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Role of Adiponectin in Neuroinflammation & Neuroprotection

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Abstract

Microglial cells play a significant role in defense of the brain. However, in certain disease states, their response can lead to inflammation that can be detrimental to the survival of brain cells and have harmful effects on a person's brain activity. Currently, the treatment options for microglial induced neuroinflammation are relatively limited. Adiponectin has recently appeared as a potential moderator of neuroinflammation as well as a promoter of neuroprotection. Adiponectin is a naturally occurring cytokine that has been shown to play a role in a multitude of processes throughout the body including potential as a microglial induced neuroinflammation. Adiponectin's role in reducing neuroinflammation and promoting neuroprotection is investigated in this review.

One sentence summary: This review investigates recent studies on microglial cells role in neuroinflammation and possible treatment options for microglial induced neuroinflammation.

Role of Adiponectin in Neuroinflammation

Microglial Neuroinflammation in Disease and Hemorrhage

Microglial cells have been shown to cause inflammation in disease specifically in Alzheimer's Disease. Amyloid plaque production has been shown to be common in Alzheimer's disease. These amyloid plaques, specifically Aβ oligomer (AβO), may be extremely neurotoxic in cases of Alzheimer's Disease [1, 2]. Harmful effects of AβO include injury to synapses, damage to neurons, loss of memory, and initiation of neuroinflammation[2]. Neuroinflammation caused by Alzheimer's disease is caused by microglia-mediation, as microglial cells seem to respond to amyloid plaques and help with their clearance[3, 4]. Chronic microglial cell activation causes the upregulation of interleukin-1β (IL-1β), tumor necrosis factor α (TNFα), and interferon-γ (IFN-γ); these cytokines stimulate inflammation. These cytokines also increase Aβ assembly [5, 6].

Microglial cells are generally driven towards two phenotypes (polarization states) when causing neuroinflammation: M1 and M2. The M1 polarization state increases the production of inflammatory cytokines like interleukin 6 (IL-6), interleukin 1 beta (IL-1β), tumor necrosis factor-alpha (TNF-α), and increased levels of both CD16, CD32, and inducible nitric oxides synthase (iNOS). Whereas, microglial cells in the M2 polarization state enhance phagocytosis, promote the release of anti-inflammatory cytokines such as interleukin (IL-10) and transforming growth factor-beta (TGF-β), and increase expression of CD206 (a pattern recognition receptor) on the microglial cell surface after intracerebral hemorrhage [7].

Adiponectin

Adiponectin is a naturally occurring cytokine, otherwise termed adipokine, that is produced by white adipocytes. It has been shown to have a substantial impact on metabolism

throughout the whole body [8]. Specifically, adiponectin is a large contributor to the sensitization of insulin. Adiponectin stimulates the phosphorylation of AMP-activated protein kinase and binds to adiponectin receptors in peripheral tissues to help regulate glucose metabolism when in the presence of insulin [9]. Adiponectin is also expressed in high molecular weight multimers and low molecular weight monomers [10]. Levels of adiponectin throughout the body have many different regulation factors [8].

Insulin levels throughout the body have shown to have a significant impact on adiponectin regulation. More specifically insulin plays a role the release of adiponectin from an adiponectin-containing compartment within the white adipocytes. The main compartments of adiponectin within the cell are stored just near the plasma membrane and near high-density microsomes. A study by Lim, C.Y, W. Hong, and W. Han found that insulin signaling inspired the release of the adiponectin from the compartments near the plasma membrane rather than new synthesis of adiponectin. This is consistent with the observation that after 6 hours of insulin treatment, the mRNA expression of adiponectin remained unchanged. They also found that the pool of adiponectin was secreted from the compartments near the plasma membrane rather than the compartments near high-density microsomes. The plasma membrane adiponectin pool was determined to be the main pool of adiponectin release via subcellular fractionation [9].

Adiponectin release can be stimulated through exercise, specifically running. A recent study found that, in healthy young adults, a 90-minute session of running altered adiponectin levels within the cerebrospinal fluid. High intensity aerobic exercise lowered the level of adiponectin and other cytokines within the cerebrospinal fluid. It is speculated that this could be due to changes in the permeability of the brain cerebrospinal fluid barrier, increased turnover of cerebrospinal fluid, and/or increased uptake of cytokines in the brain [11].

