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The H1-receptor antagonist chlorpheniramine decreases the ending phase of the mismatch negativity of the human auditory event-related potentials

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Abstract

Auditory event-related potentials (ERPs) were recorded in 20 healthy male humans, who received either a single 4 mg dose of *d*-chlorpheniramine or a placebo, according to a double-blind design. Subjects were instructed to read a book and to ignore random sequences of 90% standard (1000 Hz) and 10% deviant (1100 Hz) tones, presented with stimulus-onset asynchrony (SOA) of 480 ms. Deviant tones elicited the mismatch negativity (MMN) response, which was smaller at its ending phase in the chlorpheniramine group. The auditory exogenous components (N1 and P2) were similar in both groups. Results demonstrate that the antihistamine chlorpheniramine selectively affects the automatic stimulus-change detector associated with MMN, and suggest an involvement of the histamine H1-receptor in the genesis of the MMN.

Keywords: Mismatch negativity; Chlorpheniramine; H1-receptor; Antihistamine; Sensory memory; Automatic auditory discrimination; Event-related potential; Man

Antihistamines are primarily used for their antiallergic properties, and also as a common ingredient of compound preparations for symptomatic treatment of coughs and colds [9]. A major problem of antihistamine therapy is its adverse side effects [2], and in particular, the H1-receptor antagonist chlorpheniramine has been shown to lead to a degree of sedation [16] and impaired cognitive abilities, as indexed by digit symbol substitution [16], and delayed latency of P3b [10], an event-related potential (ERP) component associated with conscious discrimination of target stimuli [18]. These results indicate a detrimental effect of chlorpheniramine on attentional controlled processes, but the underlying neural mechanisms of these effects remain unclear. For instance, chlorpheniramine-induced attentional deficits may be due to early effects on pre-attentional processes. Moreover, it has recently been shown, by using the mismatch negativity (MMN) ERP component [13], that attentive auditory target detection depends on a pre-attentive sensory memory system, which automatically detects novel stimuli as long as they do not match a neural template of the acoustic environment built in the auditory cortex [23].

The MMN is elicited when a repetitive (standard) stimulus is randomly replaced by a physically deviant sound. The MMN peaks at 150–250 ms from stimulus onset, is presumably generated in the temporal and frontal cortex [1], and overlaps the exogenous N1 and P2 components, which in contrast to MMN, are elicited by both the standard and the deviant stimuli. Thus, it has been proposed that the MMN reflects a neural response to stimulus change generated by an automatic [15] comparison process between an afferent input caused by the deviant stimulus and a neural trace encoding the physical features of the standard stimulus in the sensory memory [11,12,14].

In the present study, the effects of the antihistamine chlorpheniramine on the automatic processing of stimulus novelty were addressed by recording the MMN in healthy humans.

Twenty healthy paid male subjects (mean age 21.1 ± 1.7 years; mean weight 71.1 ± 8.5 kg; hearing thresholds

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below 45 dB) participated in the study. The experimental procedure was approved by the ethical committee of the Ministry of Health, and the subjects gave informed consent to their participation.

Subjects abstained from alcohol and caffeine consumption 24 h before their participation in the experiment. Half the subjects received a capsule containing 4 mg of *d*-chlorpheniramine, and the other half received a capsule containing a placebo, in a double-blind design. The session started at 0900 h with the ingestion, and the ERP recording began 120 min later, when the plasma level of the active substance reached its peak [19].

Pure tones of 60 ms duration (including 5 ms of rise/fall time) were presented monaurally with an intensity of 85 dB through TDH-39 headphones to the subjects' right ear. The stimulus-onset asynchrony (SOA) was 480 ms. Four blocks of 500 stimuli, containing 90% standard (1000 Hz) and 10% deviant (1100 Hz) tones in random order, were used. The subject was instructed to read a self-selected book and to ignore the auditory stimulation. The Stim unit (Neuroscan, Inc.) controlled the stimulus generation and presentation. During the recording, the subject sat comfortably in a sound-proof, electrically shielded room, in which the temperature (22 ± 1°C) and light (340 lux) were kept constant.

