A new drug approach increases cognition in rats

In a new study the α4β2 nicotinic acetylcholine receptors, a subtype of nicotinic acetylcholine receptors was studied in relation to their role in attention and cognition. This research presents a novel approach using a positive allosteric modulator on α4β2 nicotinic acetylcholine receptors to increase cognition in rats. This approach can be used in cognitive deficit disorders such as Alzheimer's Disease and schizophrenia, which show a reduction of α4β2 nicotinic acetylcholine receptors in several parts of the brain.

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In a paper recently published in *Pharmacological Reports*, Agnieszka Nikiforuk and her colleagues investigated the cognitive effects of desformylflustrabromine (dFBr), a positive allosteric modulator of a α4β2-containing nicotinic acetylcholine receptors. The study found that this modulator increased procognitive activity, improved recognition memory, and rescued drug-induced cognitive deficits in rats. These results indicated that positive allosteric modulator could have pro-cognitive activity effect on α4β2-containing nicotinic acetylcholine receptors which could potentially be implemented to treat cognitive deficits associated with schizophrenia and Alzheimer's disease.[1] Allosteric modulators are substances that bind to the receptors of cells to alter the receptor's response to the stimulus. Among the various allosteric modulators are positive, negative, and neutral modulators. Positive allosteric modulators such as the dFBr presented in this study increase the response of the receptor by increasing the probability that the receptor will be activated.[2] By increasing the affinity and efficacy of agonists, positive allosteric modulators can modulate the effect agonists have on the targeted cells.[3]

The involvement of α4β2-containing nicotinic acetylcholine receptors in cognition has been determined by mounting evidence. Postmortem studies indicated reduction in these receptors in Alzheimer's Disease (AD) and schizophrenia.[4] Additionally, studies have indicated that beta-amyloid accumulation, one of the hallmarks of AD significantly increased in the brains as α4β2 nicotinic receptors significantly decreased, establishing a connection between the two factors.[5] Regions in the brain showing the reduction of these receptors included the hippocampus, amygdala, and the neocortex as well. These regions of the brain are also areas affected the most in AD.[1] Nicotinic acetylcholine receptors are found in all layers of the neocortex regulating the excitatory activity by inhibiting excitatory signals. In layers II and III, pyramidal neurons are inhibited by nAChRs stimulation, and pyramidal neurons in cortical layer V are activated by nAChRs stimulation.[6] Thus, each cortical layer is modulated differently and that is in part due to the different types of nAChRs present in each layer. Furthermore, pyramidal neurons in layer V of the neocortex are modulated by inhibitory interneurons which are mediated by the dis-inhibitory effect of α4β2 nAChRs, which increase GABA release onto interneurons.[7] In other words, these receptors inhibit interneurons such as PV basket cells that inhibit the activity of pyramidal neurons therefore disinhibiting or removing the inhibitory effect of interneuron.

The effects of dFBr modulators on cognition were determined by two animal tests: the attentional set-shifting task (ASST) and the novel object recognition task (NORT). These tests determine cognitive flexibility and recognition memory, respectively. In the ASST test rats

initially learned a rule and developed an attentional set for the initial rule. This was followed by the extra-dimensional (ED) shift stage where animals switched attention to a previously irrelevant stimulus dimension and differentiating between the odors and not the media covering the bait. This part of the test measures cognitive flexibility. Additionally, the ability to alleviate the cognition deficits induced by a competitive antagonist called by dihydro-β-erythroidine on α4β2-nAChRs was also determined in this study.[1] Agonists are substances that bind to the receptors and activate receptors to produce a response.[3] Antagonists block or reduce the activity of agonists when they bind to receptors. Therefore, agonists and antagonists have opposing effects on receptors. Competitive antagonists bind to the same sites as the agonists, without activating the receptors and by blocking the action of the agonist. On the other, non-competitive antagonists bind to different sites on the receptors to prevent the activation of the receptor.[3]

