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Effects of a sedative and of a non-sedative H_1-antihistamine on the event-related potential (ERP) in normal volunteers

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Abstract. Measurements of the amplitude and latency of the P3b component of the event-related potential (ERP), simple reaction time (SRT) and four psychomotor tests (VAS, DSST, DSp and CFF) were made on 12 male subjects (aged 19–24 years) 1.0–1.5 and 4.0–4.5 h after single oral doses of triprolidine (7.5 mg), terfenadine (60 mg) and placebo. Neither triprolidine nor terfenadine changed P3b amplitude or latency although VAS, CFF and DSST scores were significantly altered by triprolidine at 1.0–1.5 h after dosage. These results suggest that the P3b is too robust to reflect the mild sedative properties of an H_1-receptor antihistamine, or that H_1-receptors are not involved in P3b generation.

Key words: Antihistamines – Sedation – Event-related potentials

Many H_1-antihistamines possess sedative properties (Uzan et al. 1979) including decreased attention, increased sleep duration and EEG changes (Faingold 1978). The mechanism for this remains unclear but is probably related to occupation of central H_1-receptors (Quach et al. 1979; Uzan et al. 1979), demonstrated biochemically by Hill et al. (1978). Sedation in turn leads to impairment of psychomotor performance, a consistent finding in a large number of experiments (e.g., Bye et al. 1974; Clarke and Nicholson 1978; Nicholson 1979).

Histaminergic pathways are widespread in the brain, originating from the reticular formation and projecting diffusely into the cerebral cortex (Garbarg et al. 1980). This distribution closely resembles that of monoaminergic pathways (Nicholson et al. 1985), and both systems have been implicated in the control of states of wakefulness (e.g., Rose et al. 1982; Nicholson et al. 1985).

The recording of event-related potentials (ERP) from the scalp can be used to monitor central nervous function. The "P3b" is a robust and distinct endogenous component of the ERP (Squires et al. 1977) easily elicited to task-relevant stimuli in a simple "oddball" paradigm (Kutas et al. 1977; Courchesne et al. 1978). The exact functional significance of P3b remains obscure although many authors have pointed to its association with decision making (e.g., Hillyard and Kutas 1983) or cognitive processing time (Brown et al. 1982). Other factors postulated as influencing P3b have included attention (Cooper et al. 1978; Roth et al. 1978) and arousal (Cant 1980). These psychological correlates, together with anatomical and topographical data, have led to the suggestion that P3b is generated in the cortex by noradrenergic locus coeruleus neurones (Pineda et al. 1986; Courchesne et al. 1987), the reasons for which have been reviewed by Courchesne et al. (1987).

Thus there exists an apparent anatomical and functional similarity between noradrenergic pathways postulated as generating P3b, and the histaminergic system thought to be involved in wakefulness and sleep. It therefore seemed likely that sedative H_1-antihistamines would change the amplitude or latency of P3b. The objective of this investigation was to test this possibility using triprolidine (sedative) and terfenadine (non-sedative), both well documented and clinically useful H_1-antihistamines. In addition, a range of psychomotor tests was included to provide a profile of impairment (Broadbent 1984).

Methods

Subjects

Twelve healthy male students volunteered to take part in this experiment and gave their informed consent. The protocol was approved by an Ethical Committee. Ages ranged from 19 to 24 (mean = 21) years and body weights from 66 to 87 (mean = 74) kg. Three subjects had taken H_1-antihistamines on previous occasions, but none used them clinically. Two subjects had had previous experience of ERP techniques. Before admission to the trial, subjects completed a questionnaire to exclude neurological deficit, relevant allergies, and current use of any drugs including tobacco. They also underwent a hearing test, and only subjects with normal thresholds (< 10 dB) in the 500–8000 Hz frequency range were included.

ERP recordings

Ag/AgCl electrodes were used with the vertex (Cz) as the active site referenced to linked earlobes. Impedance was kept below 5 kΩ. The amplifier band pass was 0.32–32 Hz. A post-stimulus sweep of 512 ms was averaged, using a Nicolet Med-80.

