Rac1 in Stroke

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Short Communication

A fatal and debilitating brain illness called a stroke has few warning signals. It is a direct result of a blockage or blood clot in the blood vessels, which causes a rapid, unexpected loss of steady blood and oxygen supply to the brain. One in four people over the age of 25 will experience a stroke in their lifetime, according to the World Stroke Organization's 2019 report [1], and 87% of strokes are ischemic strokes.

According to certain research, in vitro and in vivo models of post-stroke functional recovery have both shown higher Rac1 activity to be beneficial. Other research, however, has demonstrated that an increase in Rac1 activity, both in vivo and in vitro models, affects post-stroke recovery [2]. These contradicting results imply that depending on the cell type in which Rac1 is activated and the timing of Rac1 activation, Rac1 can both favourably and negatively alter post-stroke outcomes [3].

In one study, endothelial cells were stimulated to overexpress Rac1 in order to examine if Rac1 can recover cognitive and sensorimotor skills in mice following ischemic stroke. Up regulating the expression of Bcl-2 (a downstream effector of Rac1) led to improvements. According to research, BCL2 has neuroprotective benefits after stroke because it reduces the size of the infarct and the apoptosis of neuronal cells. After Middle Cerebral Artery Occlusion (MCAO) was used to cause ischemic stroke in mice, the animals' brains were subsequently injected with a lentivirus that overexpressed endothelial Rac1 by expressing Rac1 under the control of the ENG promoter. Based on the single pellet reaching, adhesive removal, and novel object recognition tests, mice treated with ENG-Rac1 on the seventh day following a stroke showed considerable improvements in the recovery of memory and sensorimotor abilities. Another study that used a Rac1-expressing lentivirus to widely overexpress Rac1 in the brains of mice following stroke discovered similar outcomes. Rac1 overexpressed mice had much larger axonal densities and performed better on measures of motor and sensory function than control mice.

Cultured mouse cortical neurons were given Oxygen-Glucose Deprivation (OGD) to simulate an ischemic stroke in order to research the effects of Rac1 in vitro. In comparison to control cells that had undergone OGD, mouse cortical neurons co-cultured with the Rac1 inhibitor NSC23766 showed a noticeably shorter axonal length and fewer axons. In contrast, mice that received a direct injection of the Rac1 inhibitor NSC23766 into the brain experienced severe impairments in angiogenesis and axonal density as well as motor and sensory function. However, there was no discernible change in the loss of brain tissue. Rac1 deletion was discovered to have a detrimental effect on mice's post-stroke recovery in another investigation. In this study, Intraperitoneal (IP) tamoxifen administration caused the delayed deletion of Rac1 in neurons. At 28 days after the stroke, sensorimotor and cognitive tests showed that mice given daily tamoxifen by IP injection from seven to eleven days post-stroke performed considerably worse than control Rac1-floxed animals.

Rac1 was shown to be neuron-specific, and immunohistochemistry revealed that it reduced axonal regrowth but did not affect the loss of brain tissue in ischemic stroke mice. However, in mice after an ischemic stroke, overexpression of Rac1 in neurons generated by the production of GFP-Rac1 promoted axonal regeneration without affecting the degeneration of brain tissue. Glial Fibrillary Acidic Protein (GFAP) intensity increased in mice with neuron-specific Rac1 deletion, whereas it decreased in animals with neuron-specific Rac1 overexpression. Evidence from a clinical investigation suggested a favourable correlation between patient GFAP intensity and stroke severity. These findings imply a link between Rac1 levels and the severity of a stroke [4].

Additionally, it has been discovered that Rac1 has a positive impact on intracerebral haemorrhage stroke. The second most frequent life-threatening subtype of stroke is Intracerebral Haemorrhage (ICH). Despite being less frequent than ischemic stroke, ICH has a higher mortality and morbidity rate and a very low long-term functional independence recovery rate [5]. The most common cause is a blood artery in the brain ruptures, which causes bleeding inside the intracranial vault. Blood-Brain Barrier (BBB) permeability disturbance, neurotoxicity, brain oedema, and neuroinflammation are a few of the effects that lead to subsequent brain injury after ICH. Following ICH, there is an increase in BBB permeability, which has been linked to long-term neurological impairments and secondary brain injury. In one study, it was discovered that the activation of Rac1 via the PI3K-Akt signalling pathway, which is mediated by fibroblast growth factors (FGFs), protects the BBB after ICH. Endothelial cells are what make up the BBB, which is designed to prevent any unwanted flow of hazardous substances into the brain. By blocking the RhoA/Rho-associated coiled-coil containing kinases (ROCK) pathway, Rac1 activation aids in maintaining and balancing the BBB. According to research, the RhoA/ROCK pathway has been shown to damage tight junction proteins, which in turn weakens the BMEC barrier and causes vasogenic oedema to occur after an ICH. Another study discovered that boosting Rac1 activation using JWH133 (a cannabinoid receptor 2 (CNR2) antagonist) therapy 1 hour before ICH significantly reduced perihematomal brain oedema and improved sensorimotor impairments 24 and 72 hours later. The same study discovered that the benefits of JWH133 treatments might be undone by blocking Rac1 (with NSC23766) afterwards [6]. A significant downstream target of RAC1 is Pak1. According to a clinical report, Pak1 expression is elevated in the infarcted and peri-infarcted areas of stroke patients based on results from RT-PCR and western blotting. According to RT-PCR, Pak1 mRNA expression increased two to six days after a stroke, and according to western blotting, Pak1 protein expression increased three and fifteen days after a stroke in people. Similar western blotting results were shown in stroke mice 12 hours and 24 hours after the stroke, however, after the third post-stroke day, the protein levels reverted to normal. Human brain endothelial cells were exposed to OGD in vitro to simulate the ischemic stroke environment to determine whether the role of the Rac1 downstream effector Pak1 in endothelial cell proliferation and migration after ischemic stroke is important. In an in vitro investigation, cells co-cultured with IPA3, a PAK1 inhibitor, showed dramatically reduced cell proliferation and migration after exposure to OGD as compared to control cells not treated with the inhibitor. Accordingly, Pak1 might play a neuroprotective role following an ischemic stroke [7].

