

## **Human psychopharmacology of histaminergic manipulations**

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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 H<sub>1</sub>, H<sub>2</sub>, H<sub>3</sub> and H<sub>4</sub> 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' H<sub>1</sub>-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 H<sub>1</sub>-antagonists terfenadine, ebastine, fexofenadine and desloratadine (Theunissen, Vermeeren, Vuurman, & Ramaekers, 2006). A suggested mechanism from animal studies is that some H<sub>1</sub>-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 H<sub>3</sub>-antagonists have drawn attention by showing cognition enhancing effects in animals (Passani *et al*, 2000). The H<sub>3</sub> receptor functions as an auto- and heteroreceptor. Activation of the H<sub>3</sub> autoreceptor primarily inhibits synthesis and release of histamine and generally impairs cognitive performance. In contrast, blockade of the H<sub>3</sub> receptor leads to increased release of histamine and improves cognitive performance, especially in cases where 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; Wijtman *et al.*, 2007). For example, H<sub>3</sub>-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 H<sub>1</sub>-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 H<sub>1</sub>-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 H<sub>3</sub> 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 H<sub>1</sub>-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 H<sub>3</sub>-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 H<sub>1</sub> 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 H<sub>1</sub> 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 H<sub>3</sub>-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 H<sub>1</sub>-antagonism on BOLD responses during sensori-motor processing.

## References

- Browman, K. E., Komater, V. A., Curzon, P., Rueter, L. E., Hancock, A. A., Decker, M. W., et al. (2004). Enhancement of prepulse inhibition of startle in mice by the H<sub>3</sub> receptor antagonists thioperamide and ciproxifan. *Behav Brain Res*, 153(1), 69-76.
- Brown, R. E., Stevens, D. R., & Haas, H. L. (2001). The physiology of brain histamine. *Prog Neurobiol*, 63(6), 637-672.
- Chen, C., Hanson, E., Watson, J. W., & Lee, J. S. (2003). P-glycoprotein limits the brain penetration of nonsedating but not sedating H<sub>1</sub>-antagonists. *Drug Metab Dispos*, 31(3), 312-318.
- Chen, Z., Li, Z., Sakurai, E., Izadi Mobarakeh, J., Ohtsu, H., Watanabe, T., et al. (2003). Chemical kindling induced by pentylentetrazol in histamine H<sub>1</sub> receptor gene knockout mice (H<sub>1</sub> KO), histidine decarboxylase-deficient mice (HDC(-/-)) and mast cell-deficient W/W(v) mice. *Brain Res*, 968(1), 162-166.
- Esbenshade, T. A., Fox, G. B., & Cowart, M. D. (2006). Histamine H<sub>3</sub> receptor antagonists: preclinical promise for treating obesity and cognitive disorders. *Mol Interv*, 6(2), 77-88, 59.
- Higuchi, M., Yanai, K., Okamura, N., Meguro, K., Arai, H., Itoh, M., Iwata, R., Ido, T., Watanabe, T., Sasaki, H. (2000). Histamine H<sub>1</sub> receptors in patients with Alzheimer's disease assessed by positron emission tomography. *Neuroscience*, 99(4), 721-729.
- Leurs, R., Blandina, P., Tedford, C., & Timmerman, H. (1998). Therapeutic potential of histamine H<sub>3</sub> receptor agonists and antagonists. *Trends Pharmacol Sci*, 19(5), 177-183.
- Mehta (2008) Effects of an H<sub>3</sub>-antagonist in healthy volunteers: an imaging study. Paper presented at the 7th Dutch Endo-Neuro-Psycho meeting, Doorwerth NL, 4-6 June 2008.
- Mahar Doan, K. M., Wring, S. A., Shampine, L. J., Jordan, K. H., Bishop, J. P., Kratz, J., et al. (2004). Steady-state brain concentrations of antihistamines in rats: interplay of membrane permeability, P-glycoprotein efflux and plasma protein binding. *Pharmacology*, 72(2), 92-98.
- O'Hanlon JF, Haak TW, Blaauw GJ, Riemersma JB (1982) Diazepam impairs lateral position control in highway driving. *Science* 217: 79-81
- O'Hanlon, J. F., & Ramaekers, J. G. (1995). Antihistamine effects on actual driving performance in a standard test: a summary of Dutch experience, 1989-94. *Allergy*, 50(3), 234-242.
- Passani, M. B., Bacciottini, L., Mannaioni, P. F., & Blandina, P. (2000). Central histaminergic system and cognition. *Neurosci Biobehav Rev*, 24(1), 107-113.
- Passani, M. B., Lin, J. S., Hancock, A., Crochet, S., & Blandina, P. (2004). The histamine H<sub>3</sub> receptor as a novel therapeutic target for cognitive and sleep disorders. *Trends Pharmacol Sci*, 25(12), 618-625.