The ERPs were recorded from seven scalp electrodes (Fz, F3, F4, Cz, C3, C4, Pz), using an electrode located on the tip of the nose as reference. Eye-blinks as well as horizontal and vertical eye movements were recorded with two electrodes, located at the canthus and supraorbitally to the left eye. After amplification (band-pass 0.15–100 Hz; sampling rate 250 Hz), EEG epochs of 390 ms including 40 ms of baseline period preceding the stimulus onset were averaged per stimulus class. Epochs exceeding ±60 μV were automatically excluded from the averages, as well as the first ten trials of each block. The ERPs were low-pass filtered at 30 Hz.

The N1 to the standard stimulus was identified in the latency window 70–130 ms, and the P2 to the standard stimulus within 120–200 ms. The MMN peak was identified as the largest negativity within 100–250 ms in the difference wave, obtained by subtracting the ERP to the standard tones from the ERP to the deviant tones. The MMN was analyzed as the mean amplitude in seven consecutive 50 ms intervals from stimulus onset. All amplitude measurements were made against the mean amplitude of the baseline period.

Analyses of variance for repeated measures, with treatment and electrode location (F3, Fz, F4, C3, Cz, C4) as factors, were applied to N1, P2 and MMN amplitudes and latencies. When appropriate, *P* values are reported after the Greenhouse–Geisser correction.

The standard stimulus elicited, in both groups, an N1 peak (mean peak amplitude and latency at Cz: −1.8 μV, 97 ms in the chlorpheniramine group; and −2.1 μV, 100 ms in the placebo group), which was followed by a

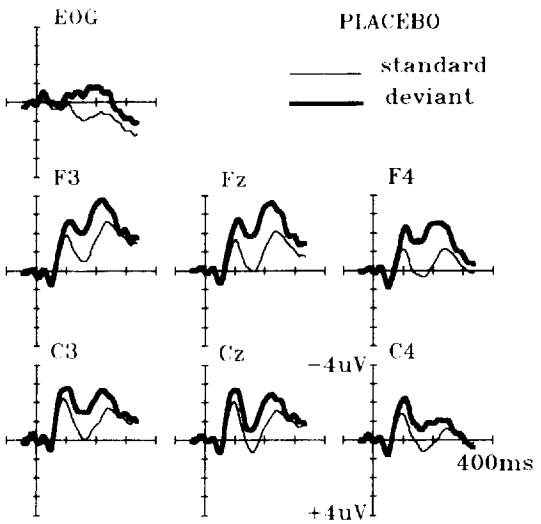

Fig. 1. Grand-average (ten subjects) ERPs to standard and deviant tones in the control (placebo) group.

P2 peak (1.5 μV, 162 ms, and 0.9 μV, 163 s at Cz in the chlorpheniramine and placebo groups, respectively) (Figs. 1 and 2). The analysis of variance of the N1 amplitude revealed a main effect of the electrodes ($F_{(5,90)} = 10.57$, $P < 0.0002$), which was due to a larger amplitude over the central scalp. There were no significant differences in the N1 amplitude between the chlorpheniramine and the placebo groups ($F_{(1,18)} = 0.7461$, n.s.), nor in its latency ($F_{(1,18)} = 0.46$, n.s.). Similarly, a main effect was found due to the electrodes for the P2 amplitude ($F_{(5,90)} = 12.30$, $P < 0.0000$), with larger amplitudes over the central scalp, but not for the factor treatment ($F_{(1,18)} = 1.19$, n.s.).

