COMMENTARY
Attractin’ more attention – new pieces in the obesity puzzle?
Giles S. H. YEO and Kenneth SIDDLE
Department of Clinical Biochemistry, University of Cambridge, Addenbrooke's Hospital, Cambridge CB2 2QR, U.K.

Genetic, biochemical and pharmacological studies in humans and rodents have established that signalling through the G-protein-coupled melanocortin-4 receptor (MC4R) by pro-opiomelanocortin (POMC)-derived ligands plays a critical role in the central suppression of appetite. As a consequence, malfunction of this signalling system leads to the development of obesity. It has been shown previously that melanocortin signalling can be modulated by the type 1 transmembrane protein attractin, apparently acting as a co-receptor for the inhibitory ligand agouti. Work reported in this issue of Biochemical Journal (Haqq et al.) demonstrates that the cytosolic tail of an attractin-like protein (ALP) binds directly and specifically to the C-terminal region of MC4R, raising the possibility that proteins of the attractin family influence melanocortin receptor function through multiple mechanisms.

Key words: agouti, appetite, attractin, G-protein-coupled receptor (GPCR), melanocortin, obesity.
lyosomal degradation. Recent work has shown that MC4R conforms to this pattern and undergoes agonist-mediated desensitization and internalization through GRK-β, arrestin- and dynamin-dependent processes [8].

It is now recognized that β-arrestins can also function positively as scaffold proteins that couple receptors to MAPK (mitogen-activated protein kinase)-signalling pathways involving ERKs (extracellular-signal-regulated kinases) and/or JNKs (c-Jun N-terminal kinases), and thus direct new signals from the very receptors they desensitize in terms of G-protein-mediated signalling [7]. Moreover, β-arrestins are by no means the only scaffolds that have been demonstrated to interact with GPCRs. Numerous different cytosolic proteins have been shown to bind to GPCRs, including PDZ-domain proteins, protein kinases and cytoskeletal proteins [9,10]. Binding is generally sequence-specific, commonly involving the C-terminal tail of receptors, and therefore particular scaffolds associate with particular receptors. Such interactions have the potential to modulate function in various ways, including allosteric regulation of signalling, clustering with potential effectors or targeting to specific subcellular compartments or plasma membrane domains.

There is little published information on proteins that interact with melanocortin receptors. One such protein, attractin, was identified as the product of the murine Mahogany gene [11]. Mahogany mutations that impair attractin function are associated with altered pigmentation and with obesity, indicating that attractin can modulate function of both MC1R and MC4R. Unlike most previously studied GPCR-interacting proteins, attractin is not cytosolic, but a type I transmembrane protein of 1428 amino acids with a large extracellular domain and a relatively short cytosolic tail of 128 amino acids. It appears to function as a co-receptor for the endogenous MCR-inhibitory protein agouti [12] (but not the agouti-related protein AGRP, which had been previously implicated in appetite regulation [13]). However, the mechanism of interaction of attractin with MCRs is not altogether clear. Further complexity is introduced, as if it were needed, by the existence of isoforms of attractin with different C-termini, which are secreted, rather than transmembrane, proteins. One other example of a transmembrane protein which modulates GPCR functions is the D₁ dopamine receptor-interacting protein calcyon [14]. This is a protein of only 24 kDa, which apparently regulates the affinity state of receptors as well as cross-talk between G₁-receptors and heterologous G₂-receptors again. The mechanism of interaction between this regulatory protein and the D₁ receptor has not been delineated at a molecular level.

Into the fray then come a group of MC4R investigators from the Vollum Institute in Portland, OR, U.S.A., and their collaborators from Harvard Medical School and the Rockefeller University. In this issue of the Biochemical Journal, Haqq et al. provide tantalizing evidence for a novel binding partner for the MC4R identified in a yeast two-hybrid screen of a mouse brain cDNA library [15]. Out of this screen popped an attractin-like protein (ALP), apparently the murine orthologue of a human protein for which the sequence was already known (KIAA0534). ALP is a transmembrane protein of 1371 amino acids (KIAA0534 has just 1175 amino acids) and its cytosolic tail is 63% identical in sequence with the corresponding region of mouse attractin-1. Nothing is divulged by Haqq et al. about the structure of the extracellular domain of ALP and its relationship to attractin. However, the ALP–MC4R interaction is mapped to specific regions of the cytosolic C-terminal tail of ALP and the C-terminal tail of MC4R (spanning Thr₁₁², one of the phosphorylation sites implicated in β-arrestin binding and agonist-induced desensitization [8]). There is also evidence of specificity, in that the MC4R tail binds the C-terminus of ALP but not attractin, whereas the C-terminus of ALP binds MC4R but not β₁-adrenergic receptor. Many interesting details remain to be addressed, not least whether ALP interacts with other MCRs and whether the interaction is affected by receptor phosphorylation. No data are presented on the functional consequences of the ALP–MC4R interaction, but circumstantial evidence of physiological significance is provided by the co-localization of ALP and MC4R in a number of brain regions known to be important to the regulation of energy homoeostasis, although expression of ALP is by no means confined to such sites. Precisely what the physiological function of ALP might be is unclear at this stage. The authors speculate that it might act as a co-receptor for AGRP, or otherwise facilitate inhibition of MC4R function by AGRP, in a manner analogous to the role of attractin in mediating effects of agouti. However, other roles of ALP in clustering and synaptic localization of MC4R are not ruled out. The demonstration that attractin is but one of a family of related proteins capable of interacting with melanocortin receptors is certain to act as a spur to further studies designed to elucidate the physiological consequences of such interactions, and the biochemical mechanisms underlying them.

REFERENCES