The Potential of PRE-084: A Profile of Possibilities

History of PRE-084

PRE-084 was discovered in the early 1990`s in Baltimore in the US State of Maryland.[1] The original aim was to create structural analogs to the widely applied drug Phencyclidin (PCP). It turned out, however, that PRE-084 has a different pharmacological profile and does not activate the same processes in the body compared to PCP. In contrast to PCP, PRE-084 has a high affinity to the σ1-receptor, a generally not well understood class of receptors involved in neural function and cell repair. However, it is very ineffective in activating the NMDA and D2 receptors activated by PCP.

The σ1-receptor was later found to be a so-called chaperone, a protein that helps other proteins fold into their correct states and thereby making sure the cell works correctly. It can be found on many tissues throughout the body.[2] Especially in stressful situations, chaperons are essential to prevent cell damage and death. As most studies suggest, this is exactly how PRE-084 works. It activates the σ1-receptor, which in turn helps to prevent cell damage in tissues under stressful situations. We can therefore conclude that PRE-084 can be classified as an adaptogen.

However, the σ1-receptor also seems to have further effects on the brain, especially on learning and motivation. Mice without this receptor show a depressive-like behavior.[3] PRE- 084 therefore could be expected to have mood-enhancing and nootropic effects as well, although only few studies explore this side of PRE-084. There is also solid evidence that the σ1-receptor is directly involved in the function of neurons.[4]

After its discovery, the pharmacological profile of PRE-084 has led many groups to study its effect on cells and conduct animal trials with mice & rats. PRE-084 showed clear neuroprotective properties in many experiments, but also has some other beneficial effects like enhancement of neurodevelopment. In the following sections, the positive effects of PRE- 084 on different cells will be presented.

Neuroprotective Effects of PRE-084

A number of studies shows that PRE-084 protects neurons from damage that arises from over-activity or low nutrient supply. For example, mice with an artificial stroke had a much lower amount of pro-inflammatory cytokines in the damaged brain area after the administration of PRE-084 compared to a control group. It was also shown that these rats had had a reduced volume of

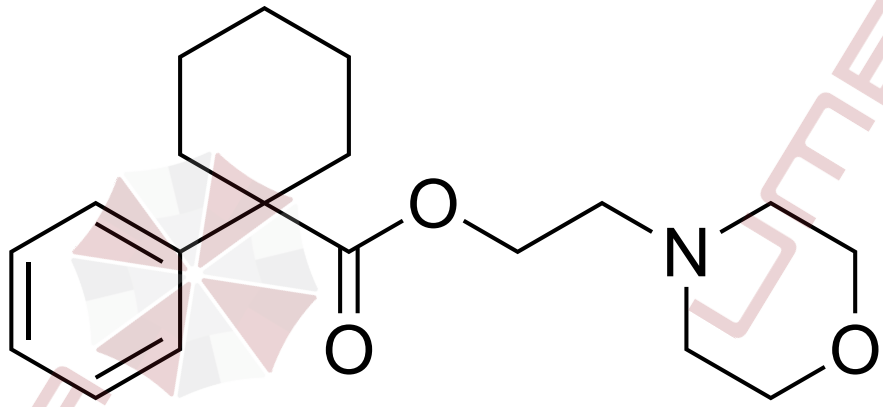
damage in their brain.[5]

Similarly, PRE-084 showed the ability to decrease brain damage to mice during birth, either due to trauma or to a prolonged lack of oxygen. Similarly to a stroke, the damaged areas are significantly smaller if PRE-084 was injected 1 hour after birth and resulted in an overall decrease in cell death and better tissue quality.[6]

Research was additionally conducted in mice with epilepsy. A seizure does under usual circumstances lead to a damage to neurons and promotes pro-inflammatory processes, which further lead to an environment in which more seizures are reinforced. PRE-084 did not only reduce the level of inflammatory mediators, but also decreased damage to the hippocampus, a brain area with important function for memory formation.[7]

