Glial Contributions to Origins of Strokes and Seizures: A Review

For over 100 years, glial cells were thought of as being the “support” for neurons, having a very insignificant role. It was known that glial cells provide oxygen, nutrients, stability and structure to neurons; but recently, science has found that glial cells play a much more exciting role - one that is still largely unknown in full. Evidence for glial cells having a role in the actual electrical and/or chemical synaptic transmission has been found (Fields, 2009). According to R. Douglas Fields, Oligodendrocytes can fire action potentials in neuronal circuits (Fields, 2008). Not only can glial cells send electrical signals, but they also have immunity roles. Neuroinflammation of glial cells causes the release of proinflammatory cytokines, which in turn may cause certain neurodegenerative illnesses, including but not limited to ischemia and epilepsy (Glass et. al, 2010). Certain proinflammatory cytokines such as TNF-α and IL-1β can activate astrocytes once released from microglia, ultimately causing for increased inflammation by further eliciting microglia to produce more proinflammatory cytokines (Saijo et al., 2009). In cases such as strokes and seizures, these proinflammatory cytokines play a noteworthy and similar role in the underlying causative factors. The effects and origins of neuroinflammation is worthy of more investigation, as finding the origins could lead to finding remedies in certain illnesses.

Inflammation in the brain is caused by proinflammatory cytokines such as: f IL-1β, IL-6, TNF-α, Nrf2 and MCP-1, to name a few (Zhao et. al, 2016). These cytokines usually appear when there is a virus, infection, trauma or immune response (Dinarello, 2000). In the case of a subarachnoid hemorrhage from a brain aneurysm, the likelihood of a patient or subject suffering from life-threatening vasospasms is great, due to proinflammatory cytokines. Cerebral vasospasms (CVS) occur when narrowing of the arteries result, essentially causing ischemia (Weir, 1978). In a subarachnoid hemorrhage patient or subject, death or likelihood of death is most likely to occur from cerebral vasospasms in the brain (Zhao, 2016). Inflammation is necessary for the birth of vasospasms, (Eisenhut, 2014; Miller et al., 2014). In turn, vasospasms cause strokes and seizures. There have been many theories regarding the origins of vasospasms, as well as strokes and seizures. Similarly, the underlying cause of each is not well-known. However, we do know certain common denominators involved in each. We know that vasospasms can cause strokes and seizures, but what causes the vasospasms is a bigger question. Some theories to link these commonalities are: glial cell activity, synchronization, and proinflammatory enzymatic activity.

In the paper "Sulforaphane activates the cerebral vascular Nrf2–ARE pathway and suppresses inflammation to attenuate cerebral vasospasm in rat with subarachnoid hemorrhage" by Xudong Zhao, it was noted that cruciferous vegetables attenuate vasospasms in the brain after a subarachnoid hemorrhage (2016). The sulforaphane contained in particular vegetables suppressed the release of proinflammatory cytokines, further showing that these cytokines' contribution of inflammation are a key factor in the origins of vasospasms. The Nuclear factor erythroid 2- related factor 2 (Nrf2) pathway is known to be responsible for having protective factors in the brain following an occurrence of subarachnoid hemorrhage (Zhao, 2016). Nrf2 positive cells in the subarachnoid hemorrhage (SAH) group vs the control group (non-SAH) were greater, indicating the upregulation of Sulforaphane to cease vasospasms caused by proinflammatory cytokines.

In order to see these results, a Western Blot, RT-PCR, ICC, ELISA kit, arterial area measurements, and behavioral tests were performed. Arterial area in the SAH group with Sulforaphane (SFN) was tremendously increased, showing a reduction in constriction, compared to SAH group. Appetite and activity levels in SAH+SFN group were extensively better than the SAH group. The expression of Nrf2 in the SAH+SFN group, discovered by using ICC, was shown to be more present than that of SAH and control groups alone. This is suggesting of the Nrf2 pathway's role to eliminate inflammation, which would otherwise lead to excess injury during recovery of a subarachnoid hemorrhage. The Western Blot showed a higher amount of Nrf2 in the SAH and SAH+SFN groups than control groups, with the most being in the SAH+SFN group, correlating with those results of the ICC tests. The RT-PCR tests indicated results along the same findings as the ICC and Western Blot. Oxidative stress indicators, like the expression of mRNA HO-1 and NQ01, antioxidant factors that the protective Nrf2 pathway take up, were shown to be effective in reducing vasospasms, according to the analyses of the RT-PCR tests. Proinflammatory cytokines IL-1β, IL-6, and TNF-α were all greatly reduced with the addition of SFN after a subarachnoid hemorrhage, indicating that these cytokines are the possible origins for certain types of ischemia.