† It is with deep regret that we have to record that Miss Flora Swire was killed in the Lockerbie air disaster in December 1988

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Electrophysiological paradigm (the "oddball" task)

Binaural stimuli of 40 dB nHL and 60 ms in duration (including 10 ms rise and fall times) were presented with an interstimulus interval (ISI) of 1 s. Target tones (1050 Hz) and non-target tones (2140 Hz) were presented in a random order with a target probability of 0.1. The test lasted for approximately 8 min, during which period the subject reclined on a bed with eyes open and fixed on a point on the ceiling (to reduce artifacts caused by eye-muscle potentials). The subject was instructed to ignore non-target stimuli but selectively to attend to target stimuli and to depress a small hand-held pushbutton upon target detection. Speed and accuracy were equally stressed. ERPs were recorded and averaged separately for 35 target and 35 non-target presentations (distributed randomly among the total presented). Simple reaction time (SRT) was also recorded.

Performance psychomotor tests

Visual-Analogue Scales (VAS). Subjective assessments of impairment were measured using the VAS rating system of Bond and Lader (1974). Subjects had to rate themselves (by marking 10 cm scales) between the following pairs of extremes without access to previous sheets: Elated/Depressed, Interested/Bored, Sad/Happy, Sociable/Withdrawn, Discontented/Contented, Clear-headed/Muzzy, Dreamy/Attentive, Self-centered/Outward-going, Proficient/Incompetent, Antagonistic/Friendly, Quick-witted/Mentally slow, Lethargic/Energetic, Tense/Relaxed, Troubled/Tranquil, Alert/Drowsy, Feeble/Strong, Calm/Excited, Well Co-ordinated/Clumsy. Coefficients for psychomotor incoordination (VAS1) and anxiety (VAS2) were extracted from these scales.

Digit Symbol Substitution Test (DSST). This was taken from the Wechsler Adult Intelligence Scale (WAIS) (Wechsler 1955), the score being taken as the correct number of substitutions of figures for numbers in 90 s. In this and the digit span (DSp) test, equivalent new material was provided for each session.

Digit Span Test (DSp). In this simple recall task (again from the WAIS) paired spans of random digits were read to the subject, starting with 3 digits and increasing in number until 2 pairs had been incorrectly recalled. This was also done with the numbers repeated in reverse order. The score was the total number of correct spans (forward and backward).

Critical Flicker Fusion (CFF). The CFF is the frequency at which a flickering light gives rise to the subjective sensation of a steady light, provided caffeine, nicotine and alcohol are excluded (Smith and Misiak 1976). This frequency was measured using as stimulus a red stroboscope at a distance of 1 m, with a 2 mm diameter artificial pupil. The measurement was performed 6 times, 3 with rising and 3 with falling frequency, for each eye. A mean score of all 12 values was recorded.

Drugs

Single oral doses of two H_1-antihistamines were used: triprolidine hydrochloride (7.5 mg) and terfenadine (60 mg). Each subject received an identical capsule containing one drug or placebo on three occasions in a balanced, random order (using a Latin square design), each separated by at least three full days. The trial was double-blind.

Procedure

Before taking any drugs, subjects were required to practise all the tests to asymptote, each practice session being separated by 2–4 days. On the day before drug administration, alcohol was avoided from 08.00 hours, stimulant beverages from 18.00 hours and food from 24.00 hours (midnight). Subjects were instructed to go to bed at their usual times.

Drug ingestion took place at 08.00 hours and subjects were required to remain in the laboratory from that time until 13.00 hours. No food was permitted but water and decaffeinated coffee were provided. Measurements were made between 09.00 and 09.30 hours and between 12.00 and 12.30 hours (i.e., $1–1^1/_2$ h and $4–4^1/_2$ h after a dose). During each session (including practices) the tests were performed in the following order: (i) ERP (and SRT); (ii) VAS; (iii) DSST; (iv) DSp; (v) CFF; and (vi) ERP and SRT (repeat).