- Sambeth, A. (2008) Cognitive effects of histidine depletion and tyrosine/phenylalanine depletion in man. Paper presented at the 7th Dutch Endo-Neuro-Psycho meeting, Doorwerth NL, 4-6 June 2008.
- Saper, C. B., Scammell, T. E., & Lu, J. (2005). Hypothalamic regulation of sleep and circadian rhythms. *Nature*, 437(7063), 1257-1263.
- Theunissen EL, van Kroonenburgh MJ, van Deursen JA, Blom-Coenjaerts C, Ramaekers JG (2006) Stimulating effects of the antihistamine fexofenadine: testing the dopamine transporter hypothesis. *Psychopharmacology* 187: 95-102
- Theunissen EL, Vermeeren A, Vuurman EFPM, Ramaekers JG (2009) A review of the effects of antihistamines on the standard highway driving test. In: JC Verster, SR Pandi-Perumal, JG Ramaekers, JJ De Gier (eds): *Drugs, Driving & Traffic Safety*. Bentham Publishers
- Theunissen, E. L., Vermeeren, A., & Ramaekers, J. G. (2006). Repeated-dose effects of mequitazine, cetirizine and dexchlorpheniramine on driving and psychomotor performance. *Br J Clin Pharmacol*, 61(1), 79-86.
- Theunissen, E. L., Vermeeren, A., van Oers, A. C., van Maris, I., & Ramaekers, J. G. (2004). A dose-ranging study of the effects of mequitazine on actual driving, memory and psychomotor performance as compared to dexchlorpheniramine, cetirizine and placebo. *Clin Exp Allergy*, 34(2), 250-258.
- Theunissen, E. L., Vermeeren, A., Vuurman, E. F., & Ramaekers, J. G. (2006). Stimulating effects of H1-antagonists. *Curr Pharm Des*, 12(20), 2501-2509.
- Van Ruitenbeek, P., Vermeeren, A., Smulders, F.T.Y., Sambeth, A., Riedel, W.J. (*In preparation*). An antihistamine and benzodiazepine affect specific stages of information processing.
- Van Ruitenbeek, P., Vermeeren, A., Riedel, W.J. (2008). Histamine H<sub>1</sub> receptor blockade affects psychomotor performance but not memory. *Journal of psychopharmacology* in press
- Vermeeren, A., & O'Hanlon, J. F. (1998). Fexofenadine's effects, alone and with alcohol, on actual driving and psychomotor performance. *J Allergy Clin Immunol*, 101(3), 306-311.
- Vermeeren, A., Ramaekers, J. G., & O'Hanlon, J. F. (2002). Effects of emedastine and cetirizine, alone and with alcohol, on actual driving of males and females. *J Psychopharmacol*, 16(1), 57-64.
- Verster JC, de Weert AM, Bijtjes SI, Aarab M, van Oosterwijck AW, Eijken EJ, Verbaten MN, Volkerts ER (2003) Driving ability after acute and sub-chronic administration of levocetirizine and diphenhydramine: a randomized, double-blind, placebo-controlled trial. *Psychopharmacology* 169: 84-90
- Vuurman EF, van Veggel LM, Sanders RL, Muntjewerff ND, O'Hanlon JF (1996) Effects of semprex-D and diphenhydramine on learning in young adults with seasonal allergic rhinitis. *Ann Allergy Asthma Immunol* 76: 247-252

- Vuurman, E. F., van Veggel, L. M., Uiterwijk, M. M., Leutner, D., & O'Hanlon, J. F. (1993). Seasonal allergic rhinitis and antihistamine effects on children's learning. *Ann Allergy*, 71(2), 121-126.
- Vuurman, E., Theunissen, E., van Oers, A., van Leeuwen, C., & Jolles, J. (2007). Lack of effects between rupatadine 10 mg and placebo on actual driving performance of healthy volunteers. *Hum Psychopharmacol*, 22(5), 289-297.
- Wijtmans, M., Leurs, R., & de Esch, I. (2007). Histamine H<sub>3</sub> receptor ligands break ground in a remarkable plethora of therapeutic areas. *Expert Opin Investig Drugs*, 16(7), 967-985
- Witkin, J. M., & Nelson, D. L. (2004). Selective histamine H<sub>3</sub> receptor antagonists for treatment of cognitive deficiencies and other disorders of the central nervous system. *Pharmacol Ther*, 103(1), 1-20.