RNA as a small-molecule drug target – Letter to the Editor

A recent review article, entitled *RNA as a small-molecule drug target: Doubling the value of genomics*[1], might inadvertently lead a reader to conclude that there are no successful stories of small-molecule discovery against an RNA target. A recent publication describes the discovery of small molecules that bind selectively to the RNA component of the Tat–TAR (transactivation response element) complex[2], in which one reported compound displays activity in HIV-1-infected cells. This information supplements the superb review.

REFERENCES

1 Ecker, D.J. and Griffey, R.H. (1999) RNA as a small-molecule drug target: Doubling the value of genomics. *Drug Discovery Today* 4, 420–429

2 Mei, H-Y. *et al.* (1998) Inhibitors of protein–RNA complexation that target the RNA: Specific recognition of HIV-1 TAR RNA by small organic molecules. *Biochemistry* 37, 14204–14212

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Histamine control of sleep, learning and memory

The neurotransmitter, histamine, mediates its regulatory activity via three distinct receptor subtypes: H_1, H_2 and H_3. For many years, H_1-receptor antagonists (such as Claritin®) have been available for the treatment of allergic conditions while H_2-receptor antagonists (such as Tagamet®) have been available for the treatment of gastric ulcers. By contrast, the H_3-receptor subtype was only discovered in 1983 and, until recently, no antagonists of this subtype had entered clinical trials. Now, following successful Phase I clinical trials, Gliatech (Cleveland, OH, USA) is preparing to initiate Phase II clinical testing of its H_3-receptor antagonist, Perceptin™, for the treatment of CNS disorders.

Histamine activity in the CNS

H_3 receptors are presynaptic G-protein coupled receptors (GPCRs) that regulate the release and synthesis of histamine using a feedback mechanism[1]. Increases in histamine levels raises H_3-receptor binding, leading to an inhibition of the production and release of more histamine. Hence, antagonists of this receptor inhibit this molecular 'brake', stimulating the release of histamine.

Histamine-containing neurons in the hypothalamus project into several regions of the brain, indicating that H_3 receptors might be involved in many brain functions. Furthermore, H_3 receptors are known to regulate the release of other neurotransmitters involved in cognitive processes, such as acetylcholine, noradrenaline and dopamine. The observation that histamine-containing bodies in the posterior hypothalamus project into the cerebral cortex gave the first suggestion of an involvement of H_3 receptors in maintaining arousal and controlling the sleep–wake cycle. Histamine release in rats is known to be associated with periods of activity and wakefulness. Furthermore, H_3 receptors are concentrated in the frontal cortex and hippocampus, areas of the brain associated with higher-level learning processes in mammals. Thus, selective H_3-receptor antagonists could have clinical uses in disorders of sleep, attention and memory.

Perceptin (Fig. 1) is a potent and selective H_3-receptor antagonist developed by Gliatech with an affinity K_i value of 0.125 nM against CNS H_3 receptors. In pre-clinical studies, it crossed the blood–brain barrier effectively, enhanced wakefulness and improved learning in developmental rat models[2]. Double-blind, placebo-controlled single- and multiple-dose Phase I trials of Perceptin in healthy volunteers have now been completed and showed good tolerance, with the side effects (principally CNS symptoms such as dizziness) being mild and transient. With Perceptin having a plasma half-life of 12–14 hours, Thomas O. Oesterling (Chairman and CEO of Gliatech) said, 'These Phase I studies…confirm that Perceptin is safe and amenable to once-daily dosing'.

Attention-deficit hyperactivity disorder

Although H_3-receptor antagonists increase levels of arousal, they are not psychostimulants and, hence, the undesirable side effects often associated with the psychostimulants should be absent. Clinical trials using Perceptin might now be conducted for several conditions that are relatively poorly served by stimulant medication, such as attention-deficit hyperactivity disorder (ADHD), which is diagnosed in childhood. Administering stimulants (which are scheduled drugs because of their potential to be abused) to children, will always be controversial.

