The gastric ulcers, found in a small percentage of animals, appeared to be typical stress ulcers, similar to those produced by exertion[9] and restraint[10], and probably resulted from the severe stress of digitoxin intoxication. On the other hand, the duodenal ulcers produced by digitoxin are not due to stress, since other types of stress, e.g. restraint, exertion, exposure to cold, starvation, fail to produce duodenal ulcers while regularly producing gastric ulcers. Therefore, the duodenal ulcers described in the present study are due to a specific effect of digitoxin.

Résumé. L'administration i.p. de digitoxine (0,75 mg) à des rats femelles de 220 g produit en 3 à 4 jours un ulcère duodénal chez 50% des animaux. L'estomac reste intact. Les rats mâles sont presque totalement réfractaires. La digitoxine distent aussi l'estomac par rétention alimentaire. La pathogénie de l'ulcère duodénal par la digitoxine reste inexpliquée.

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Anhydrotic Effect of Benzodiazepines in Mice

Benzodiazepines are not believed to inhibit secretion; however we have been able to show an inhibitory effect of the drugs on palmar sweating in mice.

Methods. Swiss mice weighing 16–20 g, randomized into groups of 10, were used in accordance with a method already fully described[1]. The anhydrotic effect was assessed by the inhibition of palmar skin conductivity (IPSC %). The benzodiazepines tested were administered in increasing doses; the animals of each group all received the same concentration. The drugs were given i.p. as a suspension in carboxymethylcellulose 20 min before reading the PSC.

Results. Administration of benzodiazepines to mice resulted in IPSC secondary to an inhibition of sweating. This IPSC is dosebound, as can be seen from the graphs of the regression equations in the Figure.

Calculated from the corresponding regression equations, the doses (mg/kg) producing a 50% inhibition of the conductivity (IPSC 50) as follows: nitrazepam: 3.82 (3.09–4.95); lorazepam: 4.87 (3.62–7.50); diazepam: 5.21 (3.57–9.56); clorazepate: 37.61 (15.04–129.30); oxazepam: 46.98 (22.0–128.90); chlordiazepoxide: 54.19 (24.70–143.10); tetrazepam: 72.10 (37.52–156.90); medazepam: 105.10 (25.55–866.90).

Discussion. The occurrence of IPSC by benzodiazepines is established by the preceding regression equations. Now, many writers agree that PSC depends on the intensity of sweating[2–7], so this IPSC can be interpreted as an inhibition of palmar sweating (IPS). If this is so, what mechanism is involved in the phenomenon?

Actually, it can hardly be said that benzodiazepines have a noticeable anticholinergic effect. Indeed the antagonistic activity of diazepam on acetylcholine in the guinea-pig ileum test is 20,000 times lower than that of atropine[8].

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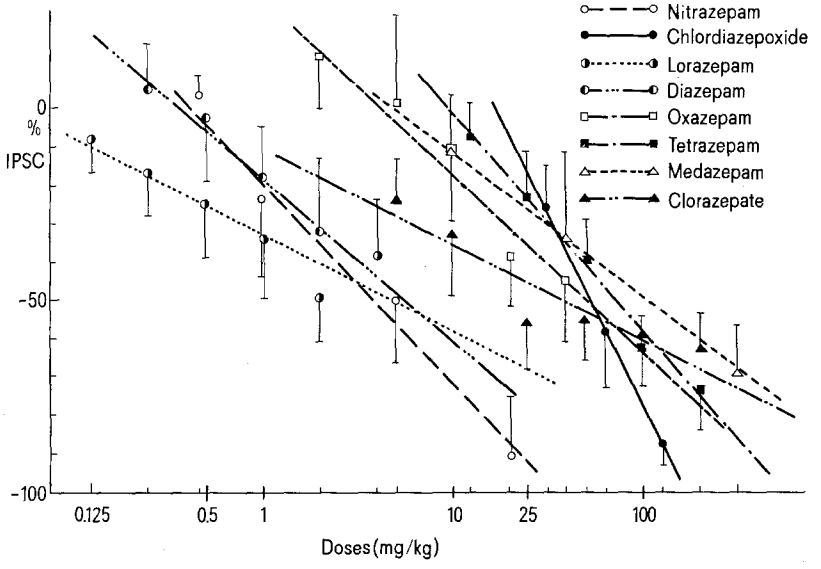

Dose-related inhibition of palmar skinconductivity (IPSC %) by benzodiazepines.