In the ERP to the deviant tone, the N1 wave was followed in both groups by the MMN (Figs 1 and 2), which can easily be seen in the 'deviant–standard' difference curves. The MMN peak (latency at Fz, 186 ms in the

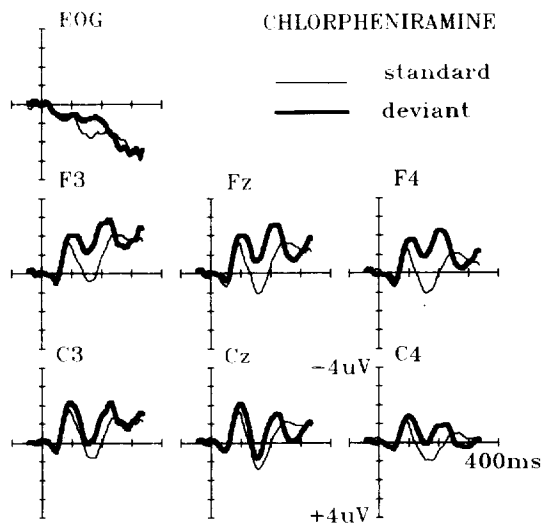

Fig. 2. Grand-average (ten subjects) ERPs to standard and deviant tones in the chlorpheniramine (single 4 mg dose) group.

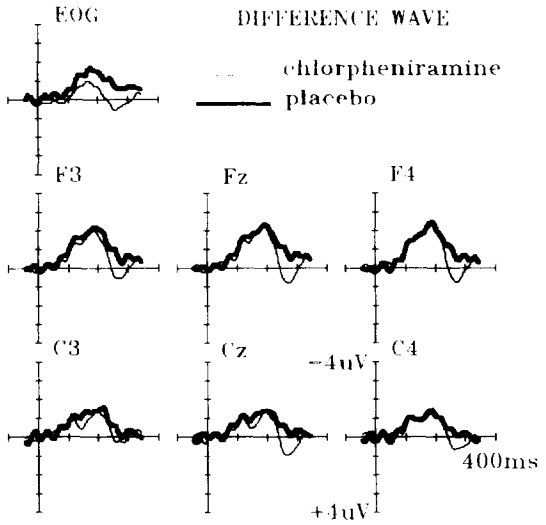

Fig. 3. Grand-average difference waves (ERP to deviants minus ERP to standards) in the chlorpheniramine (thin line) and placebo (thick line) groups.

chlorpheniramine group, 198 ms in the placebo group; $F_{(1,18)} = 1.36$, n.s.) was larger over the frontal scalp ($F_{(5,90)} = 6.91$, $P = 0.0014$), and similar in the two groups (−2.7 μV and −2.9 μV at Fz in the chlorpheniramine and control groups, respectively; $F_{(1,18)} = 0.07$, n.s.). However, the MMN was decreased at its ending phase by 1.3 μV (at Fz) in the chlorpheniramine group (Fig. 3) (250–300 ms interval; $F_{(1,18)} = 5.37$, $P = 0.0325$), but was similar in both groups in the remaining six 50 ms intervals analyzed.

The present results show that a single 4 mg dose of *d*-chlorpheniramine was enough to decrease the amplitude of MMN significantly. This reduction cannot be explained in terms of a general impairment of auditory analysis, since the exogenous N1 and P2 ERPs were not affected. Further, this last result also suggests the independence of MMN attenuation from the sedative effects of chlorpheniramine, at least at the low dose used here, since it has been shown that, for instance, alcohol, a typical sedative substance [25], affects both the MMN and the exogenous ERPs [5,6]. Consequently, our results strongly support a specific effect of the H1-receptor antagonist chlorpherinamine on the neural mechanisms generating the MMN, and thus on the brain mechanisms of the preattentive auditory discrimination function [22,23].

The underlying neural mechanisms explaining the adverse effects of chlorpheniramine, and of antihistamines in general, on cognitive functions [2,10,16] remain unclear. However, according to our results, and taking into account that the automatic discrimination function indexed by the MMN [11,12,14,15,22] is an antecedent brain operation needed for the later, actively controlled process of voluntary target detection indexed by the P3b [17], the adverse cognitive effects of chlorpheniramine on conscious discrimination [10,18] may rely, at least partly [17], on an previous adverse effect on the brain mechanism of pre-attentive discrimination.