Adiponectin secretion has also been shown to be stimulated via an adrenergic route. In mouse cells, adiponectin was determined to be secreted in short term through cyclic AMP and adrenergic signaling. Forskolin (FSK) and 3-isobutyl-1-methylxanthine (IBMX) in conjunction were shown to stimulate adiponectin secretion by double the basal amount. FSK and IBMX were successful in stimulation as they encourage activation of adenylyl cyclase and inhibit phosphodiesterase respectfully, which increases the amount of cyclic AMP within the cell. Adrenaline and CL 316243 (a beta-3 adrenoceptor agonist) were also shown to stimulate adiponectin secretion. Adrenaline and CL were not as effective as the FSK/IBMX combination, but they were effective. Adrenaline and CL were shown to increase the amount of cyclic AMP present in the cell as well, just not to the extent as FSK/IBMX (Figure 1 will be inserted here if possible) [8]. Adrenaline also increases the amount of calcium (Ca^{2+}) present. Calcium increases cAMP production via activation of Ca^{2+} -dependent adenylyl cyclase. Ca^{2+} -dependent adenylyl cyclase enzymes are responsible for the conversion of ATP to cAMP [12].

Diet, obesity, and disease have also displayed the ability to alter adiponectin secretion. Obesity and type 2 diabetic mice (triggered by a high fat diet) have been shown to induce a defect in the secretion of adiponectin. It is proposed that obesity and type 2 diabetes lead to a low amount of beta-3 androgenic receptors and the exchange protein directly activated by cAMP (Epac1) within the inguinal white adipose tissue leaving the cell in a catecholamine resistance state. Catecholamine binds to adrenergic receptors and leads to epinephrine secretion which leads to production of cAMP (the major stimulator of adiponectin secretion). Epac is a cAMP-binding protein that stimulates adiponectin exocytosis when bound to cAMP [12].High Fat diets often translated to obesity and diabetes in mice. These obese/diabetic mice had double the amount of gonadal white adipose tissue (gWAT) than the mice fed chow. The gWAT adipocytes

of the obese/diabetic mice were unable to release adiponectin in response to adrenaline and CL [8].

While inguinal white adipose tissue (iWAT) and gWAT adipocytes both have a decrease in adiponectin secretion via the catecholamine/CL stimulation pathway, their mechanisms are different. IWAT adipocytes have lower secretion within high fat diet mice, this is largely the result of decreased expression of Epac1and beta-3 androgenic receptors [12]. GWAT adipocytes, on the other hand, have adequate expression of beta-3 androgenic receptors and Epac1 in high fat diet fed mice. It is proposed that gWAT adipocytes of high fat diet mice have lower adiponectin secretion due to the mediators and proteins downstream of Epac, although what those mediators and proteins are unknown [8].

Adiponectin and Treatment of Neuroinflammation

According to research adiponectin has an effect on the central nervous system as well [10]. The presence of adiponectin in the central nervous system is known as low molecular weight (LMW) adiponectin as it can transverse the blood brain barrier [11]. LWM adiponectin can interact with the central nervous system by binding to adiponectin receptors within the brain. Adiponectin is able to bind to the receptors within the hypothalamus, brainstem, pituitary gland, endothelial cells, and the cortex. Adiponectin receptor 1 (AdipoR1) and adiponectin receptor 2 (AdipoR2), both 7 transmembrane receptors, are present within the brain [10].

Adiponectin treatment has been identified as having positive effects on brain disorders such as Ischemic stroke, Alzheimer's, anxiety, and depression [13]. Adiponectin may offer a treatment solution to Alzheimer's Disease because Alzheimer's disease is linked with the

resistance of insulin within the brain, and adiponectin has been shown to have insulin-sensitizing properties [14-16].

In terms of preventing neuroinflammation from microglial cells, adiponectin has been shown to be beneficial, particularly in Alzheimer's Disease induced microglial activation. In a recent study, they were able to find that adiponectin was able to subdue neuroinflammation caused by AβO. Proinflammatory cytokine, TNFα and IL-1β, production was inhibited by adiponectin in immortalized microglial cells (BV2) that were exposed AβO. It was also noted that the microglial cells, when in presence of AβO, changed their morphology to have larger cell bodies and no extended processes. After they identified proinflammatory cytokine release, they wanted to see how adiponectin affected the release. They we able to identify that adiponectin was able to inhibit the expression of proinflammatory cytokines from AβO in quite a strong manner. Adiponectin treatment also did not alter the morphology of the microglial cells [2]. This is important as AβO induced release of TNFα has been shown to inhibit the long-term potentiation within the hippocampus and induce neuronal distress via neuronal cell cycle events caused by microglial cell activation [17, 18]. The study also found that because adiponectin was able to exert an anti-inflammatory effect on microglial cells, hippocampal cells (HT-22 neuronal cells) were protected from cytotoxic effects. Jian et. al identified that hippocampal cells that were exposed to AβO-activated microglial cells had significantly decreased cellular viability, but when the microglial cells exposed to AβO were treated with adiponectin and then exposed to hippocampal cells the hippocampal cells had a cellular viability that was similar to that of normal hippocampal cells[2].

