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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