Numerous researches have revealed that Rac1 has detrimental effects on post-stroke recovery. This is in contrast to the results mentioned above that show the favourable effects of Rac1 after stroke. Intriguingly, one study discovered that overexpressing Rac1 in primary cortical neurons cultured with agomir miR-42-3p after they had undergone oxygen-glucose deprivation/reoxygenation (OGD/R) decreased the viability of the primary cortical neurons while increasing the percentage of LDH leakage. This reversed the neuroprotective effects of miR-42-3p on the cultured cells. Comparing Rac1-overexpressing cells cultivated with agomir miR-42-3p and subjected to OGD/R to Rac1-overexpressing cells treated with OGD/R, it was found that the percentage of LDH leakage was much higher and the percentage of cell viability was significantly lower.

One study used the anti-diabetic drug pioglitazone to investigate Rac1's negative impact on stroke. It has been demonstrated that the anti-diabetic drug pomglitazone, used to treat type 2 diabetes, lowers the inflammatory response and lowers the frequency of stroke occurrences in type 2 diabetic patients. This study revealed that pioglitazone can have neuroprotective effects after ischemic stroke by suppressing Rac1 activity through its anti-inflammatory actions. Pioglitazone significantly reduced Rac1 activity in cultured primary astrocytes that had been treated with OGD as well as stroke rats, according to Western blotting and Rac1 activation assays. Rac1 activity was significantly decreased in pioglitazone-treated mice, and these mice also had significantly smaller infarcts and improved neurological deficiency scores. But this study did not directly interfere with Rac1 activation because pioglitazone has a wide range of pharmacological effects. Although the outcomes of a stroke may not have been impacted by the changes in Rac1 activity seen after therapy [8], they may have been consequential.

In a different investigation, Rac1 was found to have negative effects on mouse endothelium cells. Since total Rac1 knockout in mice results in death, it was examined if down-regulating endothelial Rac1 expression had a neuroprotective impact. EC-Rac +/- animals were used for the assessment. According to qRT-PCR results, Rac1 expression and activity significantly decreased by 50% in EC-Rac1 +/- mice compared to EC-Rac1+/+ mice. Brain swelling and infarct size were considerably reduced in EC-Rac1 -/+ mice following MCAO and 22 hours of reperfusion compared to control (Rac1flox/+) mice. Animals with EC-Rac1 +/- mice showed neurological impairment ratings that were less severe than control mice, which was consistent with the morphological findings. Similar outcomes were observed by another study that employed NSC23766, a Rac1 inhibitor, to lower Rac1 expressions. The intracranial injection of the Rac1 inhibitor was administered to mice. According to the data, animals given NSC23766 showed a neurological deficit score and infarct volume in the brain that were much lower than those of control mice. The same study hypothesised that Rac1 activation leads to NF-kB and Nox2 activation, which then encourages inflammation and oxidative stress to cause neuronal death and exacerbates brain injury following ischemic stroke. Because Rac1 probably has a positive impact on the recovery of post-stroke processes like plasticity, angiogenesis, and axonal remodelling, which may cause cell death in the acute phase after stroke, there may be inconsistencies between the findings of studies from different laboratories.

According to studies, targeting Rac1 before a stroke has negative effects while activating Rac1 gradually throughout the healing phase has favourable results. Therefore, the effectiveness of inhibiting the Rac1 sig-

-nalling pathway after a stroke depends significantly on the time of the treatment intervention. Rac1's unique function in various cells may be another factor in the inconsistent results. Rac1's pleiotropic actions may contribute to the understanding of why Rac1-activated molecular pathways play distinctive roles in determining outcomes in various stages of stroke and cell-specific roles. However, our findings imply that Rac1 may have significant therapeutic utility following strokes involving intracerebral haemorrhage and brain ischemia.

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