The main take away from Jian et al.'s study was the signaling pathway that was altered within the microglial cells that were exposed AβO and adiponectin treatment. The study found that adiponectin was able to inhibit proinflammatory cytokine release from microglial cells that were exposed to AβO by the AMPK-NF-κB pathway [2]. 5'Amp-activated protein kinase, or AMPK, is a downstream signal of adiponectin binding to adiponectin receptor 1 that subdues inflammation and inhibits activation of NF-κB [19, 20]. They first investigated if adiponectin altered the phosphorylation of AMPK (*Figure 1 a*). They found that Adiponectin helped rescue some phosphorylated AMPK levels in microglial cells after exposure to AβO and adiponectin treatment. They then investigated how adiponectin alters expression of NF-κB (*Figure 1 b*). They did this by testing levels of phosphorylated IκBα which can be quickly degraded into phosphorylated NF-κB p65. Normally AβO increase levels of both phosphorylated and normal IκBα but, Jian et al. found that when microglial cells were treated with adiponectin, they inhibited production of phosphorylated IκBα, thus decreasing total IκBα levels. In turn, this

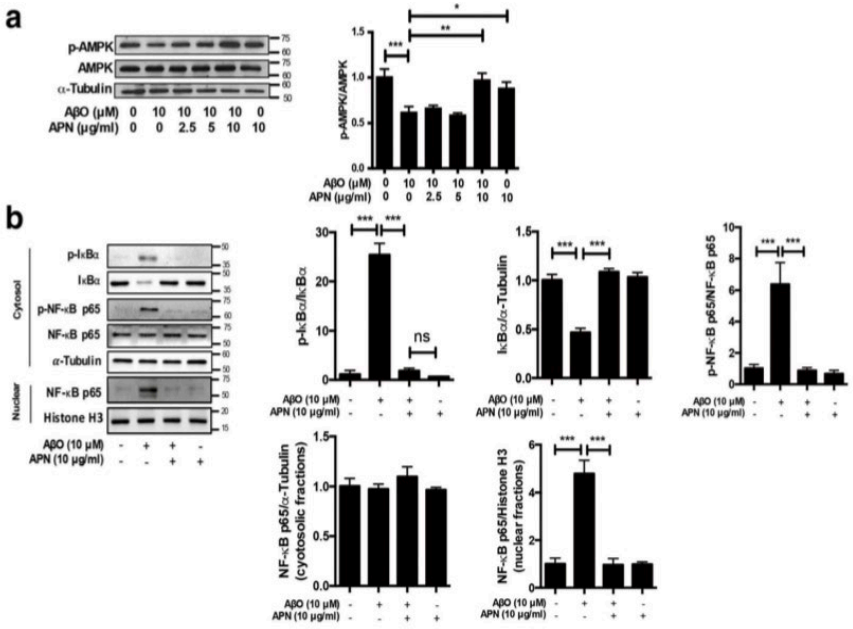

Fig 1: (a) Western blot analysis was preformed to detect phosphorylation of AMPK in microglial cells. (b) Western analysis was preformed to determine activation of NF-κB in microglial cells. Both cystolic and nuclear fractions of NF-κB were determined. Results from theses test indicate adiponectin was able to suppress proinflammatory cytokine release through the AMPK-NF-κB signaling pathway [2].(need right to fair use).

study concluded that adiponectin decreases the release of proinflammatory cytokines from microglial cells via the AMPK-NF-κB pathway [2].

Adiponectin Receptor Agonist Treatments

It appears that adiponectin may have some draw backs though. Adiponectin has a short half-life in blood plasma and a complex protein structure. The half-life and complex structure of adiponectin cause difficulties in production, administration, and cost when being used as a treatment [21]. Thus, the search for more stable molecules that can bind to adiponectin receptor 1 and activate the same pathway may prove to be more effective treatment options. Studies performed using AdipoRon and CTRP9 have shown to have positive results in reducing neuroinflammation [22, 23]

A study performed by Zheng et al. was able to identify that treatment with AdipoRon was able to alter microglial polarization towards the M2 phenotype. AdipoRon is a derivative of adiponectin that serves as an agonist of adiponectin receptors [24]. They first identified the expression of cellular markers on the surface of microglial cells (Iba1) after intracerebral hemorrhage and treatment with control (Vehicle) and treatment with AdipoRon. Expression of M1 phenotype surface markers, CD16 and CD32, was greatly reduced when treated AdipoRon after Intracerebral hemorrhage. The expression of the M2 phenotype surface marker, CD206, was increased with AdipoRon treatment [22]. It should be noted that CD206 is expressed only on M2a polarized microglial cells [25]. This indicates that AdipoRon is successful at inducing the M2a phenotype for microglial cells after intracerebral hemorrhage [22]. It was also found that

