Emerging molecular targets

D_3 receptors and cocaine abuse

Use of cocaine is known to alter dopaminergic pathways in the brain, and recent studies indicate that the dopamine D_3 receptor may be an effective target for cocaine therapies. Dr G. Koob (Scripps Research Institute, La Jolla, CA, USA) reported at the 1996 American Association for the Advancement of Science Annual Meeting, held in Baltimore, MD, USA in February, that rats that have been trained to self-administer a cocaine solution intravenously take less of the drug if they are given specific D_3 agonists. Koob reported a direct correlation between the affinity of the various D_3 agonists for the dopamine receptor and their effectiveness in reducing cocaine self-administration by the rats.

Koob speculated that the rats may take less cocaine because, when given in combination with the D_3 agonist, the smaller quantity may induce the same sensation as if they had taken a large dose of drug. That is, the D_3 agonist may enhance the reinforcing properties of cocaine. However, studies suggest that the D_3 agonist does not have the potential for abuse; the rats did not self-administer the D_3 agonist when they were allowed free access to the drug.

The D_3 receptors responsible for the modulation of cocaine use by the rats are thought to be located on the underside of the midbrain in the area known as the shell of the nucleus accumbens. There appear to be no motor function side-effects when highly specific D_3 receptor agonists are used. D_3 receptors are mostly associated with emotional and endocrine functions and are not concentrated in areas associated with motor function. Koob has recently published his findings in *Behav. Pharmacol.* (1995) 6, 333–347.

Leptin receptor

The identification of the role of the protein leptin in controlling body weight was an important advance in obesity research in 1995. Now receptors for leptin have been reported from both mice and human tissue by research teams from Millennium Pharmaceuticals (Cambridge, MA, USA) and Hoffman-LaRoche (Basel, Switzerland) [Tartaglia *et al.* (1995) *Cell* 83(7) 1263–1271]. The receptors were cloned from mRNA taken from both mouse and human brain tissue. The receptor, termed OB-R, resembles a class 1 cytokine receptor with a very short intracellular tail. Because of the short tail, the authors speculate that the receptor may function to move leptin from the peripheral circulation into the CNS. The researchers also identified a homolog of OB-R with a much longer cytoplasmic tail, which they speculate is likely to be involved in signaling.

The biology of the leptin system is in its infancy, but the discovery of these receptors is likely to generate considerable research interest in the role of leptin in body weight regulation and stimulate the search for small molecule agonists and antagonists.

Robert W. Wallace

About *Monitor*....

New combinatorial chemistry section

I am delighted to report that, as of the May issue of *Drug Discovery Today*, Dr Nick Terrett (Pfizer Central Research, Sandwich, Kent, UK) will provide regular monthly updates on the latest literature, information and events in combinatorial chemistry. In this month's Editorial, Dr Terrett outlines the increasingly important role that these techniques are playing in drug discovery. I hope that all readers will find this new section of great value.

Contributions to Monitor

Profiles offers commentary on promising lines of research, new technologies, emerging molecular targets, novel strategies, controversies and legislative issues. We welcome contributions to this section of the magazine. Articles extending to approximately 500–1,000 words should provide an accurate summary of the essential facts together with an expert commentary to provide a perspective. Please provide one hard copy of the article together with a copy on disk stating the computer and software used (Microsoft Word is preferred, although other formats will be acceptable). Illustrations are encouraged. Contributions or proposals for articles should be directed to: Dr Andrew W. Lloyd, *Monitor* Editor, Department of Pharmacy, University of Brighton, Moulsecoomb, Brighton, UK BN2 4GJ. tel +44 1273 642049, fax: +44 1273 679333, e-mail: a.w.lloyd@brighton.ac.uk

Authors should be aware that articles for publication in *Monitor* are subject to peer-review; occasionally, *Monitor* articles may be rejected or, as is more likely, authors may be asked to revise their contribution. Articles may also be edited after acceptance.

Andrew W. Lloyd

  1359-6446/96/$15.00 S1359-6446(96)30030-5