Data analysis

ERP and SRT data. All analysis was performed on averaged waveforms. In each case the response to non-target stimuli was subtracted from the response to target stimuli to yield the difference wave. The three ERP channels and SRT data were stored on disk for off-line analysis. The baseline was defined as the mean voltage over the first 40 ms of the recording. Peak amplitudes (from this baseline) and latencies (from the stimulus onset) were measured for all the manifest component peaks (designated N1, P2, N2 and P3b), using the cursors incorporated into the software of the averager, as was average reaction time for each run.

Statistics. Drug effects were separated by morning (1.0–1.5 h post-dosage) and afternoon (4.0–4.5 h after drug) session and analysed for each test score using the MANOVA package available on SPSS, univariate results being corrected for significance levels using the Greenhouse-Geisser Epsilon (GGE) correction. Post-hoc comparisons between drugs were performed using Tukey's multiple comparison procedure (if $GGE > 0.7$) or multiple *t*-tests at a corrected significance level (if $GGE < 0.7$). Time effects were similarly analysed under placebo conditions, comparing morning and afternoon session results.

Results

ERP data and performance

Figure 1 shows an example average from one subject (HD) for 70 sweeps per stimulus type by drug class. The difference wave (target minus non-target response) is also shown and the manner in which P3b amplitude and latency measures were obtained. From the reaction time data, performance was virtually error free on target identification (99.8%), so errors due to stimulus misclassification may safely be ignored.

Antihistamine effects on ERPs and SRT

Table 1 gives mean P3b amplitude and latency and SRT measures with SEs for repeated measures ANOVA by drug