AdipoRon treatment for intracerebral hemorrhage increased the expression of Phosphorylated-AMK and adiponectin receptor 1 in both microglial cells and neurons when compared to the control group. This leads to conclusions that intracerebral hemorrhage, AdipoRon treatment, or both in conjunction could increase in both adiponectin receptor 1 and phosphorylated-AMPK levels in microglial cells (*Figure 2: A and B)*. Zheng et al. further found that AdipoRon treatment after intracerebral hemorrhage increased the expression of Sirtuin3, decreased the ratio of acetylated-superoxide dismutase 2 to superoxide dismutase 2, and decreased the level of reactive oxygen species (*Figure 2: C,D, and E).* As can be seen in *Figure 2* when AdipoRon treatment was most effective in the AdipoRon + ICH and AdipoRon + ICH + Scramble siRNA groups at increasing Adiponectin receptor 1 expression, increasing phosphorylation of AMPK, deacetylating superoxide dismutase 2, increasing Sirtuin3 expressing, and decreasing reactive oxygen species levels. It is important to note that the groups that were treated with AdipoRon but also had compound C and adiponectin receptor 1 siRNA were not as effective as compound C and adiponectin receptor 1 siRNA are inhibitors of AdipoRon [22].

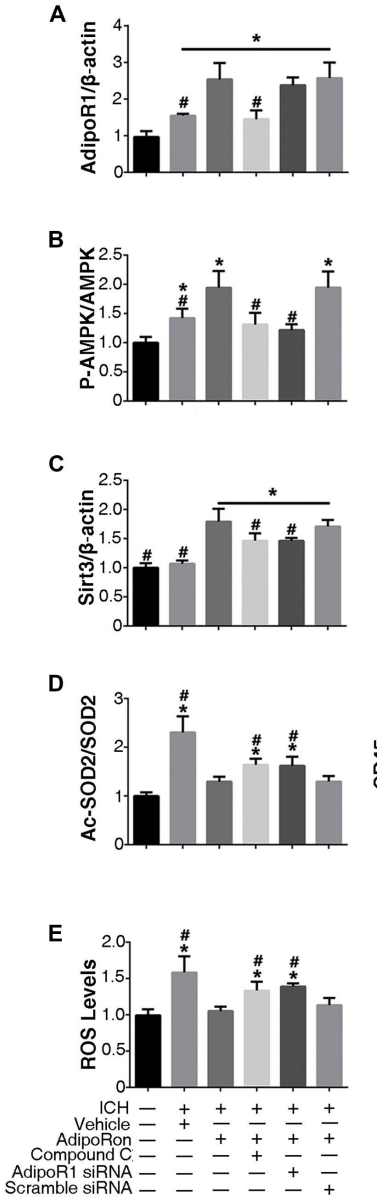

Fig 2: Expression level present on microglial cells after intracerebral hemorrhage and treatment with AdipoRon [19]. (need to get right to fair use)

AdipoRon isn't the only non-Adiponectin molecule that has shown the ability to bind with adiponectin receptors. A study performed by Zhao et al investigated the effects of CTRP9

treatment after intracerebral hemorrhage and found it was able to weaken neuroinflammation by stimulating adiponectin receptor 1 in mice. C1q/TNF-related protein 9 (CTRP9) is an agonist of adiponectin receptor 1 as its globular C1q domain has a high degree of amino acid sequence homology with adiponectin [23, 26, 27]. CTRP9 has exhibited the ability to reduce inflammation is systemic diseases by shielding vascular endothelium, relaxing blood vessels, controlling metabolism, and decreasing the number of inflammatory factors [23, 28, 29]. Zhao et al found that endogenous CTRP9 levels and adiponectin receptor 1 expression in neurons, astrocytes and microglial cells peaked at 24 hours after intracerebral hemorrhage when compared to the control and the levels of both CTRP9 and adiponectin receptor 1 decreased at 72 hours. Neurobehavioral test and brain water content were then evaluated to determine the most effective treatment dosage of recombinant CTRP9. Recombinant CTRP9 was administered intranasally, at concentrations of 0.03 μg/g, 0.1 μg/g, and 0.3 μg/g, q hour after intracerebral hemorrhage was induced. Zhao et al found that when recombinant CTRP9 was administered intranasally at concentrations of 0.1 μg/g, and 0.3 μg/g it both significantly decreased brain water concentration in the cortex and right basal ganglia and significantly improved neurological function. To identify if recombinant CTRP9 was able to have anti-inflammatory effects western blot tests were performed by randomly dividing 42 mice into groups of 6: control (sham), Intracerebral hemorrhage + vehicle (PBS), Intracerebral hemorrhage + 0.1 μg/g recombinant CTRP9, Intracerebral hemorrhage + 0.1 μg/g recombinant CTRP9 + Adiponectin receptor 1 small interfering RNA (siRNA), Intracerebral hemorrhage + 0.1 μg/g recombinant CTRP9 + scramble siRNA, Intracerebral hemorrhage + 0.1 μg/g recombinant CTRP9 + dorsomorphin, and