In addition to its sedative effects, chlorpheniramine may affect the cognitive ability of subjects to detect relevant signals automatically, preventing them from developing compensatory strategies to cope with this subtle unconscious dysfunction. This possibility should be taken into account in patients carrying out high risk tasks, such as driving public vehicles or controlling air traffic. Further, a practical implication of our results comes from the fact that the MMN, unlike other cognitive ERPs, as the P3b, can be obtained irrespective of the direction of the attention [15], thus allowing the evaluation of drug side-effects in subjects who are unwilling or unable to cooperate.

A possible important implication of the present finding may be related to the neurochemical substrates underlying the genesis of MMN. Contributions to this field are urgently needed, in order to guide further research, especially in order to define clinical areas of interest. Animal studies have implicated the glutamatergic and GABAergic systems, in excitatory and inhibitory mechanisms involved in stimulus-evoked activity in the supragranular cortex [8,21]. Further, an injection of MK-801 blocking agent in monkeys has been shown to suppress the MMN, thus involving the *N*-methyl-D-aspartate (NMDA) receptor in its genesis [7]. In the present experiment, the specific attenuation of the human MMN after a single dose of *d*-chlorpheniramine suggests an involvement of the histamine H1-receptor in its genesis, or at least in that of its ending phase. Since the neural generators of MMN have been located in the temporal [4,20] and frontal [3] cortices, additional support may come from the similar selective localization of H1-receptors found in the temporal and frontal human cortex, as revealed in post-mortem studies [24], and by positron emission tomography (PET) [24]. However, this suggestion needs further research by means of more specifically addressed methods.

In summary, the present data indicate a specific decreasing effect of the antihistamine chlorpheniramine on the ending phase of the MMN, which may explain, at least partly, the well-known side effects of chlorpheniramine on cognitive functions. Since the exogenous components of the ERPs were not affected by the substance, this effect may be independent of the general sedative effects of chlorpheniramine. Further, our results suggest an involvement of the histamine H1-receptor in the neurochemical genesis of the last phase of the MMN.

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[1] Alho, K., Cerebral generators of mismatch negativity (MMN) and

its magnetic counterpart (MMNm) elicited by sound changes, Ear Hearing, 16 (1995) 38–51.

[2] Fastner Z., Antihistamines (H1-receptor antagonists). In M.N.G. Dukes (Ed.), Meyler's Side Effects of Drugs, Elsevier, New York, 1984, pp. 284–289.

[3] Giard, M.H., Perrin, F., Pernier, J. and Bouchet, P., Brain generators implicated in the processing of auditory stimulus deviance: a topographic event-related potential study, Psychophysiology, 27 (1990) 627–640.

[4] Hari, R., Hämäläinen, M., Ilmoniemi, R., Kaukoranta, E., Reinikainen, K., Salminen, J., Alho, K., Näätänen, R. and Sams, M., Responses of the primary auditory cortex to pitch changes in a sequence of tone pips: neuromagnetic recordings in man, Neurosci. Lett., 50 (1984) 127–132.

[5] Jääskeläinen, I., Lehtokoski, A., Alho, K., Kujala, T., Pekkonen, E., Sinclair, J.D., Näätänen, R. and Sillanaukee, P., Low-dose of ethanol suppresses mismatch negativity of auditory event-related potentials, Alcoholism Clin. Exp. Res., 19 (1995) 607–610.

[6] Jääskeläinen, I., Pekkonen, E., Alho, K., Sinclair, J.D., Sillanaukee, P. and Näätänen, R., Dose-related effect of alcohol on mismatch negativity and reaction time performance, Alcohol, (1996) in press.

[7] Javitt, D.C., Schroeder, C.E., Steinschneider, M., Arezzo, J.C., Ritter, W. and Vaughan, H.G., Cognitive event-related potentials in human and non-human primates: implications for the PCP/NMDA model of schizophrenia. In G. Karmos, M. Molnár, V. Csépe, Z. Czigler and J.E. Desmedt (Eds.), Perspectives of Event-Related Potentials Research, Elsevier, Amsterdam, 1994.

