Afferent and Central Activating Effects of Histamine on the Brain

Previous investigations by CROSSLAND and MITCHELL[1], BOVET et al.[2], GOLDSTEIN et al.[3], MONNIER et al.[4] showed that histamine administered intravenously or intra-arterially has an activating effect on the brain, detectable as an electrographical arousal reaction. Since exogenous intravenous histamine does not pass the blood-brain barrier (in contrast to its precursor histidine) we have to elucidate the mechanism of its activating effect on the brain, when administered intravenously.

Method. For this purpose we infused with an automatic pump 1 mg of histamine dihydrochloride into the jugular vein at a constant flow of 1 ml/min during 30 min. We recorded concurrently the spontaneous electrical brain activities and quantified, with an automatic frequency analyser, the slow delta activities of the motor cortex. An increase of these delta activities means relaxation or sleep, whereas their decrease is symptomatic of arousal or alertness. For further specifications of the histamine waking mechanism, we analysed with a computer the *potentials evoked in the cortex* by electrical stimulation of the midbrain reticular formation, of the medio-central intralaminary thalamus and of the dorsal hippocampus. For each test we used a series of 5 rabbits and a series of 5 control animals.

Results. Histamine dihydrochloride i.v. infused during 30 min, at a total dose of 0.37 mg/kg, produces an EEG arousal reaction with decreased delta activities in the cerebral cortex (Figure 1A). This reaction, which out lasts the end of the infusion, is accompanied by a concurrent increase of the first potential evoked in the cortex by electrical stimulation of the midbrain reticular system (Figure 1B and C). We may therefore conclude that *histamine stimulates the reticulo-cortical activating projections concerned with arousal.*

During the EEG arousal reaction there is also an increase of the potentials evoked in the cortex by stimulation of the medio-central intralaminary thalamus. The first component of this evoked response is due to reticulo-cortical activating fibres running from the midbrain through this thalamic area to the cortex. Consequently, *histamine also stimulates the reticulo-thalamo-cortical activating projections.*

Histamine, i.v. infused, activates not only the reticulo-cortical and reticulo-thalamo-cortical projections to the neocortex, but also the hippocampo-cortical projections. Infact, this substance increases the first potential evoked in the neocortex by stimulation of the dorsal hippocampus. Therefore, *histamine* also *activates the paleocortical hippocampal system* involved in the EEG arousal reaction.

All these activating effects did not occur in the control animals, in which a tyrode-like solution was i.v. infused under the same conditions as histamine.

In order to specify further the activating mechanism of histamine, we investigated whether this substance acts, like *amphetamine*, on the unspecific afferent reticular system concerned with the regulation of wakefulness. According to BRADLEY and KEY[5] and BRADLEY[6], this system is stimulated by *amphetamine* at the site where collaterals from specific afferent fibres impinge on the unspecific afferent reticular neurones. *Histamine, like amphetamine*, elicits a strong EEG arousal reaction with decreased delta activities and a marked increase of the reticulo-cortical evoked potentials. Therefore, histamine seems to act on the unspecific afferent reticular system at the same site as amphetamine, that is where specific afferents impinge on the unspecific afferent system.

It remains to be investigated how i.v. histamine, which does not pass the blood-brain barrier, may activate the reticular waking system.

(A) *Afferent (reflex) activating effect of histamine.* Were the reticular activating system stimulated reflexly by histamine through nociceptive pain afferents running from the vessels and tissues to the brain stem, this effect should be suppressed by a non-narcotic analgesic like acetyl-salicylic acid.

Indeed, the reticulo-cortical evoked potentials, normally enhanced by i.v. histamine, are now significantly depressed by peroral analgesia with 100 mg/kg acetyl salicylic acid ($p < 0.025$). (Figure 2.) Infusion of this analgesic alone does not alter the previous evoked cortical activities. This *confirms that i.v. histamine stimulates reflexly* (partly by pain afferents, possibly also by chemoceptive afferents) the reticulo-cortical activating system.

