrier. The BCSFB is formed by the deeper epithelial cells of the choroid plexus that have direct contact with CSF, creating tight junctions between the cells and the CSF. CSF flows between the brain and the choroid plexus, allowing for water movement and flow of volume between the brain and the surrounding CSF. Some drugs can enter through the BCSFB to the brain, but they also usually target the BBB (Abbott, 2004; Abbott, 2010). The third obstacle to reaching the brain is the arachnoid barrier. The arachnoid membrane is created from the avascular arachnoid epithelium and lies under the dura, the outermost layer of protective tissue for the brain that attaches to the inside of the skull. The arachnoid membrane completely encases

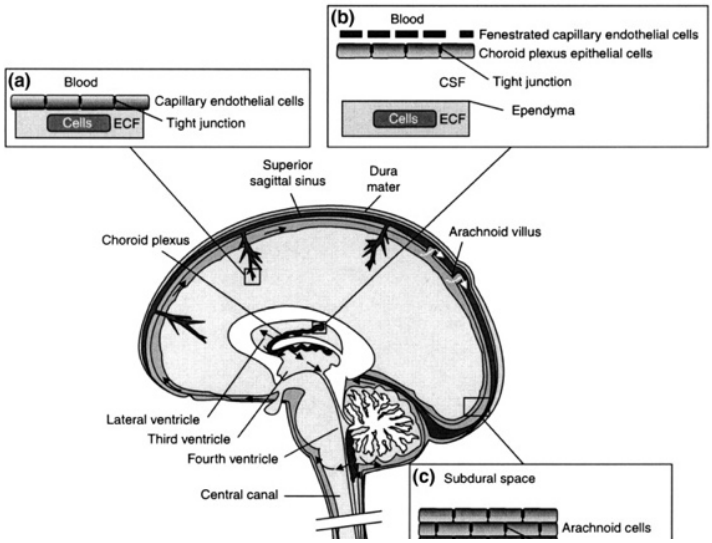

Figure 4: The largest challenge with creating medications/treatments targeting neurogenesis will be accessing the brain directly through the blood brain barrier. Its many layers and tight junctions prevent toxins from reaching the brain and impairing function, but it also makes it extremely difficult to treat neurological issues/disorders (Abbott et al., 2010).

the entirely of the CNS and separates it from the rest of the body (Abbott et al., 2006). Similar to the BBB and BCSFB, the arachnoid membrane is also held together by tight junctions. However, the membrane also has villi that project into the sagittal sinus of the brain. These villi drain CSF to the sinus, ultimately clearing old CSF from the brain and into the blood to move through circulation and be reused elsewhere. Since the arachnoid membrane specializes in moving fluids out of the brain and because it is avascular, it is not a target for medications to enter the brain (Abbott, 2010).

Additionally, there is always the possibility that there is no reptilian adult neurogenesis gene that can also be found in mammalian brains. If this is the case, then the idea of using reptilian models to identify a gene for adult neurogenesis would have to be abandoned, and research would instead have to start directly with mammalian cells and begin from scratch. Since adult neurogenesis in some reptiles is already highly documented, it would jumpstart mammalian research through findings in analogous structures to then be applied to mammalian models.

Future Uses: Alzheimer's Disease, Brain Damage, and Rabies

Neurodegenerative disorders that eat away at neural tissue, like Alzheimer's disease, and other reasons for cause of loss of tissue like traumatic injuries could be treated or potentially healed with adult neurogenesis.

Alzheimer's disease is a progressive, irreversible, and incurable neurodegenerative disorder primarily impacting individuals 65 years old or older (Uddin et al., 2016[A]; Mendiola-Precoma et al., 2016). The reason behind the damage to the brain is still being researched, but telltale signs for it are large deposits of extracellular amyloid β (or Aβ) forming senile plaques and intracellular tau proteins restructuring into abnormal neurofibrillary tangles (Uddin et al., 2016[B], Uddin et al., 2018[A]). Some neurons might be more susceptible to higher

accumulation of Aβ and abnormal tangles due to oxidative stress in the cell from reactive oxygen species, but it is unknown how exactly this might occur (Aliev et al., 2008; Moneim, 2015). This aggregation of Aβ and neurofibrillary tangles causes the progression of Alzheimer's disease, but the exact mechanism is still unknown (Murphy & LeVine, 2010; O'Brien & Wong, 2011). What is known is that neural cells in the brain become increasingly damaged as time progresses. As neural damage increases, the typical symptoms of Alzheimer's disease continually progress as well, usually ending with the subsequent death of the individual (Singh et al., 2012). Uddin et al. (2019) proposes several treatment options for Alzheimer's disease, including the use of both modern and natural medicine, but there is still no substantial cure or treatment for the progressive degeneration of the patient's brain in Alzheimer's disease.

