Zygote 8 (Supplement), pp. S24–S25. © 2000 Cambridge University Press Printed in the United Kingdom

The guanylyl cyclase receptors

David L. Garbers
Cecil H. and Ida Green Center for Reproductive Biology Sciences, Howard Hughes Medical Institute, and the Department of Pharmacology, University of Texas Southwestern Medical Center, Dallas, TX 75235-9050, USA

In the early 1980s both our group (Hansbrough & Garbers, 1981; Garbers *et al.*, 1982) and that of Norio Suzuki (Suzuki *et al.*, 1981) identified the active material in sea urchin egg conditioned media that could stimulate sperm motility and metabolism. In the sea urchins *Hemicentrotus pulcherrimus* or *Strongylocentrotus purpuratus*, the active material was a small peptide that we named speract, and the Suzuki group named this and subsequent peptides SAPs, for sperm activating peptides. Subsequently, both groups identified other peptides (see Suzuki & Yoshino, 1992 for review), one of the most interesting being one named resact, the active material in *Arbacia punctulata* egg conditioned media. This peptide turned out to be the first animal sperm chemoattractant identified (Ward *et al.*, 1985*a*). A peptide also turned out to be the active principle that explained previous observations of Ward and Vacquier (Ward *et al.*, 1985*b*; Suzuki *et al.*, 1984) that egg conditioned media could cause the rapid dephosphorylation of a major membrane protein of spermatozoa. The apparent receptor for resact was later identified as a guanylyl cyclase, establishing a new paradigm for low-molecular-weight second messenger signalling, and the major phosphoprotein regulated by resact was also the receptor itself.

The sea urchin sperm guanylyl cyclase served as a prototype for most membrane guanylyl cyclases subsequently discovered, in that each contained a single transmembrane segment, an extracellular ligand binding domain, and both an intracellular protein kinase-like and a cyclase catalytic domain (Fig. 1). Using the coding region of the intracellular region, mammalian guanylyl cyclase receptors were then discovered. Three possess known ligands and four remain orphans (for review see Foster *et al.*, 1999). Of the three with known ligands, one binds atrial natriuretic peptide and regulates blood volume/pressure. The exact function of the other two known receptors remains unclear. One is responsible for acute secretory diarrhoea in adults, which is induced by bacterial pathogens that produce a specific peptide, and the other responds to a natriuretic-like peptide produced locally throughout the body. The orphans are found in the retina, olfactory neuroepithelium, or in various peripheral tissues. The remaining number of receptors to expect in the mammal is not known, since *Caenorhabditis elegans* contains more than 25 orphan guanylyl cyclase receptors, many of which are in sensory neurons (Yu *et al.*, 1997), and yet *C. elegans* contains about one-tenth the number of functional genes compared with the human. Recently, Potter and Hunter (1999) have further demonstrated the importance of the sea urchin cyclase as a prototype, in that phosphorylation sites were identified on the ANP receptor which, when mutated, resulted in a failure to desensitise the receptor; this replicates the model for desensitisation established for the sea urchin sperm cyclase receptor.

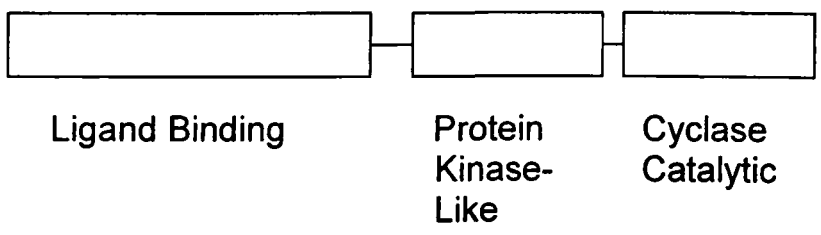

Figure 1 The sea urchin sperm guanylyl cyclase receptor.

Within the last few months new structures of membrane guanylyl cyclases have been reported (e.g. Linder *et al.*, 1999). These apparent guanylyl cyclases contain 12 or more transmembrane segments and two internal catalytic domains analogous to the vertebrate adenylyl cyclases. Amino acids that, when mutated, result in conversion of guanylyl cyclases to adenylyl cyclases (Sunahara *et al.*, 1998) are also changed in the 12 transmembrane forms to those amino acids predicted for guanylyl cyclases.

References

Foster, D.C., Wedel, B.J., Robinson, S.W. & Garbers, D.L. (1999). *Rev. Physiol. Biochem. Pharmacol.* **135**, 1–39.
Garbers, D.L., Watkins, H.D., Hansbrough, J.R., Smith, A. & Misono, K.S. (1982). *J. Biol. Chem.* **257**, 2734–7.
Hansbrough, J.R. & Garbers, D.L. (1981). *J. Biol. Chem.* **256**, 1447–52.
Linder, J.U., Engel, P., Reimer, A., Kruger, T., Plattner, H., Schultz, A. & Schultz, J.E. (1999). *EMBO J.* **18**, 4222–32.
Potter, L.R. & Hunter, T. (1999). *Mol. Biol. Cell* **10**, 1811–20.
Sunahara, R.K., Beuve, A., Tesmer, J.J., Sprang, S.R., Garbers, D.L. & Gilman, A.G. (1998). *J. Biol. Chem.* **273**, 16332–8.

https://doi.org/10.1017/S0967199400130114 Published online by Cambridge University Press

Suzuki, N. & Yoshino, K. (1992). *Comp. Biochem. Physiol. [B]* **102**, 679–90.

Suzuki, N., Nomura, K., Ohtake, H. & Isaka, S. (1981). *Biochem. Biophys. Res. Commun.* **99**, 1238–44.

Suzuki, N., Shimomura, H., Radany, E.W., Ramarao, C.S., Ward, G.E., Bentley, J.K. & Garbers, D.L. (1984). *J. Biol. Chem.* **259**, 14874–9.

Ward, G.E., Brokaw, C.J., Garbers, D.L. & Vacquier, V.D. (1985*a*). *J. Cell. Biol.* **101**, 2324–9.

Ward, G.E., Garbers, D.L. & Vacquier, V.D. (1985*b*). *Science* **227**, 768–70.

Yu, S., Avery, L., Baude, E. & Garbers, D.L. (1997). *Proc. Natl. Acad. Sci. USA* **94**, 3384–7.

https://doi.org/10.1017/S0967199400130114 Published online by Cambridge University Press