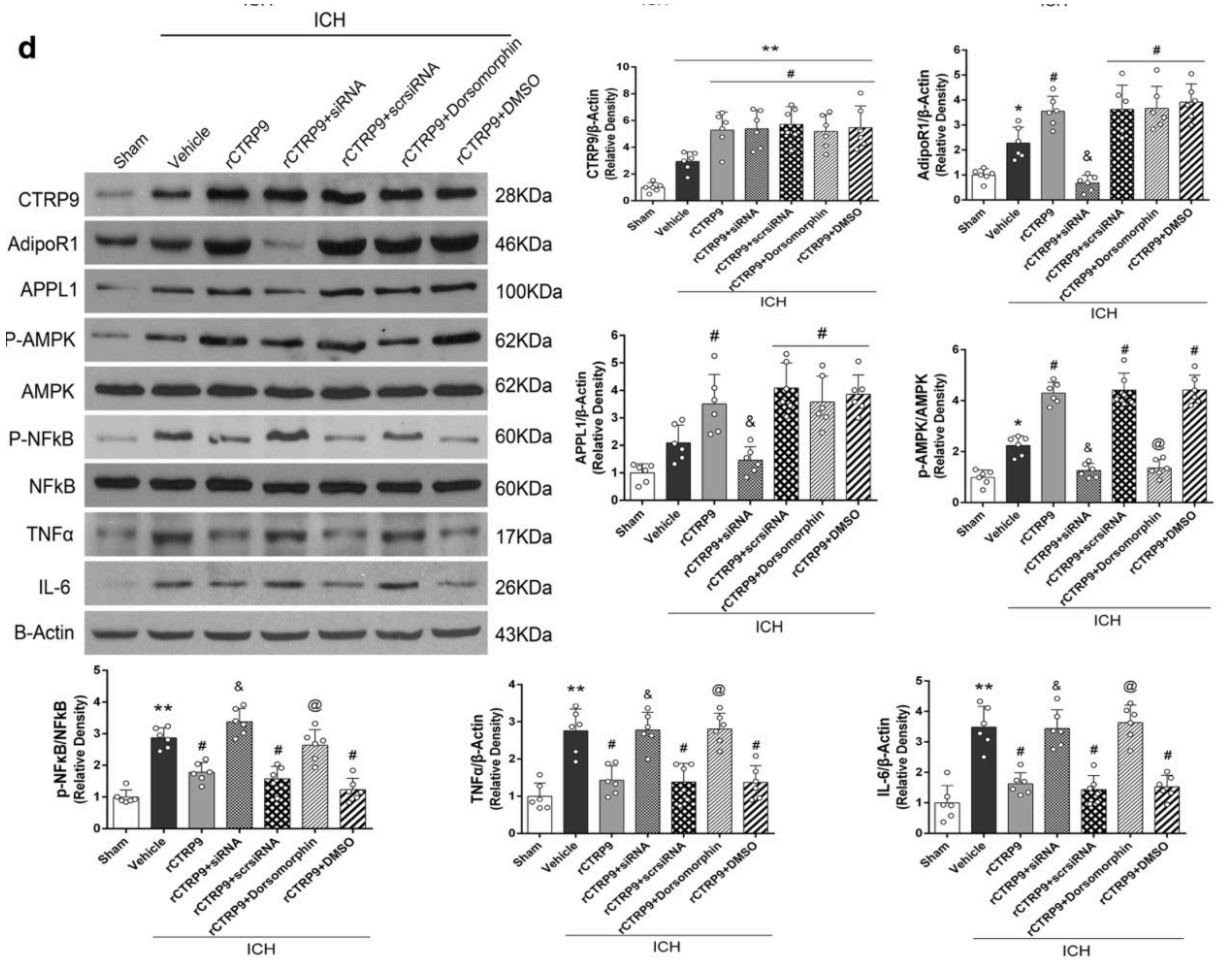

Fig 3: Western blot and expression levels of Adiponectin receptor 1, APPL1, CTRP9, phosphorylated NF-κB/NF-κB, phosphorylated AMPK/AMPK, IL-6, and TNF-α 24 hours after intracerebral hemorrhage [23].