(B) *Central activating effect of histamine.* In order to investigate the *central effects of histamine*, we infused with an automatic pump 0.05 mg/kg and 0.1 mg/kg of histamine

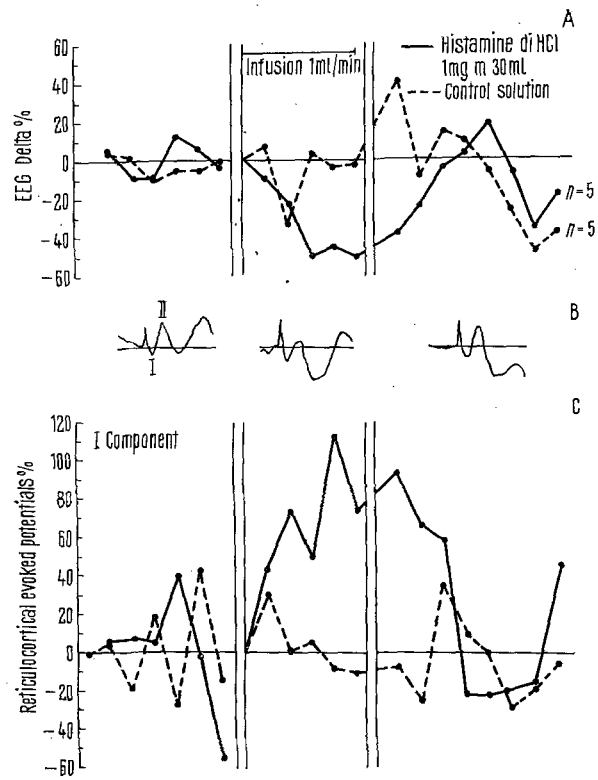

Fig. 1. Intravenous infusion of *histamine* produces: (A) EEG arousal reaction with decreased delta activities. (B and C) Increased amplitude of the reticulo-cortical evoked potentials (I component). This does not occur in the control animals.

[1] J. CROSSLAND and J. F. MITCHELL, J. Physiol. *132*, 391 (1956).

[2] D. BOVET, R. KOHN, M. MAROTTA and B. SILVESTRINI, Br. J. Pharmac. Chemother. *13*, 74 (1958).

[3] L. GOLDSTEIN, C. C. PFEIFFER and C. MUNOZ, Feds. Proc. *22*, 424 (1963).

[4] M. MONNIER, M. FALLERT and I. C. BHATTACHARYA, Experientia *23*, 21 (1967).

[5] P. B. BRADLEY and B. J. KEY, EEG clin. Neurophysiol. *10*, 97 (1958).

[6] P. B. BRADLEY, Int. Rev. Neurobiol. (C. C. PFEIFFER and R. SMYTHIES; Academic Press, New York, London 1968).

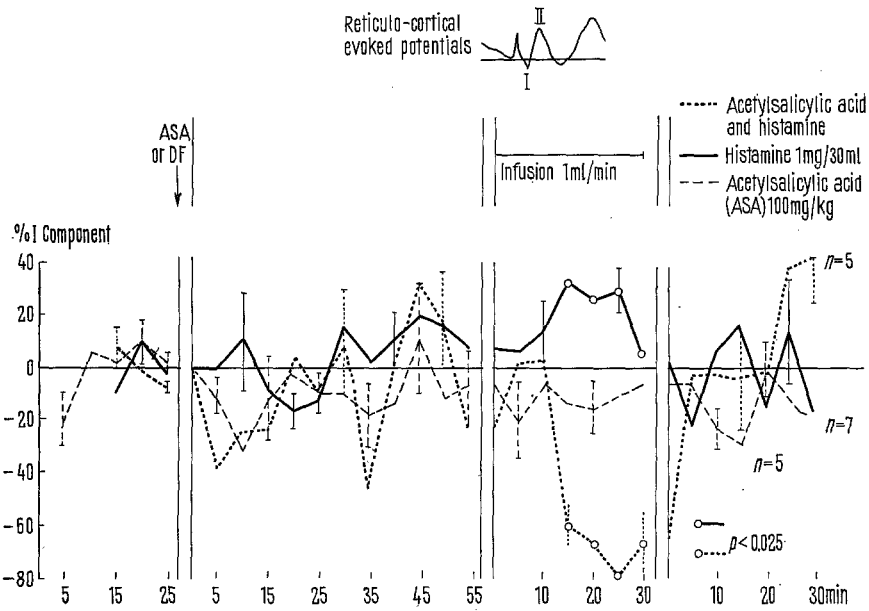

Fig. 2. The reticulo-cortical evoked potentials, enhanced by i.v. histamine (——), are markedly *depressed by peroral analgesia* with acetyl salicylic acid (. . . . .). Infusion of this analgesic alone does not alter the previous evoked cortical activities.

