Coffee could offer key ingredient for new treatments for Parkinson's disease

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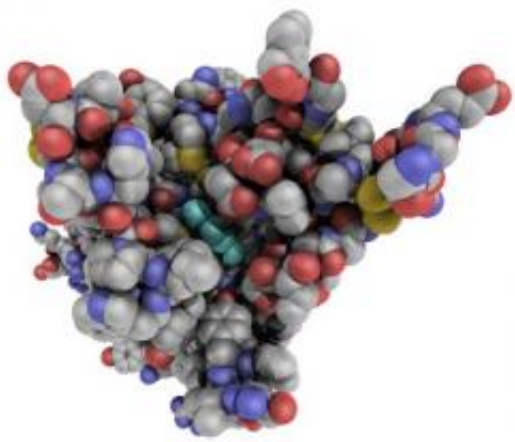


An image shows a view from the extracellular side of the A2A receptor. Protein is shown as spheres: blue = nitrogen, red = oxygen, grey = carbon, gold = sulphur and the caffeine ligand is teal.

Scientists from Heptares Therapeutics have used Diamond Light Source, the UK's national synchrotron facility, to understand the structure of a protein involved in Parkinson's disease and other neurological disorders. Their findings, published this week in the journal *Structure*, could pave the way for a new generation of targeted drug treatments.

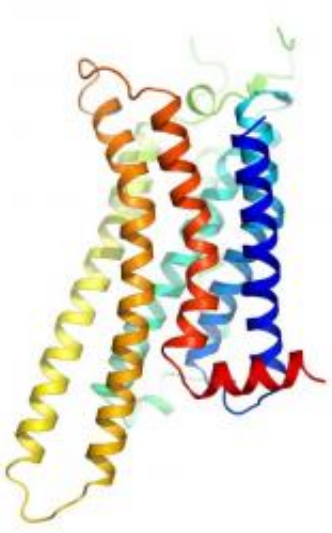
The team used Diamond's Microfocus Macromolecular Crystallography

(MX) beamline (I24) to reveal the complex structure of the vital adenosine A2A receptor and show how xanthine-based drugs such as caffeine bind to their target. Adenosine A2A receptors regulate the effects of neurotransmitters in the brain, cardiovascular and immune systems, and are of particular interest as a drug target for Parkinson's disease. Although it was known that caffeine inhibits the action of the adenosine, the exact molecular mechanism involved was not fully understood.

"These co-structures of xanthines in complex with the adenosine A2A receptor advance our understanding of what is happening at the molecular level when the drug binds to its target and blocks the receptor's response. Along with novel chemotypes discovered by our team, the structural data we collected at Diamond is enabling us to develop highly optimised next-generation drug candidates for Parkinson's disease and other neurological disorders," said Dr. Fiona Marshall, Chief Scientific Officer at Heptares.

The adenosine A2A receptor is a G-protein-coupled receptor (GPCR). GPCRs are responsible for transmitting chemical signals into a variety of different cell types. There are over 700 GPCRs encoded in the human genome and as many as 75 of these have clinical validation, presenting a wide range of opportunities as therapeutic targets in areas including cancer, diabetes, central nervous system disorders, obesity and pain.

Dr. Andrew Doré, Senior Scientist at Heptares, says: "GPCRs represent the single most important family of drug targets in the human body because they are central to so many biological processes. The design of drugs for GPCRs is hampered by the lack of structural information so access to a facility like the Diamond synchrotron is vital to our research. It has enabled us to solve the 3D structure of the adenosine A2A receptor in complex with caffeine and other xanthines as well as our own novel drug candidates."



The image above shows a ribbon diagram of the A2A receptor.

Caffeine is a methylxanthine, a stimulant derivative of xanthine, as is theophylline (in tea), and theobromine (in chocolate). Methylxanthines are among the most widely consumed substances in the world. Caffeine is present in many foods and drinks and reportedly consumed at an average rate of 200mg per day by Americans (Ref. 1). In 2000, the *Journal of the American Medical Association* (*JAMA*) published research showing a correlation between higher intake of caffeine and lower incidence of Parkinson's disease, a devastating and incurable neurological disorder (Ref. 2).

While caffeine exerts a broad range of adverse effects, and is therefore poorly suited for use as a drug, pharmaceutical researchers have generated more potent and selective adenosine receptor modulators. A2A receptor antagonists, in particular, have shown clinical efficacy in the treatment of Parkinson's disease. First generation A2A antagonists using older furan and xanthine type chemical structures have been associated with various safety, tolerability, and pharmacokinetic

limitations. Heptares have used structural information to generate the next-generation of A2A antagonists.

More information: Structure of the adenosine A2A receptor in complex with ZM241385 and the xanthines XAC and caffeine. Doré, AS et al. *Structure* (2011) 19, 1–11. doi:10.1016/j.str.2011.06.014

References:

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Provided by Diamond Light Source