Intracerebral hemorrhage + 0.1 µg/g recombinant CTRP9 + DMSO. Results from the western blot indicate that recombinant CTRP9 is able to enforce its anti-inflammatory effects by binding to adiponectin receptor 1 and triggering the phosphorylation of AMPK and decreasing the expression of phosphorylated-NF-κB (*Figure 3)*. When adiponectin receptor 1 was knocked out (siRNA) levels of phosphorylated-NF-κB, interleukin-6, and tumor necrosis factor-α significantly increased; whereas levels of phosphorylated-AMPK and Adaptor Protein phosphotyrosine interacting with PH domain and leucine zipper 1 (APPL1) significantly decreased when compared to the recombinant CTRP9 + scramble siRNA group (*Figure 3)*[23].

APPL1 plays a pivotal role in the activation of adiponectin receptor pathways as it binds to the intracellular NH2 domain on adiponectin receptor. APPL1 is currently the only protein known to interact with adiponectin receptors [30]. Phosphorylation AMPK was deemed to be significant in reducing inflammation as when the phosphorylation of AMPK is inhibited by dorsomorphin levels of phosphorylated-NF-κB, interleukin-6, and tumor necrosis factor-α were significantly increased when compared to recombinant CTRP9 + DSMO group (*Figure 3*) [23].

Adiponectin and Neuroprotection

Not only does adiponectin have anti-neuroinflammation effects via altering the polarization of microglial cells caused by ischemia; it has also been shown to have some neuroprotective effects via preventing apoptosis of neurons. In a study conducted by Xu et al. it was discovered that adiponectin was able to prevent neuronal apoptosis is by binding to Adiponectin Receptor 1 on the neuronal cells and activating an adaptor protein (APPL1) and liver kinase B1 pathway to phosphorylate (activate) AMPK [31]. APPL1, otherwise known as Adaptor Protein phosphotyrosine interacting with PH domain and leucine zipper 1, is an immediate effector of Adiponectin receptor binding that aides in the phosphorylation of the Thr172 site of AMPK [32]. Liver Kinase B1 is a kinase that is normally housed in the nucleus and is proposed to translocate to the cystol when APPL1 binds to Adiponectin receptor 1. Once in the cystol liver kinase B1 interacts with APPL1 and leads to the phosphorylation of AMPK [33]. The phosphorylation of AMPK lead to a decrease in the amount of Cleaved Caspase 3, a pro-apoptotic marker, in neurons [31].

Xu et al. first investigated the expression of adiponectin within the CNS and the expression of adiponectin receptors on neurons. It was determined that hypoxic ischemia induced a time dependent increase in the amount of endogenous Adiponectin and expression of

Adiponectin receptor 1 on neurons in neonatal mouse models. It is also important to note that expression of Adiponectin receptor 2 levels in the brain were not altered by hypoxic ischemia, signifying that Adiponectin receptor 1 plays more of a role in response to hypoxic ischemia than Adiponectin receptor 2 [31]. Next the study explored if intranasal treatment with exogenous recombinant human adiponectin affected the infarct area caused by hypoxic ischemia, short-term neurological function, and the dosage of recombinant human adiponectin was the best. Xu et al. tested three doses, 0.05 mg/kg, 0.1 mg/kg, and 0.3mg/kg, of recombinant human adiponectin [31, 34]. It was identified intranasal administration with 0.1 mg/kg and 0.3 mg/kg of recombinant human adiponectin resulted in a significant decrease in infract area, whereas treatment with 0.05 mg/kg of adiponectin showed no significant effect on infarct area when compared to the vehicle group. To test how treatment affected short term neurological function geotaxis and righting reflex tests were performed. Results from the geotaxis and righting reflex tests exhibited that treatment with 0.3 mg/kg of recombinant human adiponectin significantly enhanced neurological function when compared to the vehicle group. From this Xu et al. were able to conclude that intranasal administration of 0.3mg/kg of exogenous recombinant human adiponectin was the most effective (out of the doses tested) treatment option [31]. This doesn't necessarily mean that 0.3mg/kg is the best treatment. One drawback of the study, is that its highest dose tested was the dose that proved to be the most effective, leaving one to question if a higher dose would be more effective.

Xu et al then set out to discover how intranasal administration of exogenous recombinant human adiponectin interacted with the neurons. It was identified via immunofluorescent staining that recombinant human adiponectin increased adiponectin expression on neurons, upregulated

adiponectin receptor 1 expression and colocalization with neurons, and increased APPL1 expression and colocalization with neurons when compared to control and vehicle groups [31].