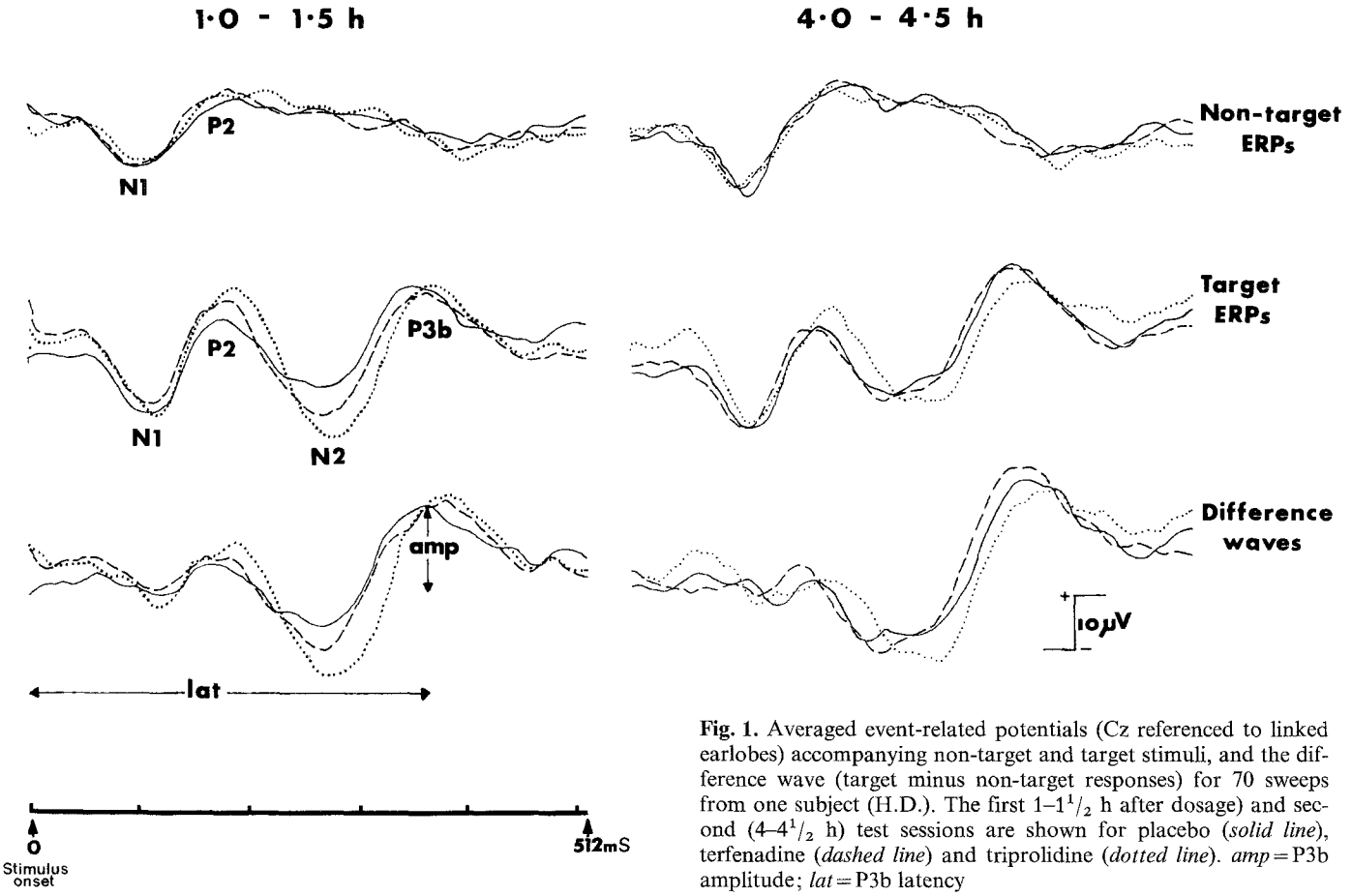

Fig. 1. Averaged event-related potentials (Cz referenced to linked earlobes) accompanying non-target and target stimuli, and the difference wave (target minus non-target responses) for 70 sweeps from one subject (H.D.). The first 1–1$^1/_2$ h after dosage) and second (4–4$^1/_2$ h) test sessions are shown for placebo (*solid line*), terfenadine (*dashed line*) and triprolidine (*dotted line*). *amp* = P3b amplitude; *lat* = P3b latency

Table 1. Latency and amplitude of P3b component of the ERP and SRT by drug class and test session. The value given is the group average ± standard error

		P3b amplitude (uV)	P3b latency (ms)	SRT (ms)
Placebo	1.0–1.5 h	16.4±2.2	355± 7	297± 8
	4.0–4.5 h	14.9±2.1	356± 8	298±10
Triprolidine	1.0–1.5 h	15.5±2.3	365± 9	309±10
	4.0–4.5 h	15.0±2.4	366±11	304± 9
Tefenadine	1.0–1.5 h	16.2±2.0	361± 7	298± 8
	4.0–4.5 h	15.3±2.9	351± 9	301± 9

class and test session. Although a slight increase in mean P3b latency and SRT with the sedative antihistamine, triprolidine, was noted, this was not significant. None of the comparisons made, either between drugs or between test sessions, was significantly different. This result is also apparent from inspection of the ERP waveforms (Fig. 1). The other ERP components measured (N1, P2, N2) also showed no significant differences.

Psychomotor tests and H_1-antihistamines

Mean scores and SE, from the psychomotor tests are given in Table 2, with indications of significant comparisons from the MANOVA (corrected with the Greenhouse-Giesser Epsilon) and Tukey's multiple comparison procedure for post-hoc analysis. In the first test session (1–1$^1/_2$ h after dosage), triprolidine significantly increased VA1 (psychomotor incoordination $P<0.05$) and decreased digit symbol substitution ($P<0.01$) and critical flicker fusion ($P<0.01$) compared to placebo. Digit symbol substitution was also significantly decreased relative to terfenadine ($P<0.01$). By the second test session (4–4$^1/_2$ h after dose), only the comparison between triprolidine and terfenadine on the digit symbol substitution test remained significant ($P<0.05$). These results verify that triprolidine was producing a measurable CNS effect from 1 to 1$^1/_2$ h after ingestion.

