Histamine acts as neurotransmitter in the central nervous system. It is involved in behavioural functions such as wake regulation and cognition through interactions with the H₁, H₂, H₃ and H₄ receptors (Brown, Stevens, & Haas, 2001; Saper, Scammell, & Lu, 2005).

**Sedation and car driving**

The role of histamine in sleep-wake regulation was initially mainly evident from the sedative effects of centrally active, so-called ‘first generation’ H₁-antagonists used to treat allergies. The sedation associated with the use of these antihistamines gave rise to concern that these drugs may impair daytime functioning and cause accidents, in particular in patients driving a car. In response, less sedative so-called ‘second generation’ antihistamines were developed, that are less able to pass the blood brain barrier and enter the CNS or be actively pumped out (Chen, Hanson, Watson, & Lee, 2003; Mahar Doan et al., 2004).

Over the years, many studies have been conducted assessing the sedating effects of antihistamines, using various measures to assess the effects on attention, psychomotor performance and other cognitive functions. The diversity in methods makes it difficult, however, to objectively compare the sedating potential of various drugs and doses. Yet, there is one test that has been used in the same way to study the effects of almost every antihistamine on the market: the standardized highway driving test (O’Hanlon 1982). This test has been used for over 25 years, testing more than 40 psychoactive drugs, including many antihistamines (O’Hanlon & Ramaekers, 1995; Theunissen, Vermeeren, & Ramaekers, 2006; Theunissen, Vermeeren, van Oers, van Maris, & Ramaekers, 2004; Vermeeren & O’Hanlon, 1998; Vermeeren, Ramaekers, & O’Hanlon, 2002; Verster, de Weert, Bijtjes, Arab, van Oosterwijck, & Eijken, 2003; Vuurman, Theunissen, van Oers, van Leeuwen, & Jolles, 2007). In this test, subjects operate a specially instrumented vehicle over a 100 km (61 mi) primary highway circuit in normal traffic. They are accompanied by a licensed driving instructor having access to dual controls. The subject’s task is to maintain a constant speed of 95 km/h (58 mi/h) and a steady lateral position between the delineated boundaries of the slower traffic lane. The vehicle’s speed and lateral position are continuously...
recorded, and these signals are edited off line to yield the tests’ primary outcome variable: Standard Deviation of Lateral Position (SDLP in cm). SDLP is a measure of road tracking error or “weaving”. It is a very reliable characteristic of individual driving performance and has proven sensitive to many sedating agents, including alcohol in blood concentrations (BAC) as low as 0.35 mg/ml. Studies using the highway driving test have shown that antihistamines causing driving impairment after single therapeutic doses comparable to or larger than the effect of alcohol while blood concentrations (BAC) are 0.5 mg/ml (the legal limit in most countries), all belong to the so called first generation antihistamines. Effects of second generation antihistamines are less severe than the effect of 0.5 mg/ml BAC, yet they are not free of sedating effects: driving impairment has been demonstrated after higher doses, after repeated administration and/or in female subjects. Consequently the term ‘non-sedating antihistamine’, which is often used as a synonym for the second generation drugs, does not seem justified (Theunissen, Vermeeren, Vuurman & Ramaekers in press).

In contrast to the well known sedative effects, a few studies also found mild stimulating effects on performance for the H1-antagonists terfenadine, ebastine, fexofenadine and desloratadine (Theunissen, Vermeeren, Vuurman, & Ramaekers, 2006). A suggested mechanism from animal studies is that some H1-antagonists directly or via GABA-ergic interneurons enhance dopaminergic activity. However, a SPECT study with fexofenadine in healthy volunteers has not been able to support this hypothesis (Theunissen et al 2006).

Cognition

Recently H3-antagonists have drawn attention by showing cognition enhancing effects in animals (Passani et al, 2000). The H3 receptor functions as an auto- and heteroreceptor. Activation of the H3 autoreceptor primarily inhibits synthesis and release of histamine and generally impairs cognitive performance. In contrast, blockade of the H3 receptor leads to increased release of histamine and improves cognitive performance, especially in cases were it was first impaired (Passani et al, 2004; Witkin & Nelson, 2004).

Currently it becomes increasingly apparent that histamine plays a role in cognitive disturbances associated with neurological disorders like ADHD, schizophrenia, epilepsy, Alzheimer’s disease and sleep disorders (Esbenshade et al., 2006; Wijtmans et al., 2007). For example, H3-antagonists have been shown to successfully enhance cognitive performance and normalize motor disturbances in animal models of ADHD (Leurs, et al, 1998), and reverse deficits in prepulse inhibition of the startle response in mouse models of schizophrenia (Browman et al., 2004). Studies showing that H3-receptor knock-out mice and histidine decarboxylase deficient mice develop seizures faster than wild type mice suggest a seizure suppressive role for histamine (Chen et al., 2003), and studies showing decreased H3-receptor binding in frontal and temporal
brain areas of patients with Alzheimer’s dementia (Higuchi et al., 2000) support a role for histamine in cognition. Consequently, several pharmaceutical companies are developing H₃ ligands to treat these disorders, but so far none has been approved for use in humans.

Our group studied the role of histamine and the effects of H₁-antagonists in cognitive performance of healthy volunteers and allergic patients. Vuurman et al (1994, 1996) found allergic rhinitis reduced learning ability in children and adolescents, and showed that these effects could be partially counteracted by second generation antihistamines, whereas they were aggravated by first generation antihistamines.

Based on these findings and results from animal studies showing effects of H₂-ligands on memory and learning, we studied the effects of dexchlorpheniramine on cognitive functioning as a possible model for memory and learning deficits associated with histaminergic dysfunction (Van Ruitenbeek et al 2008). Results failed to show an effect of H₁ antagonism on performance in memory tests, however, whereas the drug had significantly impaired performance in sensori-motor tests. Results of a subsequent study, designed to disentangle the effects of dexchlorpheniramine on perceptual and motor processes, suggest that H₁ antagonism primarily affects perceptual processes such as stimulus identification (Van Ruitenbeek et al., In Prep.). A third study exploring an alternative model of memory and learning deficits associated with histaminergic dysfunction in humans, probed the effects of L-histidine depletion as a method to decrease histamine levels in the CNS through reduction of precursor availability for synthesis. Preliminary results suggest that L-histidine depletion impaired motor functioning (Van Ruitenbeek et al., In Prep.). It seems therefore that histamine may be involved in both sensory and motor processes, but via different receptors and pathways.

**Future**

A promising way and a next step to gain more insight into the role of histamine in human cognition is by studying the effects of histaminergic drugs on cognitive processing using brain imaging techniques, such as fMRI. An fMRI study by Mitul Mehta and colleagues with healthy volunteers on the effects of an H₃-antagonist on brain activity during a number of cognitive tasks has already shown significant changes in blood oxygen level–dependent (BOLD) responses in the hypothalamic area during learning (Mehta, in prep.). In the near future, our group intends to study the effects of H₁-antagonism on BOLD responses during sensori-motor processing.
References


