A chemical modified version of the second messenger cAMP

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Second messengers are small molecules that transmit signals in the cell. A single second messenger typically interacts with several signalling proteins. "Even though this may give the impression of promiscuity, the interactions are in fact highly specific" Assistant Professor Rehmann from the University Medical Center Utrecht explains. "It is just that one second messenger functions in multiple signalling pathways. This is not a problem, as its concentration is tightly controlled. But it probably turns into a problem if we would flood the body with a drug just mimicking this second messenger. What we need is a drug influencing only one process."

The study, publishing January 20 in the open access journal *PLOS Biology*, describes the development of a cAMP analogue that specifically activates only Epac2, one of several cAMP-responsive proteins. Furthermore, the analogue activates Epac2 more potently than cAMP itself. About 100 analogues were synthesised in an interactive design process. Several crystal structures of Epac2 in complex with cAMP analogues were determined. The research helps to explain the molecular basis for the selectivity and the strong activation potential.

"We started the project 12 years ago and were driven by scientific curiosity. Our aim was to understand the regulation of the Epac2 protein but also to learn in general about the interaction between proteins and drug-like small molecules. The principal challenge was identifying and understanding small differences in the cAMP-binding domains of cAMP-regulated proteins and matching these differences with suitable

modifications of the cAMP molecule. During that time other laboratories found a function of Epac2 in insulin secretion." Rehmann says. His team also showed that their cAMP analogue augments glucose-induced secretion of insulin from human pancreatic islets.

Rehmann believes that this cAMP analogue will be a valuable tool to gain more insight in the function of Epac2: "I do not think that we fully understand the role of Epac2, but I am confident that we will soon have clarity about whether or not Epac2 is a suitable pharmacological target. Let me be clear on this we are far from a drug, it is rather basic research what we are doing."

More information: Schwede F, Bertinetti D, Langerijs CN, Hadders MA, Wienk H, Ellenbroek JH, et al. (2015) Structure-Guided Design of Selective Epac1 and Epac2 Agonists. *PLoS Biol* 13(1): e1002038. DOI: 10.1371/journal.pbio.1002038

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