Data were also analysed under placebo conditions, for evidence of differences between first and second test sessions. None of the comparisons made were significant using MANOVA, although VA2 score (anxiety coefficient) only just failed to reach significance ($P=0.056$).

Discussion

The results of this study show that although 7.5 mg triprolidine did produce a sedative effect from 1.0 to 1.5 h after dosage (as indicated by VAS, DSST and CFF scores) it did not at the same time alter the amplitude or latency of the P3b component of the ERP nor the SRT compared to placebo. Terfenadine 60 mg produced no sedative effect and did not change any of the test results compared to placebo.

The effects of the sedative H_1-antihistamine on VAS, DSS and CFF scores were similar to those obtained in

Table 2. Mean results ($N=12$) and standard errors from the psychomotor tests. VAS1 and 2 are visual analogue scale scores (psychomotor incoordination and anxiety respectively); DSST = digit symbol substitution test score; DSp = digit span score and CFF = critical flicker fusion frequency

		Scores				CFF (Hz)
		VAS1	VAS2	DSST	DSp	
Placebo	1.0–1.5 h	$+0.112\pm0.15$[a]	-0.670 ± 0.11	80.1 ± 2.9[b]	21.8 ± 1.2	35.1 ± 0.7[b]
	4.0–4.5 h	$+0.062\pm0.13$	-0.845 ± 0.08	79.4 ± 2.9	21.4 ± 1.0	35.1 ± 0.8
Triprolidine	1.0–1.5 h	$+0.589\pm0.13$[a]	-0.709 ± 0.11	75.4 ± 2.5[b,d]	21.8 ± 0.8	33.5 ± 0.6[b]
	4.0–4.5 h	$+0.140\pm0.13$	-0.892 ± 0.09	77.8 ± 2.7[c]	22.0 ± 0.9	34.1 ± 0.6
Terfenadine	1.0–1.5 h	$+0.235\pm0.12$	-0.735 ± 0.12	80.2 ± 2.5[d]	22.1 ± 1.0	34.6 ± 0.7
	4.0–4.5 h	-0.091 ± 0.10	-0.979 ± 0.05	80.7 ± 3.1[c]	23.2 ± 1.3	34.7 ± 0.8

[a] $P<0.05$; [b] $P<0.01$ for comparisons between triprolidine and placebo; and [c] $P<0.05$, [d] $P<0.01$ for comparisons between triprolidine and terfenadine using MANOVA and Tukey's multiple comparison procedure

other studies (e.g., Nicholson et al. 1982; Nicholson and Stone 1986), both of which also demonstrated terfenadine's lack of central action which has been attributed to its relative difficulty in crossing the blood-brain barrier. The deficits produced by triprolidine seemed to be non-specific sedation rather than a direct decrement in one particular skill, and it is thought the histaminergic system is more concerned with vigilance than the underlying state of sleep and wakefulness (Nicholson et al. 1985).

According to Herbert (1987) a test is more sensitive to vigilance impairment if it is familiar, lasts for a long time, demands sustained output and maintained concentration and is not perceived as interesting or novel. The P3b elicited in this two-stimulus oddball paradigm should thus have been highly susceptible to a general sedative effect of an H_1-antihistamine, as the task fulfils all of those criteria. There are several possible explanations for the lack of effect of H_1-antihistamines on P3b. Firstly, P3 latency is thought to reflect cognitive processing time (Brown et al. 1982), and given the very simple task requirements, set to maximise P3b amplitude and minimise latency, it is conceivable that the level of task demand was so low as to remain unaffected by so subtle an alteration in overall preparedness. Secondly, as Broadbent (1984) pointed out, drugs may affect the mechanism that selects strategies rather than the execution of a strategy. In such a case, the initial practise sessions under no drug conditions could have rendered the chosen strategy sufficiently well learned as to override any drug-induced change. A third possibility is that the timing of the test sessions (1.0–1.5 and 4.0–4.5 h after drug administration) missed any changes in electrophysiology which could have been earlier or later than alterations in psychomotor tests.