In the attentional set-shifting task the rats showed cognition improvement with dFBr in a α4β2-dependent manner. To test that the result was in fact because of the allosteric modulator, administration of the antagonist was used to block the effect of the modulator. In the object recognition task, the rats were treated so that they could not discriminate the novel object from the familiar objects – creating a natural forgetting in rats. This forgetting was improved by the administration of the modulator. Similar to the attentional set-shifting task, the antagonist blocked the procognitive effects in the recognition task. In addition to the procognitive effects on object recognition and attentional set-shifting task, the allosteric modulator reversed the ketamine- and scopolamine-induced novel object-recognition deficits in rats. When ketamine or scopolamine were administered, the animal's ability to discriminate novel and familiar objects was eliminated but was revered with the administration of the allosteric modulator. Therefore, ketamine and scopolamine were used to test that the drugs do in fact improve cognition by inducing cognitive deficits in rats. The co-administration of inactive doses of the allosteric modulator and agonist lead to procognitive effects.[1] Another positive allosteric modulator on α7-nAChR, a different type of nicotinic acetylcholine receptors in combination with an agonist showed similar procognitive effects suggesting that conditions such as AD have compromised cholinergic functions.[8] These results show potential potent therapeutic models when positive allosteric modulators are administered together with agonists.

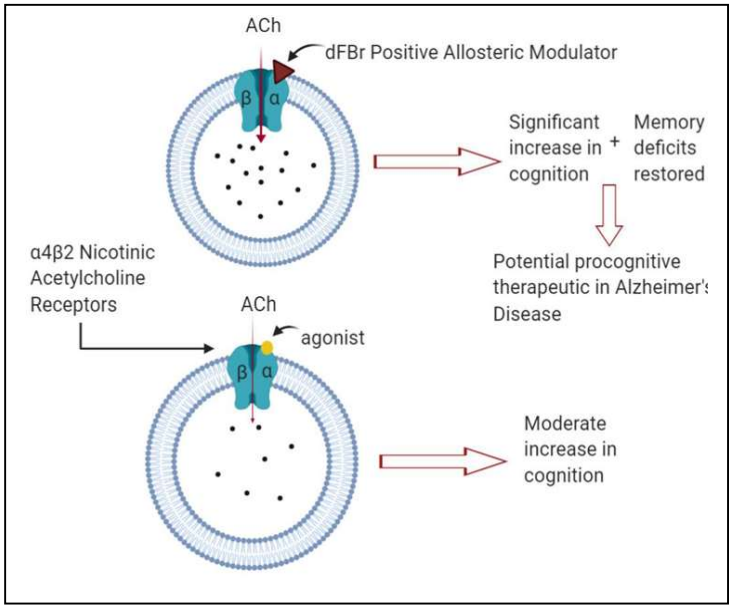

Figure 1: α4β2 nicotinic acetylcholine receptors with administration of agonist vs positive allosteric modulator (dFBr). Positive allosteric modulators increase the probability the receptors being activated having a procognitive effect in compromised cholinergic disorders.

In this article, α4β2 nicotinic acetylcholine receptors have been targeted as a potent target for improving cognitive impairments in disorders such as AD and Schizophrenia. Studies have investigated the role of α4β2 nicotinic acetylcholine receptors in relation to neurodegenerative and cognitive disorders, and potent agonists and antagonists were developed as a result to improve cognitive performance. In this study, the positive allosteric modulator targeting these receptors shows promising precognitive activity which could be implemented in cognitive impairment therapy for disorders such AD and schizophrenia. Further studies should investigate the cognitive effects of

this positive allosteric modulator in AD mouse models in combination with potent nAChRs agonists to observe changes in cognition. Studies have observed a direct relationship between the accumulation of amyloid plaques in AD and the significant reduction in nAChRs such as the interaction of α7-nAChRs and amyloid plaques to play a crucial role in cognitive decline.[9] Further studies should investigate this interaction to further determine the function of flawed cholinergic function in neurodegenerative disorders and how combinations of positive allosteric modulator and agonists on nicotinic acetylcholine receptors can increase cognition.

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