Actual brain mass and brain issue is often lost with Alzheimer's disease. Adult neurogenesis could, at the very least, slow down the degeneration process by creating new neurons to replace the damaged ones. Additionally, newly produced microglia cells have the potential to clear out the harmful Aβ plaques and neurofibrillary tangles. The creation of new neurons could potentially reverse the effects of Alzheimer's disease and extend the individual's lifespan.

Physical trauma injuries to the brain resulting in permanent damage could be treated with adult neurogenesis in a similar fashion to Alzheimer's disease. The brain would essentially repair itself through adult neurogenesis: microglia cells removing debris and dead tissue, and new neurons migrating up radial glial cells to the target area.

One of the most prolific neurological diseases that has impacted every corner of the world is rabies, a single- and negatively-stranded RNA genome (Conzelmann et al., 1990; Tordo et al., 1986). It encodes five proteins, and its genome is enclosed very tightly in a protein shell, which also gives the RNA template its functionality for infection (Schnell et al., 2009). Rabies has been present in society for over 4,000 years (Knobel et al., 2005). Currently, despite countless efforts for population control, vaccination efforts, and increased education surrounding rabies, a recorded 59,000 deaths from rabies occur around the world, according to the Centers for Disease Control and Prevention (CDC) in 2020 (Centers for Disease Control and Prevention, 2020). The CDC also calls it one of the deadliest diseases in the world because over 99% of cases lead to death and because there is no treatment once signs and symptoms occur in an individual (Centers for Disease Control and Prevention, 2019).

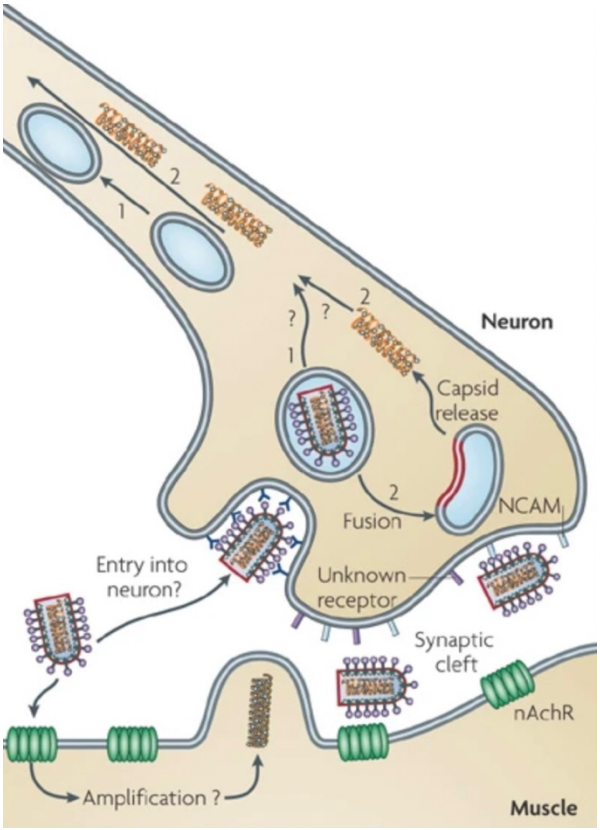

Figure 3: The exact mechanism of how rabies travels through an infected individual is unknown, but one theory is that the nicotinic acetylcholine receptor present in the neuromuscular junction either enriches the virus or helps spread it to muscle tissue through the use of an unknown receptor (Schnell et al., 2010).