However, the most favoured explanation is that histamine H_1-receptors are not involved in the generation of P3b. It is possible, but unlikely, that H_2 or H_3 histamine receptor sub-types are involved. Drowsiness due to H_1-antihistamines has been attributed to various mechanisms including occupation of central α-adrenoceptors, although this is not correlated well with sedation for this group of drugs (Nicholson and Stone 1982). So if the P3b has a noradrenergic generator also involved with control of arousal, this would explain why the H_1-antihistamine triprolidine (which has no significant α-adrenoceptor blocking potency; A.W. Peck, personal communication) failed to alter this component, and why other sedative agents, such as nitrous oxide, which exert effects on many neurotransmitter systems, do alter P3b (Fowler et al. 1988). In other words it is those parts of arousal mechanisms mediated through α-adrenoceptors which have led to the observation that P3b is susceptible to attention and arousal. Consistent with this is the observation that clonidine significantly decreases P3b amplitude (Duncan and Kaye 1986), and recent papers (e.g., Pineda et al. 1986) have suggested that P3b is generated in the cortex by the action of noradrenergic locus coeruleus (LC) neurones. The parallels between LC and psychophysiological correlates of P3b are carefully summarised in Courchesne et al. (1987).

In conclusion, the oddball parameters, practise sessions and timing of tests could account for the lack of effect of a sedative H_1-antihistamine on the P3b component of the ERP. However, the most likely explanation is that adrenoceptors and not histamine receptors are those most closely involved in the generation of P3b.

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References

Bond A, Lader MH (1974) The use of analogue scales in rating subjective feelings. Br J Med Psychol 47:211–218

Broadbent DE (1984) Performance and its measurement. Br J Clin Pharmacol 18:5s–9s

Brown WS, Marsh JT, Larue A (1982) Cognitive performance and P300 latency correlation in older normal adults. Psychophysiology 19:309

Bye C, Dewsbury D, Peck AW (1974) Effects on the human central nervous system of two isomers of ephedrine and triprolidine, and their interaction. Br J Clin Pharmacol 1:71–78

Cant BR (1980) Somatosensory and auditory evoked potentials in patients with disorders of consciousness. In: Desmedt JE (ed) Progress in Clinical Neurophysiology. vol 7. Clinical Uses of cerebral, brainstem and spinal somatosensory evoked potentials. S. Karger, Basel, pp 282–291

Clarke CH, Nicholson AN (1978) Performance studies with antihistamines. Br J Clin Pharmacol 6:31–36

Cooper R, Pocock PV, McCallum WC, Papakostopoulos D (1978) Potentials associated with the detection of infrequent events in a visual display. In: Otto D (ed) Multidisciplinary perspectives in event-related brain potential research (EPA-600/9-77-

043). US Government Printing Office, Washington DC, pp 189–193

Courchesne E, Courchesne RY, Hillyard SA (1978) The effect of stimulus deviation on P3 waves to easily recognised stimuli. Neuropsychologia 16:189–199

Courchesne E, Elmaisian R, Yeung-Courchesne R (1987) Electrophysiological correlates of cognitive processing: P3b and Nc, basic, clinical and developmental research. In: Halliday AM, Butler SR, Paul R (eds) A textbook of clinical neurophysiology. Wiley, New York, pp 645–676

Duncan CC, Kaye WH (1986) Effects of an alpha-2 adrenergic agonist on information processing: an electrophysiological analysis. In: Rohrbaugh JW, Johnson R, Parasuraman R (eds) Eighth International Conference on Event-Related Potentials of the Brain (EPIC VIII). Stanford, CA, USA, pp 69–71

