Enhancing CNS drug delivery through direct conjugation of an A_1 receptor antagonist to a retrograde transport protein

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It is known that the blood–CNS barriers can serve as an essential pharmacological road-block to translation of many therapeutics for spinal cord injury (SCI) to the clinic.[1] Our group has sought to utilise the histological principles of neuroanatomical tract tracing (NaTT) in drug delivery from peripheral neurons directly to the central nervous system, completely circumventing any blood–CNS barriers.[2] During SCI, transport of substances from synapses to soma (retrograde transsynaptic transport) typically involved in NaTT is more pronounced, as part of the injury signal and the axonal regeneration process.[3]

To that end, our group has used gold nanoparticles as a platform for linking both a retrograde tract transporter (WGA or WGA–HRP) and an adenosine receptor antagonist (such as theophylline or dipropylcyclopentyl xanthine – DPCPX) in a single substance. Indeed, this was found to be remarkably effective in treating spinal cord hemisection-driven respiratory cessation in vivo (C2Hx mouse model).[4,5] However, using gold in this way presents issues for clinical translation, including issues with colloidal stability (particularly in buffers), extended retention and an unknown long-term toxicity profile.

We addressed this challenge by developing a very simple reversible conjugation of the otherwise inert DPCPX onto WGA as a means of selectively delivering it to the central nervous system. We then characterised both the chemistry and in vitro biological activity of this conjugate. Indeed, this relatively simple chemistry inspired by well-known dialdehyde-driven protein cross-linking opens the door for conjugating various drug compounds to a retrograde transport protein to potentially revitalise their activity.

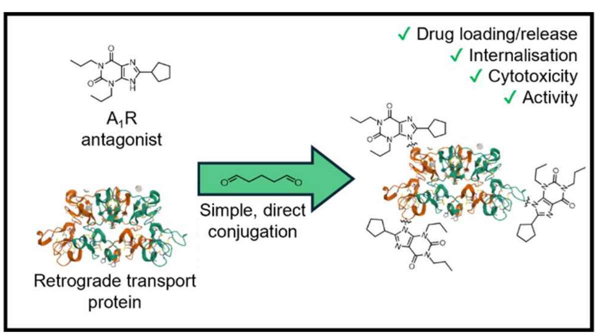

Figure 1: Direct conjugation of dipropylcyclopentylxanthine (DPCPX) with wheat germ agglutinin (WGA).

References

[1] *J. Spinal Cord Med.* 2006, *29(3)*, 227–233.
[2] *ACS Appl. Bio Mater.* 2023, *6*, 1380−1397.
[3] Bisby, M. A. Retrograde Axonal Transport and Nerve Regeneration. In *Axonal Transport in Neuronal Growth and Regeneration*; Advances in Neurochemistry, Vol. 22; Springer, 1984; pp 47–67. DOI: 10.1007/978-1-4684-1197-3_4.
[4] *J. Neurosci.* 2016, *36(12)*, 3441–3452.
[5] *ACS Chem. Neurosci.* 2021, *12*, 4438−4448.