The neuroprotective effects of PRE-084 made it an interesting compound to treat neurodegenerative diseases, like Parkinson's disease, which is linked to the death of neurons in certain brain areas, further leading to movement deficits. Mice with Parkinson's disease showed reduced Parkinson symptoms if PRE-084 was administered early in the development of the symptoms and their brains showed increased function in other areas as well.[8] Another study found that PRE-084 at a dose of 0.3mg/kg/day significantly improved the limb movement of mice with Parkinson's disease.[9] It was also found that PRE-084 is able to increase the survival of motor neurons in mice with a similar condition to Parkinson's disease,[10] but also in Huntington's disease.[11]

Another study looked at the effects of PRE-084 in a mouse model of amyotrophic lateral sclerosis (ALS), which leads to progressive muscle loss due to degeneration of neurons and eventually to death by respiratory



arrest. Mice treated with PRE-084 exhibited a better muscle function and longer survival time compared to mice which were not treated.[12] A similar study conducted on mice with spinal muscular atrophy (SMA) found that PRE-084 was able to reduce infection sign in neural tissue. Here however it did not lead to improvements in clinical outcome.[13]

PRE-084 showed an effect on the survival of motoneurons after traumatic injury to the spinal cord. At 0.25mg/kg PRE-084 significantly promoted MN survival (68% vs 43% in untreated rats) and therefore might be an interesting substance for the direct treatment after traumatic injuries and may help with symptoms of paraplegia after spinal cord injuries. It markedly increased the growth factor GDNF and repair proteins.[14]

Other Effects of PRE-084 on the Nervous System

PRE-084 also shows beneficial effects for learning. Usually, aged rats are slower to learn new information. The administration of PRE-084 did improve the cognitive function of these aged rats and allowed them to learn new information quicker. This could also mean that PRE-084 might be used to counter age related cognitive impairment in humans.[15] PRE-084 was also able to reduce the effects of drugs that usually impair learning by inhibiting neuronal changes.[16] This further indicates that PRE-084 has positive effects on neuroplasticity and may lead to increased cognitive function.

Interestingly, PRE-084 does also seem to interact with psychostimulant drugs. For example, experiments on rats have shown it does increase the self-administration of cocaine. Even when cocaine was substituted with PRE-084, the rats showed a drive to administer PRE-084 to themselves. This indicates that the σ1-receptor plays a role in learning & motivation.[17] A further role of PRE-084 in motivation and activity comes from the finding that PRE-084 has an anti-depressant like effect in rats, although in relatively high doses of 60mg/kg.[18]

PRE-084 was also able to protect neurons from a variety of toxins, including a protein that damages the brain tissue in Alzheimer's disease, the Aβ25-35 peptide.[19]

Cardioprotective Effects

Similar to the beneficial effects on brain tissue survival during strokes, some studies show that PRE-084 has positive effects on myocardial damage during heart attacks in rats. At a dose of 1 mg/kg, PRE-084 reduced the amount of tissue in apoptosis thereby leading to a lower area of damage to the heart. This also resulted in an overall better cardiac function.[20] A reduction in markers of myocardial damage have identified at the same time.

Nephroprotective Effects

Another group investigating the effects of PRE-084 on rats has yielded the conclusion, that PRE-084 is also able to increase kidney function on those animals suffering from with chronic kidney disfunction. The compound did also decrease the amount of fibrotic remodeling of the organic, leading to a better long term prognosis.[21] These results have been confirmed by similar study later on.[22]

Conclusion

There is strong evidence that PRE-084 can protect different cells under stressful situation from apoptosis, which in turn leads to a long-term benefit for organ function and overall survival. This characteristic of PRE-084 makes it interesting as drug to counter the effects of degenerative diseases, especially neurodegenerative diseases like Alzheimer`s and Parkinson`s disease. In this context, PRE-084 could be a useful compound for seniors which are looking to counter cognitive loss due to old age. Older populations may also disproportionally benefit from reduced damage sustained during ischemic events like heart attacks or strokes.

Further evidence suggests that besides its protective effects on cell survival, PRE-084 directly interacts with functional neurons. It seems to boost information intake and processing, as well a somewhat positive effect on motivation and/or mood. However, human trials with PRE-084 have not yet been conducted to this day.

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