Faingold CL (1978) Antihistamines as central nervous system depressants. In: Rocha e Silva M (ed) Handbook of experimental pharmacology, vol. XVIII/2. Springer, Berlin Heidelberg New York Tokyo, pp 561–573

Fowler B, Kelso B, Landolt J, Paulier C (1988) The effect of nitrous oxide on P300 and reaction time. Electroencephalogr Clin Neurophysiol 69:171–178

Garbarg M, Barbin G, Llorens C, Palacios JM, Pollard H, Schwartz JC (1980) Recent developments in brain histamine research: pathways and receptors. In: Essman WB (ed) Neurotransmitters, receptors and drug action. Spectrum, pp 179–202

Herbert M (1987) The duration of postanaesthetic mental impairment. In: Hindmarch I (ed) Aspects of recovery from anaesthesia. Wiley, London

Hill SJ, EMson PC, Young JM (1978) The binding of [^{3}H] mepyramine to histamine H_1 receptors in guinea-pig brain. J Neurochem 31:997–1004

Hillyard SA, Kutas M (1983) Electrophysiology of cognitive processing. Annu Rev Psychol 34:33–61

Kutas M, McCarthy G, Donchin E (1977) Augmenting mental chronometry: the P300 as a measure of stimulus evaluation time. Science 197:792–795

Nicholson AN (1979) Effect of the antihistamines, brompheniramine maleate and triprolidine hydrocloride, on performance in man. Br J Clin Pharmacol 8:321–324

Nicholson AN, Stone BM (1982) Performance studies with the H_1-histamine receptor antagonists, astemizole and terfenadine. Br J Clin Pharmacol 13:199–202

Nicholson AN, Stone BM (1986) Antihistamines: impaired performance and the tendency to sleep. Eur J Clin Pharmacol 30:27–32

Nicholson AN, Smith PA, Spencer MB (1982) Antihistamines and visual function: studies on dynamic acuity and the pupillary response to light. Br J Clin Pharmacol 14:683–690

Nicholson AN, Pascoe PA, Stone BM (1985) Histaminergic systems and sleep: studies in man with H_1 and H_2 antagonists. Neuropharmacology 24:245–250

Pineda JA, Foote SL, Neville H (1986) Effects of noradrenergic locus coeruleus lesions on squirrel monkey event-related potentials. In: Rohrbough JW, Johnson R, Parasuraman R (eds) 8th Int Conf on Event-Related Potentials of the Brain (EPIC VIII). Stanford, CA, USA, pp 358–387

Quach TT, Duchemin AM, Rose C, Schwartz JC (1979) In vivo occupation of cerebral histamine H_1-receptors evaluated with ^{3}H-mepyramine may predict sedative properties of psychotropic drugs. Eur J Pharmacol 60:391–392

Rose C, Quach TT, Llorens C, Schwartz JC (1982) Relationship between occupation of cerebral H_1-receptors and sedative properties of antihistamines. Assessment in the case of terfenadine. Arzneimittelforschung 32:1171–1173

Roth WT, Ford JM, Krainz PL, Kopell BS (1978) Auditory evoked potentials, skin conductance response, eye movement, and reaction time in an orienting response paradigm. In: Otto D (ed) Multidisciplinary perspectives in event-related brain potential research (EPA-600/9-77-043). US Government Printing Office, Washington, DC; pp 209–214

Smith JM, Misiak H (1976) Critical flicker fusion (CFF) and psychotropic drugs in normal human subjects – a review. Psychopharmacology 47:175–182

Squires KC, Donchin E, Herning RI, McCarthy G (1977) On the influence of task relevance and stimulus probability on event-related potential components. Electroencephalogr Clin Neurophysiol 42:1–14

Uzan A, LeFur G, Malgouris C (1979) Are antihistamines sedative via a blockade of brain H_1 receptors? J Pharm Pharmacol 31:701–702

Wechsler D (1955) Manual for the Wechsler adult intelligence scale. Psychological Corporation, New York

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