The rabies virus will first attach to the host cell through its rabies virus glycoprotein, but it is unclear what part of the host cell interacts with the viral glycoprotein (Schnell et al., 2009). The next mechanism of infection is also unknown, but several theories are proposed. A study done by Lentz et al. in 1982 identified nicotinic acetylcholine receptors (nAchR) as a receptor for the virus. Once the virus attaches, the

nAchR receptor, located at the postsynaptic muscle membrane, will enrich the virus and promote its replication and growth, which will allow for efficient movement from the neuromuscular junction to the actual muscle and motor neurons, leading to increased infection (Lafon, 2005). Other research found that the rabies infection begins first in the muscles and then uses the nAchR receptor to enter the neuron to move to other motor neurons, rather than just remaining in the neuromuscular junction (Murphy & Bauer, 1974; Watson et al., 1981). Another study done by Thoulouze et al. in 1998 proposes that the neuronal cell adhesion molecule (NCAM, or NCAM1) is a potential receptor for the rabies virus. The study found that mice who had deleted genetic code for NCAM had a delayed infection of rabies, compared to mice without the deletion. Additionally, there are questions as to whether the same receptor used for viral attachment is also used for viral spread (Dietzschold et al., 1985).

Much of the mechanisms for rabies infection are still being studied, but it is known that it travels through the nervous system. The virus most likely enters through the axons of neurons, as described above. However, since the virus is a single-stranded RNA virus, it does not have the means to reproduce independently of the host. Axons do not have any organelles, nor do they provide the correct environment for protein synthesis (Malgaroli et al., 2006). Therefore, the virus must travel up the axon to the cell body in order to replicate itself. Either the rabies virus capsid or the entire virion travels up the axon to the cell body (Schnell et al., 2009). After replication, the viral components come together and bud out of the host cell to infect the next one (Schnell et al., 2009).

A key factor of the rabies virus infection is its ability to evade host immune responses. Some theorize that rabies viral replication is optimized to produce enough virions to further infection while also not producing enough to be detected by the host cell or the host immune

system (Faber et al., 2002). Other studies have found that the rabies virus evades host immune response by suppressing it, interfering with host type I interferon (IFN) responses by directly preventing the activation of IFN regulatory factor 3, effectively rendering the IFN response inert (Brzózka et al., 2005). Additionally, the rabies virus is capable of inhibiting both type I and type II IFN signal transduction pathways, preventing the cascade response of IFN to the site of infection (Yang et al., 1999). By shutting down and evading the immune system, the virus is able to overtake the host extremely quickly and cause certain death to the host within a matter of weeks.

The rabies virus does not try to kill the neural cells because it needs them to replicate itself. Instead, it will cause severe swelling of the neurons, ultimately causing many of the symptoms of rabies and, ultimately, death (Johnson et al., 2008). Studies have found that apoptosis, or cell death, can reduce infection of rabies (Schnell et al., 2009).

Although there is no cure or treatment for rabies, neurogenesis could provide a possible treatment for rabies patients. By activating the creating of new neural tissue, a barrage of microglial cells can also be created to target the swelling neurons and destroying the virions inside them. As microglia activity would increase in the brain, eliminating infected cells, their migration activity and phagocytic activity would also increase (Green et al., 2019). This would allow them to travel elsewhere in the nervous system and locating and eliminating rabies virus infections in the muscles or the neural muscular junctions of motor neurons. Any permanently damaged neurons can be replaced through neurogenesis.

Conclusion

Adult neurogenesis is one of the most controversial topics in the field of neuroscience. Some reptilian species have been very well-documented to exhibit adult neurogenesis in various

areas of the brain due to injury, including the reptilian cerebral cortex and other telencephalic divisions. Adult neurogenesis very rarely occurs in mammals, only occurring in extremely specific circumstances in limited areas of the brain. The reptilian and the mammalian brains have several analogous structures, and reptiles exhibit adult neurogenesis in those analogous structures. Reptilian models of adult neurogenesis would be an effective way to study adult neurogenesis in mammals by isolating neuron-proliferating genes in the reptilian brain and applying that research to the analogous structure in the mammalian brain, specifically with the reptilian pallium and the mammalian cerebral cortex, to reliably recreate adult neurogenesis in mammal brains. Once this is accomplished, treatments or medications can be created that take advantage of this neurogenesis gene in mammalian brains to repair damage caused by injury, replenish neurons lost due to degenerative disorders, or fight off neuronal infections that would otherwise be extremely difficult to target.

Acknowledgements

Thank you to Dr. Benjamin M. Bohrer, my academic and research advisor who guided me through this process. Thank you to Dr. Pat Whittington for his continued support of my educational career. Thank you to Dr. Pasha A. Lyvers Peffer for setting me up for success when I was planning my academic years at OSU. Thank you to all who have supported me through this journey.

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