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Neuropharmacological effects of cystathionine and cysteine in cats

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The concentration of cystathionine in the brain and cerebrospinal fluid varies greatly in certain clinical conditions in which other sulphur-containing amino-acids are found in normal amounts (Berlow, 1967). There is much speculation regarding the significance of this amino-acid in the brain, so L-cystathionine HCl and its metabolic derivatives cysteine, homoserine and alpha-ketobutyric acid were administered into the left cerebral ventricle of cats to ascertain whether they produce any specific electroencephalograph (e.e.g.) and behavioural changes.

Acute experiments were performed on nine *encéphale isolé* preparations. Each of these animals was given the different amino-acids and control injections of solutions of HCl of equivalent pH and the saline vehicle. Chronic experiments were performed on two cats with implanted intraventricular cannulae and cortical recording electrodes.

In the *encéphale isolé* preparation, 2 mg of cystathionine produced an e.e.g. synchrony; whereas, 1 mg of cysteine caused an e.e.g. activation lasting about 5 min, which was accompanied in most animals by overt signs of intense alerting. In addition, cystathionine, given 2 min before, inhibited or blocked the e.e.g. activation normally induced by cysteine. Thus, solutions of these two amino-acids, which have a similar pH (1·9–2·0), produced diametrically opposite effects. Different doses in the range 1–10 mg of homoserine and alpha-ketobutyric acid failed to produce these effects, nor did the injection of solutions of HCl of equivalent pH, or normal saline.

Preliminary experiments with the chronic preparations indicate that cystathionine (5 mg) may shorten the onset of sleep " spindles " and the behavioural appearance of sleep to approximately 40% of control. In contrast, cysteine (5 mg) induced an e.e.g. activation pattern, behavioural hyperactivity, and delayed the onset of sleep about 2·5 times that of control. Homoserine and alpha-ketobutyric acid in doses of 5 mg failed to induce significant e.e.g. or behavioural changes.

The results of these experiments provide evidence in support of the hypothesis that in the free form cystathionine, and its cleavage product cysteine, may be important to normal brain function and play a role in the pathogenesis associated with certain inborn errors of metabolism.

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Some actions of nicotine and tobacco smoke on activity of the cerebral cortex and olfactory bulb

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Small amounts of nicotine (1–4 μg/kg) injected intravenously in anaesthetized cats caused changes in cortical activity and acetylcholine release from the cerebral cortex (Armitage, Hall & Sellers, 1969). These amounts of nicotine were probably similar to those absorbed by the cigarette smoker who inhales. In the present studies a direct comparison of the actions of nicotine and tobacco smoke has been made on the brain electrical activity of the unanaesthetized cat *encéphale isolé* preparation (Bremer, 1936). The *encéphale isolé* exhibits behavioural signs of sleep and wakefulness. Actions of nicotine, cigarette smoke and carbon monoxide have been compared on preparations in the sleeping state, exhibiting a synchronized electrocorticogram consisting of slow waves and spindle activity. Samples (2 ml.) of a 25 ml. puff of smoke were introduced into the lungs at 30 sec intervals from a smoking simulator (Armitage, Hall & Heneage, 1969). This volume of smoke contains approximately 7 μg nicotine (approximately 2 μg nicotine/kg for a 3 kg cat). Samples (2 ml.) of 5% carbon monoxide were introduced into the lungs using the same simulator. Doses of nicotine and other drugs, calculated as base, were injected intravenously.

Samples (2 ml.) of smoke introduced into the lungs caused desynchronization of electrocortical activity and behavioural arousal. The electrocorticogram consisted of low voltage fast waves indicative of cortical activation, the eyes opened, and movements of the ears, jaws and vibrissae were sometimes observed. These effects were matched in the same experiment by intravenous injections of nicotine, 2 μg/kg every 30 sec. Applications of smoke or injections of nicotine required to produce these effects varied between experiments.

These changes, caused by nicotine or smoke, were not modified by pretreatment with chlorpromazine (2·0–4·0 mg/kg). Atropine (0·3 mg/kg), however, prevented the cortical activation, but not the behavioural arousal. The effects of smoke on cortical activity were generally not blocked, but only reduced by the administration of mecamylamine (2 mg/kg). In contrast, the effects of nicotine were blocked by mecamylamine, suggesting the presence in smoke of other agents capable of exerting a pharmacological response. Cigarette smoke contains approximately 5·0% carbon monoxide. Introduced into the lungs of cats pretreated with mecamylamine, 2 ml. samples of 5% carbon monoxide caused changes in cortical activity similar to those caused by smoke. The most consistent effect of smoke and carbon monoxide was the appearance of spindle bursts and low voltage fast waves.

Samples (2 ml.) of smoke applied to the nostrils caused the occurrence in the olfactory bulb of a discharge or burst of "induced" waves. This discharge was sometimes accompanied by a transient period of cortical activation. This contri-