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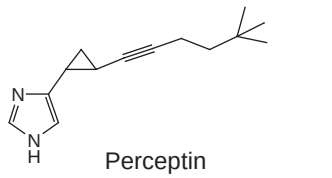

Figure 1. *The structure of Perceptin {4-[(1R,2R)-2-(5,5-dimethyl-1-hexynyl)cyclopropyl]-1*H*-imidazole}.*

ADHD sufferers are required to take medication for many years, and the adverse effects of the most commonly prescribed stimulant, Ritalin®, can include headache, insomnia and dizziness. Clark Tedford (Vice President for Product Development at Gliatech) says, 'We hope that Perceptin will fill the need for a safe, effective non-stimulant medication for ADHD'.

Narcolepsy

Narcolepsy is a disabling, incurable sleep disorder that affects 0.2–1.6 per thousand in European countries, Japan and the US. It is characterized by excessive daytime somnolence and cataplexy, which is a sudden, involuntary loss of strength in voluntary muscles and is triggered by changes in emotion. It is currently treated with stimulant and anti-depressant drugs. In a presentation at the *29th Annual Society for Neuroscience Conference* in October 1999 (Miami, FL, USA), Tedford and colleagues reported that Perceptin decreased the number and severity of cataleptic attacks in genetically induced narcoleptic dogs. Phase II clinical trials of Perceptin are therefore planned for this and other sleep disorders.

The role of H_3 receptors in learning and memory indicates that H_3-receptor antagonists could have a role in the treatment of memory disorders such as Alzheimer's disease (AD). Histamine levels in the hippocampus are significantly lower in AD sufferers compared with age-matched controls[3]. Furthermore, milder sleep and memory disorders affect millions of elderly people and, as the population ages, the occurrence of these conditions will increase. In the future, H_3-receptor antagonists might therefore play a significant role in improving the quality of life of the elderly population.

REFERENCES

1 Leurs, R. *et al.* (1998) Therapeutic potential of histamine H_3 receptor agonists and antagonists. *Trends Pharmacol. Sci.* 19, 177–184

2 Halpern, M.T. (1999) GT-2331. *Curr. Opin. CNS Invest. Drugs* 1, 524–527

3 Panula, P. *et al.* (1998) Neuronal histamine deficit in Alzheimer's disease. *Neuroscience* 82, 993–997

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News in brief

Pharmacogenomics market to explode?

It has been forecast that, by the year 2005, the pharmaceutical R&D market for pharmacogenomics-related products and services will be worth $795 million[1]. This market was valued at $47 million in 1998, giving an expected compound growth rate of >50%. The relative contribution of the different areas of research is forecast to remain relatively constant, with the major areas in 2005 being cardiovascular disease ($139.1 million) and infectious disease ($123.3 million), followed by CNS-related disorders ($72.3 million) and cancers ($41.3 million). The field of pharmacogenomics is little more than two years old, and was created following the formation of the Abbott–Geneset Alliance in July 1997. Since then, 28 pharmacogenomic collaborations have been formed, 20 of which involve the application of pharmacogenomics to drug development (especially late-stage clinical development), at least seven are involved in drug discovery, and four involve marketed drugs.

1 Financial Times Pharmaceuticals (1999) Pharmacogenomics players.

Splicing apoptosis genes

Researchers from Isis Pharmaceuticals (Carlsbad, CA, USA) have successfully used antisense oligonucleotides to both increase and decrease the levels of two functionally antagonistic proteins encoded by the *Bcl-x* gene, one of which might trigger the development of resistance to chemotherapy in human tumours[2]. These studies have shown that alternatively spliced RNA produced by the *Bcl-x* gene produces two proteins, Bcl-xS that promotes apoptosis and Bcl-xL that inhibits apoptosis. By targeting a second-generation methoxyethyl antisense inhibitor to pre-RNA from the *Bcl-x* gene, it was possible to change the RNA splicing from one form of Bcl-x to the other, hence decreasing Bcl-xL levels and increasing Bcl-xS levels in human cancer cell lines. This then sensitized the cancer cells to apoptotic stimuli and to the cytotoxic effects of chemotherapeutic drugs. It was also suggested that this technique might enable the phenotypes of other apoptosis-regulating genes to be swapped, enabling the development of new

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