The sigma-2 receptor ( $\sigma$ 2R) is a sigma receptor subtype that has been found highly expressed in malignant cancer cells, and is currently under investigation for its potential diagnostic and therapeutic uses.

Originally, it was thought that the sigma receptors were a type of opiate receptor, due to its ability to bind ligands such as benzomorphans and PCP.

Difficulties were found in distinguishing between the sigma-2 receptor and the NMDA receptors, though it is now known they have different distributions throughout the brain.

The sigma-2 receptor in particular is more densely located in parts of the brain that are responsible for motor function and emotional response. It has been found to play a role in both hormone signaling and calcium signaling, in neuronal signaling, in cell proliferation and death, and in binding of antipsychotics.

The position of the sigma-2 receptor has not yet been located on the human chromosome.

Accumulating evidence suggests that modulating the sigma 2 receptor (Sig2R) can provide beneficial effects for neurodegenerative diseases.

Yi et al report the identification of a novel class of Sig2R binding ligands and their cellular and in vivo activity in experimental models of Alzheimer's disease (AD).

They report that SAS-0132 and DKR-1051, selective ligands of Sig2R, modulate intracellular Ca2+ levels in human SK-N-SH neuroblastoma cells. The Sig2R antagonists SAS-0132 and JVW-1009 are neuroprotective in a C. elegans model of amyloid precursor protein-mediated neurodegeneration. Since this neuroprotective effect is replicated by genetic knockdown and knockout of vem-1, the ortholog of progesterone receptor membrane component-1 (PGRMC1), it indicates that Sig2R ligands modulate a PGRMC1-related pathway. Last, they demonstrate that SAS-0132 improves cognitive performance both in the Thy-1 hAPPLond/Swe+ transgenic mouse model of AD and in healthy wild-type mice. These results demonstrate that Sig2R is a promising therapeutic target for neurocognitive disorders including AD.<sup>1)</sup>.

## 1)

Yi B, Sahn JJ, Ardestani PM, Evans AK, Scott L, Chan JZ, Iyer S, Crisp A, Zuniga G, Pierce-Shimomura J, Martin SF, Shamloo M. Small molecule modulator of sigma 2 receptor is neuroprotective and reduces cognitive deficits and neuro-inflammation in experimental models of Alzheimer's disease. J Neurochem. 2016 Dec 7. doi: 10.1111/jnc.13917. [Epub ahead of print] PubMed PMID: 27926996.

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