Because the environment inside our bodies can elicit certain genes to turn on, expressing their phenotypes, Nrf2 moves from the cytoplasm to the nucleus and binds when oxidative stress occurs, promoting transcription of other protective proteins (Keum and Choi, 2014). The question of interest is "What kind of environment makes this possible?" Inflammasomes, protein platforms, are required in the immune system to activate inflammatory responses when the cell is exposed to a danger (Tschopp, 2010). But, in the case of Choi et. al's research article "Increased levels of HMGB1 and proinflammatory cytokines in children with febrile seizures," febrile seizure patients had fever-inducing seizures without any known virus, infection, or illness (Choi et. al, 2011). This raises an even bigger question - What causes an immune response without anything to defend the immune system from?

One theory to answer this question, according to the paper "Glia-neuronal interactions in ictogenesis and epileptogenesis: role of inflammatory mediators" is hypersynchronization due to glial cell activity (Allan et. al, 2005). Allan et. al, makes reference to Choi et al, regarding the immune system playing an active role in the birth of epilepsy. Both the adaptive and innate parts of the immune system look to be at work here (Choi et. al, 2008). According to R. Douglas Fields, in the paper "Oligodendrocytes Changing the Rules: Action Potentials in Glia and Oligodendrocytes Controlling Action Potentials," depending on latency in action potential spiking, oligodendrocytes could have an affect on neural circuits just like neurons can (Fields, 2008). One hypothesis is that glial cells produce proinflammatory cytokines, which in turn cause for seizures, which in turn releases more proinflammatory cytokines which produces more seizures (Vezzani et. Al, 2011). It is a revolving door question- Which comes first, the inflammation or the cytokine activity?

Just as other neurological illnesses such as: Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS), and multiple sclerosis (MS) are thought to be caused by neuroinflammation, so might strokes and seizures. New evidence has shown microglia and astrocytes contributing to neurodegenerative diseases, by releasing some of the same proinflammatory cytokines IL-1β, IL-6, TNF-α, as found in stroke and seizure patients/subjects. (Glass et. al, 2010). Understanding the immune system and learning more about the role of glial cells is instrumental in finding drug treatments that will help remedy these ongoing issues within society. According to the research article "Mechanisms Underlying Inflammation in Neurodegeneration," once tissue damage or the presence of a foreign enemy invades the brain, microglia switch from a deactivated state to an activated state, and begin releasing proinflammatory responses (Glass et. al, 2010). While this may seem to be a good thing, it may have an endogenous effect, with an ultimate positive feedback loop, causing further and irreparable damage.

Another possible explanation for this unexplainable chain reaction of events could come from studying family members of patients with a history of strokes and seizures. Genetic variation and how certain proteins bind, may contribute to the non-infectious, non-viral immune response of proinflammatory cytokines which would consequently induce strokes and/or seizures. We know that febrile seizure patients have higher IL-1B cytokine presence in promoter regions than do fever only children (Choi, et. al, 2011). We also know that the Nrf2-ARE pathway somewhat gives rise to vasospasms following a subarachnoid hemorrhage, by releasing proinflammatory cytokines (Zhao et al., 2010; Wang et al., 2010).

Nonetheless, although we do not know the exact point of origin these strokes and seizures originate from, we can use the insight we have gathered along the way to piece the puzzle together, little by little. There are so many theories that are proposed, and each one of them reviewed have certain aspects that pose as possible truths of the matter. Furthermore, there may be differing origins altogether, just depending on the system. Multiple different factors could be playing a part at the same time. Using the evidence we gather from reviewing research articles is sure to lead us in the right direction of answering these unknown questions. Research in this field is necessary for finding cures and treatments for strokes and seizures.

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