

### **The cyclic AMP/Nobel mother-lode**

Adenylyl cyclase was first described by Earl Sutherland and Ted Rall in 1962 following their discovery of cAMP as the factor mediating the effect of epinephrine on glycogenolysis in 1957 – and of cAMP mediating the effects of other hormones on e.g. lipolysis in the interval. Cyclic AMP then became the *first* “second messenger”. Essential reading for any Cell Signaller is Sutherland’s Nobel lecture, which nicely summarizes the history and background to this discovery. There are lessons to be learned from the approach that group took to what were monumentally difficult problems at that time.

<http://www.nobel.se/medicine/laureates/1971/sutherland-lecture.pdf>

Consequently many of the principles surrounding cell signalling have been based on the rich vein that was the cAMP story. Sutherland’s work drew directly from his postdoctoral work with the Coris who received the Prize in 1947 for their efforts at studying cell free glycogen metabolism.

<http://www.nobel.se/medicine/laureates/1947/cori-lecture.pdf>

He went on to show that phosphorylase was inactivated by dephosphorylation and activated by phosphorylation and then found a heat stable factor produced in response to epinephrine and glucagon, which mimicked their effects in vitro. The cAMP-dependent kinase was first described by Krebs and Fischer in 1968 (Nobel 1992). [Krebs was also a postdoctoral fellow in the Cori’s lab]

<http://www.nobel.se/medicine/laureates/1992/krebs-lecture.pdf>

The essential role of GTP in mediating the effects of epinephrine and glucagon on liver adenylyl cyclase was first shown by Rodbell in 1970, who proposed the existence of a distinct GTP regulatory protein interspersed between the hormone and the receptor and later a different G protein that inhibited adenylyl cyclase in adipocytes. Gilman set up an in vitro assay for Gs and went on to purify this and other G-proteins. They received the prize in 1994

<http://www.nobel.se/medicine/laureates/1994/rodbell-lecture.pdf>

<http://www.nobel.se/medicine/laureates/1994/gilman-lecture.pdf>

[Gilman had started working on cAMP with Ted Rall – Sutherland’s old colleague - later went on to work with Marshall Nirenberg (Nobel 1968)].[Rodbell had worked with Chris Anfinsen (1972 Nobel- protein folding)].

The last cAMP-related Nobels were in 2000 to Paul Greengard for his work on cAMP and dopamine systems in the brain and to Eric Kandel for cAMP in learning and memory.

<http://nobelprize.org/medicine/laureates/2000/greengard-lecture.html>

<http://nobelprize.org/medicine/laureates/2000/kandel-lecture.html>

Incidentally, to finish this description of the Nobel mother-lode that was cAMP, Ferid Murad, who shared the Nobel prize for the discovery of NO and its involvement with cyclic GMP in 1998, did his Ph.D. with Rall and Sutherland.

<http://nobelprize.org/medicine/laureates/1998/murad-lecture.html>

A more referenced version of this story has been presented by JA Beavo and Larry Brunton (Beavo, J.A. and L.L. Brunton, *Cyclic nucleotide research -- still expanding after half a century*. Nat Rev Mol Cell Biol, 2002. 3(9): p. 710-8. )