[8] Kraut, M.A., Arezzo, J., and Vaughan, H.J., Inhibitory processes in flash evoked potential of the monkey, Electroencephalogr. Clin. Neurophysiol., 76 (1990) 440–452.

[9] Martindale, W., The Extra Pharmacopoeia, Pharmaceutical Press, London, 1993.

[10] Meador, K.J., Loring, D.W., Thompson, E.E. and Thompson, W.O., Differential cognitive effects of terfenadine and chlorpheniramine, J. Allergy Clin. Immunol., 84 (1989) 322–325.

[11] Näätänen, R., The role of attention in auditory information processing as revealed by event-related potentials and other brain measures of cognitive function, Behav. Brain Sci., 13 (1990) 201–288.

[12] Näätänen, R., Attention and Brain Function, Lawrence Erlbaum, Hillsdale, 1992, 494 pp.

[13] Näätänen, R., Gaillard, A.W.K. and Mäntysalo, S., Early selective-attention effect on evoked potential reinterpreted, Acta Psychol., 42 (1978) 319–329.

[14] Näätänen, R., Paavilainen, P. and Reinikainen, K., Do event-related potentials to infrequent decrements in duration of auditory stimuli demonstrate a memory trace in man? Neurosci. Lett., 107 (1989) 347–352.

[15] Näätänen, R., Paavilainen, P., Tiitinen, H., Jiang, D. and Alho, K., Attention and mismatch negativity, Psychophysiology, 30 (1993) 436–450.

[16] Nicholson, A.N., Pascoe, P.A., Turner, C., Ganellin, C.R., Greengrass, P.M., Casy, A.F. and Mercer, A.D., Sedation and histamine H_1-receptor antagonism: studies in man with the enantiomers of chlorpheniramine and dimethindene, Br. J. Pharmacol., 104 (1991) 270–276.

[17] Novak, G., Ritter, W., and Vaughan, H.G., Mismatch detection and the latency of temporal judgments, Psychophysiology, 29 (1992) 412–430.

[18] Parasuraman, R. and Beatty, J., Brain events underlying detection and recognition of weak sensory signal, Science, 210 (1980) 80–83.

[19] Peets, E.A., Jackson, M. and Symchowicz, S., Metabolism of chlorpheniramine maleate in man, J. Pharmacol. Exp. Ther., 180 (1972) 464–474.

[20] Scherg, M., Vajsar, J. and Picton, T., A source analysis of the human auditory cortex, J. Cog. Neurosci., 1 (1989) 336–355.

[21] Schroeder, C.E., Tenke, C.E., Givre, S.J., Arezzo, J. and Vaughan, H.G., Laminar analysis of bicuculline-injected epileptiform activity in area 17 of the awake macaque, Brain Res., 515 (1990) 326–330.

[22] Schröger, E. and Winkler, I., Presentation rate and magnitude of stimulus deviance effects on human pre-attentive change detection, Neurosci. Lett., 193 (1995) 185–188.

[23] Tiitinen, H., May, R., Reinikainen, K. and Näätänen, R., Attentive novelty detection in humans is governed by pre-attentive sensory memory, Nature, 372 (1994) 90–92.

[24] Yanai, K., Watanabe, T., Yokoyama, H., Hatazawa, J., Iwata, R., Ishiwata, K., Meguro, K., Itoh, M., Takahashi, T., Ido, T. and Matsuzawa, T., Mapping of histamine H_1-receptors in the human brain using [^{11}C]pyrilamine and positron emission tomography, J. Neurochem., 59 (1992) 128–136.

[25] Zwyghuizen-Dorenbos, A., Roehrs, T., Lamphere, J. and Zorich, F., Increased daytime sleepiness enhances ethanol's sedative effects, Neuropsychopharmacology, 1 (1988) 279–286.