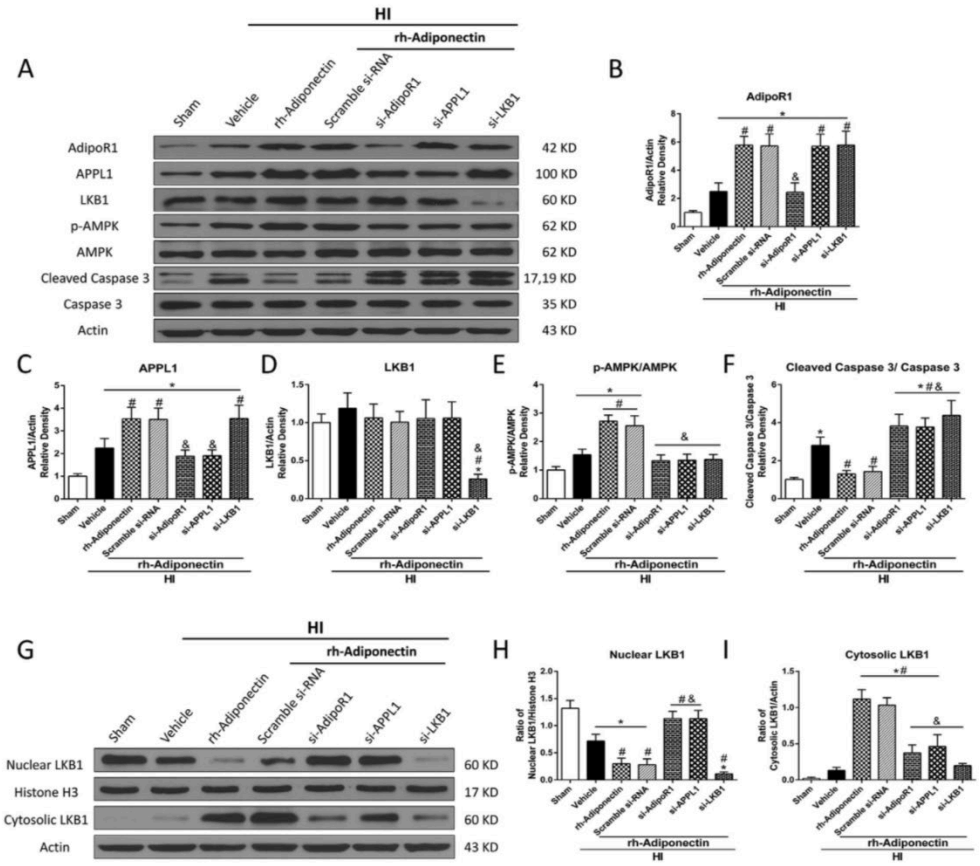

Fig 4: Western Blot test (A,G) and the expression of adiponectin receptor 1 (B), APPL1 (C), LKB1 (D), Phosphorylated AMPK/AMPK ratio (E), Cleaved Caspase 3/Caspase 3 ratios (F), Nuclear LKB1 (H), and Cystolic LKB1 (I) [31].

To identify the pathway involved in adiponectin induced neuroprotection western blot testing was used. Xu et al tested 7 groups of mice a control, vehicle, a recombinant adiponectin treatment group, a recombinant adiponectin treatment group that was injected with scramble small interfering RNA, and 3 knockout groups (adiponectin receptor 1 knock out, APPL1 knockout, and LKB1 knockout) which received adiponectin treatment. The intranasal treatment with adiponectin an hour after hypoxic ischemia and the scramble small interfering RNA group increased levels of adiponectin receptor 1, APPL1, phosphorylated-AMPK, and decreased the

levels of cleaved caspase 3 (*Figure 4 A,B,C,E,F*). It should be noted that the adiponectin treatment group and the scramble small interfering RNA group did not alter the expression on LKB1 in the neurons (*Figure 4 D*). Rather they altered the location of LKB1 with in the neurons as both groups increased the expression of cystolic LKB1 and decreased the expression of nuclear LKB1 (*Figure 4 G,H,I*). Indicating that binding of adiponectin to adiponectin receptor 1 and hence forth the subsequent binding of APPL1 drives the localization of LKB1 to the cystol [31]. This is congruent with an earlier study performed by Deepa et al which identified that adiponectin induced activation of APPL1 lead to the dephosphorylation of protein kinase C ζ by protein phosphatase 2A. The dephosphorylation of protein kinase C ζ later resulted in the dephosphorylation of the Ser307 site on LKB1. The dephosphorylation of LKB1 leads to it translocating from the nucleus to the cystol [33]. As for the knockout groups, each group resulted in the decreased expression of phosphorylated-AMPK and increased expression of cleaved caspase 3 indicating they subdued the neuroprotective effects of adiponectin treatment for intracerebral hemorrhage (*Figure 4 A,B,C,D,E,F*) [31].

