THE HISTAMINERGIC SYSTEM OF THE BRAIN: ITS ROLES IN AROUSAL AND AUTONOMIC REGULATION

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Introduction. Histaminergic neurones are located in the tuberomammillary nucleus (TMN) of the posterior hypothalamus and project to most areas of the cerebral cortex, cerebellum, hypothalamus, and many brain stem nuclei (1,2). The central histaminergic neurones have important roles in the regulation of arousal, endrocrine and autonomic functions.

The ascending histaminergic projection exerts a powerful alerting effect on the neocortex, via the activation of H_1 histamine receptors (1,2,3). Recently it has been shown that the ascending histaminergic system is one of the most important alerting systems of the brain, mediating the sedative effects of GABAergic (e.g, muscimol, propofol and pentobarbitone) (4) and of noradrenergic (e.g, dexmedetomidine) (5) anaesthetics. It has been proposed that the activity of the TMN is essential to the maintenance of wakefulness. In sleep, the activity of the TMN is switched off by a GABAergic input originating from the ventrolateral preoptic nucleus (VLPO) of the hypothalamus. In fact, in order to maintain wakefulness, it is important to switch off the activity of the VLPO: this is accomplished by the activation of a noradrenergic inhibitory input from the locus coeruleus (5). GABAergic anaesthetics act by activating inhibitory GABA receptors in the TMN, whereas noradrenergic anaesthetics act by switching off the locus coeruleus via the activation of inhibitory alpha-2 adrenoceptors (autoreceptors) on locus coeruleus neurones (6). The orexinergic neurones of the lateral hypothalamic area (LHA) play an important role in the maintenance of wakefulness, possibly by activating the TMN either directly (7), or indirectly via the locus coeruleus (8). The activation of the locus coeruleus would enhance the noradrenergic inhibition of the VLPO, which in turn would lead to the disinhibition of the TMN by the VLPO. The importance of the TMN in the maintenance of arousal is demonstrated by clinical observations: the hypersomnia observed in encephalitis lethargica by von Economo in the 1920s could be related to a discrete lesion of the posterior hypothalamus involving the TMN (1,3). Furthermore, the blockade of excitatory H1 receptors in the cerebral cortex may underlie the sedative effects of a number of drugs with affinity for H1 histamine receptors (e.g, first generation antihistamines, phenothiazine antipsychotics, tricyclic antidepressants).

The central histaminergic system also plays a role in autonomic regulation: it has been shown that the activation of central H_1 and H_2 histamine receptors results in an increase in sympathetic outflow (2,9).

Although the first generation antihistamines have well-documented sedative properties in humans, their effects on autonomic functions have not been studied in detail. In particular, it was of interest to examine how pupillary function is affected by these drugs, since the pupil is under a well-mapped-out dual sympathetic/parasympathetic regulation (6). Therefore, we have examined the pupillary effects of one such drug, diphenhydramine, and compared them with those of diazepam, a sedative drug with little effect on autonomic functions. It should be noted that diphenhydramine, like most first generation antihistamines, also block muscarinic cholinoceptors, an effect that may modify pupillary function.

Methods. Fifteen healthy male volunteers participated in three experimental sessions at weekly intervals in which they received (i) diphenhydramine 75 mg, (ii) diazepam 10 mg, (iii) placebo. The three treatments were administered in a balanced order according to a double-blind protocol. Pupil diameter was measured with a binocular pupillometer (Procyon, UK) under four light intensities (darkness, 6, 91, 360 Cd m^{-2}). Light reflex responses were evoked by green (peak wavelength 565 nm) light flashes (200 ms, 0.43 mW cm^{-2}); recordings were made with a binocular infrared television pupillometer (TVP 1015B, Applied Science Laboratories Waltham, MA. USA). The level of

alertness of the subjects was assessed using both subjective self-ratings, and measurement of critical flicker fusion frequency. The amplitude of the acoustic startle response evoked by 40 ms 115dB[A] 1kHz sound pulses was recorded from the orbicularis oculi muscle by EMG: it has been shown that this measure is reduced by sedative drugs (10). Finally, skin conductance was measured on the second and fourth digits of the left hand, as an index of sympathetic activity.

Results. Diphenhydramine caused a significant miosis at all four illumination intensities. The degree of miosis was the same at all illumination levels. Diazepam had no significant effect on pupil diameter. The amplitude of the pupillary light reflex response remained unaffected by the two drug treatments. Both active drugs decreased subjectively rated alertness. Although both drugs caused an increase in critical flicker fusion frequency, consistent with a sedative effect, this change failed to achieve statistical significance. Both drugs reduced the amplitude of the acoustic startle response and skin conductance.

Discussion. Both diphenhydramine and diazepam reduced subjectively-rated alertness and showed a tendency to increase critical flicker fusion frequency, consistent with a sedative effect of these drugs. The sedative effect of diphenhydramine is likely to reflect the blockade of excitatory H_1 histamine receptors in the cerebral cortex, thereby leading to attenuation of the wakefulness promoting effect of the TMN. It is an intriguing possibility that the sedative effect of diazepam may also have been partly mediated by the TMN: the benzodiazepine would have enhanced the inhibitory effect of GABAergic neurones in the VLPO on the histaminergic neurones of the TMN. Both drugs reduced the amplitude of the acoustic startle response, consistent with sedation. Both drugs reduced skin conductance, consistent with a reduction in sympathetic outflow. Although both diphenhydramine and diazepam reduced subjectively rated alertness, only diphenhydramine had a significant miotic effect. The diphenhydramine-evoked miosis is likely to be due to a sympatholytic effect, since the drug had no effect on the amplitude of the pupillary light reflex response, an index of parasympathetic activity. It should be noted that the preganglionic sympathetic neurones in the cervico-thoracic spinal cord, which are involved in pupillary control, receive inputs both directly from the hypothalamus and also via the noradrenergic neurones of the locus coeruleus. Therefore, the sympatholytic effect of diphenhydramine may reflect the blockade of excitatory H_1 receptors both in the hypothalamus (probably in the paraventricular nucleus) and in the locus coeruleus, two structures which receive rich histaminergic inputs from the TMN (1). Our observations suggest that central sympathetic outflow to the iris may be under tonic histaminergic control. The lack of effect of diphenhydramine on the light reflex response indicates that the drug did not exert any significant anticholinergic effect at the dosage used. The lack of effect of diazepam on pupil diameter is in agreement with previous reports (11), and is likely to reflect the relative resistance of the sympathetic control of the iris to the general sympatholytic effect of the drug (12). The present results indicate that there are differences in the abilities of sedative drugs to evoke miosis.

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