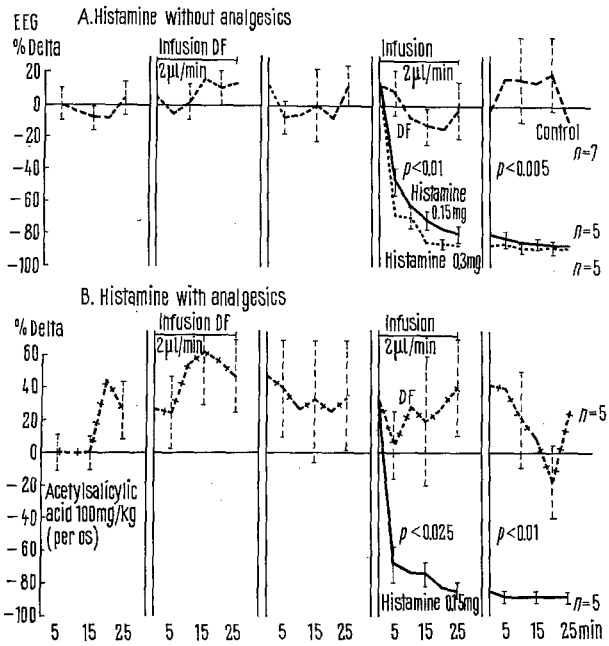

Fig. 3. The *waking effect* of intraventricular histamine (decreased delta activities in A) is *not abolished by analgesia* with acetyl salicylic acid per os in B. It is not due to reflex stimulation (pain), but to direct stimulation of activating brain centres.

di-HCl in 0.05 ml tyrode-like fluid of adjusted osmolarity during 30 min into the third ventricle of the rabbit.

Here again histamine induced a *marked EEG arousal reaction* with decreased delta activities. This waking effect is not of peripheral reflex origin; it is not due to painful afferents since it is not abolished by analgesia with acetyl salicyclic acid (Figure 3). *The activating effect of intraventricular histamine has a central origin*, due to direct stimulation of the surrounding reticulo-thalamic activating systems.

In *conclusion*, the waking effect of *intravenous histamine* (which does not pass the blood-brain barrier) must be explained reflexly by visceral afferents stimulating chiefly the reticular activating system and, to some extent also, the thalamo-cortical and hippocampal activating mechanisms. Part of the afferents are nociceptive pain inducing fibres, since their waking action is markedly reduced by analgesia.

The waking effect of *intraventricular histamine* infused into the third ventricle is central, and not attributable to pain, since it is not suppressed by analgesia[7].

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Effect of Dimethyl Sulfoxide on RNA Synthesis in S-180 Tumor Cells

Dimethyl sulfoxide (DMSO) has been found to affect a number of biological processes, both in vitro and in vivo. Concentrations of DMSO greater than 10% have been shown to inhibit protein synthesis in bone marrow cells in vitro[1]. This inhibition was found to be readily reversible by removal of the drug. NIEUWEBOER (in [2]) found that incorporation of leucine into the 10,000 *g* supernatant of rat liver homogenate was stimulated by 5–10% DMSO, but was inhibited at higher concentrations. ARCHER et al.[3] reported that DMSO caused dilatio

[1] M. J. ASHWOOD SMITH, Ann. N.Y. Acad. Sci. *141*, 45 (1967).
[2] E. GERHARDS and H. GIBIAN, Ann. N.Y. Acad. Sci. *141*, 65 (1967).
[3] J. M. ARCHER, K. B. SHILKIN, J. M. PAPADIMITRIOU and M. N. WALTERS, Proc. Soc. exp. Biol. Med. *126*, 354 (1967).