Other Treatments for Neuroinflammation

One potential nonmedicinal route to help combat neuroinflammation is *Iresine celosia (ICE)*. *Irisine celosia* is commonly used in rural areas of Mexico where medicinal plants are used to help with many health problems. It is typically used to help patients with skin problems, fevers, infections of the oral cavity, sores in oral cavity, rashes, inflammation, and anorexia [35, 36]. A recent study also found that ICE was able to inhibit production of many proinflammatory production in BV2 microglial cells that were stimulated with a lipopolysaccharide and in mouse models [37]. BV2-cells are immortalized murine neonatal microglial cells which are commonly used as an alternative to primary microglial cells[38]. ICE was shown to be able to inhibit nitric

oxide production, interleukin-6, tumor necrosis factor-α, and interleukin-1β without causing cytotoxicity. Overall, ICE managed to prevent the activation of astrocytes and microglial cells in mice that were treated with a lipopolysaccharide [37].

In a study done by Wei et al., the inhibition of Activator protein 1 was investigated as a treatment option after intracerebral hemorrhage [39]. Activator protein 1 has been shown to increase cytokine expression and target gene expression in multiple diseases like psoriasis, rheumatoid arthritis, and psoriatic arthritis [40, 41]. Wei et al. found that by inhibiting Activator protein 1 with SR11302 (a drug that inhibits Activator protein 1) neuroinflammation from intracerebral hemorrhage was reduced. Inhibition of Activator protein 1 was able to reduce neuroinflammation caused by intracerebral hemorrhage as Activator protein 1 is highly expressed on microglial cells. By inhibiting Activator protein 1 expression on microglial cells with SR11302 it reduced the amount of proinflammatory cytokines like TNF-α and IL-6 produced by the microglial cells [39].

Sphingosine 1-phosphate receptor subtype 1 ($S1P_1$) has also been shown to regulate the polarization of microglial cells during cerebral ischemia. Instead of driving polarization towards the M2 phenotype $S1P_1$ has been shown to promote M1 polarization. A study found that by suppressing $S1P_1$ with an antagonist (AUY945) reduced levels of NF-kB and increased expression of mRNA that codes for P13k/AKt which promotes M2 polarization of microglial cells. It is argued in this study that activation of NF-kB promotes M1 polarization, and by blocking NF-kB expression polarization would be driven to the M2 [42].

Future Work

Future investigation into adiponectin transport into the brain and improving adiponectin treatment is needed. Adiponectin has a short half-life in blood plasma and a complex protein

structure. The half-life and complex structure of adiponectin cause difficulties in production, administration, and cost when being used as a treatment [21]. One possible way to overcome this set back is AdipoRon. AdipoRon is a derivative of adiponectin that serves as an agonist of adiponectin receptors [24]. AdipoRon has a longer half-life in blood plasma, costs less, and has virtually the same effects as adiponectin via binding to Adiponectin receptors [21, 24]. AdipoRon has also been shown to enhance the expression of phosphorylated AMPK via binding to adiponectin receptors [24, 43]. AMPK has been identified as an upstream signal of Sirtuin3 (a NAD^+ dependent kinases typically located in the mitochondria) [44-47]. Sirtuin3 has been shown to play a vital role in the alleviation of oxidative stress, caused by reactive oxygen species, by deacetylating superoxide dismutase 2 [44, 48]. This indicates that AdipoRon treatment may lower levels of reactive oxygen species after intracerebral hemorrhage through the adiponectin receptor 1 – AMPK- sirtulin3 pathway [22].

Conclusion

Initial studies have shown positive results as to adiponectin as a treatment to microglial-induced neuroinflammation from both trauma and disease. Adiponectin is able to alter total levels of inflammatory cytokines via many different routes but, mainly via the phosphorylation of AMPK. Within the brain, adiponectin operates by binding to adiponectin receptor 1 which triggers the phosphorylation of AMPK and decreases the expression of phosphorylated NF-κB. This in turn drives microglial cells towards an anti-inflammatory state by decreasing expression of inflammatory cytokines such as interleukin-6, tumor necrosis factor-α [2]. Adiponectin has also been shown to have a neuroprotective effect on neurons. Adiponectin is able to administer its effects on neurons ins a similar manner to how it acts on microglial cells. On neurons,

adiponectin binds to adiponectin receptors which triggers an intracellular cascade that leads to the phosphorylation of AMPK. The phosphorylation of AMPK in neurons promotes cell survival by decreasing the expression of cleaved caspase 3 [31]. Further investigations are still needed however, as more efficient ways to get adiponectin into the CNS need to be discovered as adiponectin has short half-life in blood plasma [21]. One way to overcome this obstacle is by using more stable adiponectin receptor 1 agonist like AdipoRon and CTRP9 [22, 23]. None the less, adiponectin shows potential as a treatment option for microglial induced neuroinflammation caused from disease, hemorrhage, and hypoxia.

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