On the other hand, when one considers the inhibition of the peripheric cholinergic effects of oxotremorine in mice, the antagonistic activity of diazepam is only 10 times lower[8] than that of atropine. However, according to our experimental results the IPSC 50 of atropine is 0.12 mg/kg, which means that diazepam has an anhydrotic activity 43.4 times lower than atropine. The most active and the least active benzodiazepines tested on PSC – nitrazepam and medazepam – are respectively 31.8 and 876 times less active than atropine. So the hypothesis of an anticholinergic mechanism to explain the antisweating effect of benzodiazepines appears to be ruled out. Could this phenomenon be attributable to the α-adrenolytic activity of benzodiazepines[8–10]? Indeed α-adrenolytics likewise present an IPS[11]. The IPSC 50 of moxisylyte and hydergine are respectively 32.32 and 13.95 mg/kg and are therefore closer to those of benzodiazepines. Finally, one must not discount the possibility that the IPS of benzodiazepines originates centrally on account of the central depressive activity of these drugs. Indeed, hypnotics likewise present an IPS. The IPSC 50 of phenobarbital, pentobarbital and methaqualone are respectively 53.71, 27.90 and 27.92 mg/kg[12].

Résumé. Les benzodiazépines inhibent la sécrétion palmaire cutanée chez la souris proportionnellement à la dose administrée. Les différents mécanismes (cholinergique, α-adrénergique, central) qui peuvent être en jeu sont discutés.

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The Effect of Hydrocortisone on Tension and Cyclic AMP Metabolism in Tracheal Smooth Muscle

The mode of action of corticosteroids in treatment of bronchial asthma is obscure. In high concentrations, corticosteroids increased the β-adrenoceptor response of isolated human bronchial muscle[1,2]. The relaxation following stimulation of β-adrenoceptors in bronchial[3] as well as in vascular[4,5] and intestinal[6] smooth muscles is probably mediated by cyclic AMP. The nucleotide probably induces relaxation by reducing the free myoplasmic Ca^{2+} concentration by stimulating sequestering of Ca^{2+} to microsomal fractions[7]. This work was performed to investigate if glucocorticoids had any relaxing action and whether they influenced the cyclic AMP metabolism of tracheal and bronchial smooth muscles.

The action of hydrocortisone (Hydrokortisonsuccinat®, Roussel) was tested on human bronchial, muscles tracheal rings from guinea-pig and bovine trachea. The preparations were suspended in Krebs bicarbonate buffer aerated with 95% O_2 and 5% CO_2 at 37 °C. The isometric muscle tension was measured by Grass FT 03 transducers and registered on a Grass polygraph Model 7. In all these preparations, the effect of hydrocortisone was tested in a concentration range of 5×10^{-7}–5×10^{-5} *M* both on spontaneous tension and on histamine contracted muscles. The human bronchial muscle was most sensitive to hydrocortisone; in a concentration of 1.0 μ*M* a complete relaxation was produced both in muscles with spontaneous tone (Figure 1) and in muscles contracted by histamine (1×10^{-6} g/ml). In tests on bovine and guinea-pig trachea, higher concentrations of hydrocortisone were needed (Figure 1). If the preparations were pretreated with the β-adrenoceptor blocking agent sotalol (1.2×10^{-5} g/ml), the relaxing effect of hydrocortisone was decreased by about 50%. The relaxing effect of isoprenaline on guinea-pig (Figure 2) and bovine tracheal muscle (Figure 3) was potentiated if the muscles were pretreated with hydrocortisone in a concentration of 6×10^{-5} *M*.

The effect of hydrocortisone, or a combination of hydrocortisone and isoprenaline, was studied on cyclic AMP content and tension of bovine tracheal muscles, which had been suspended for 60 min in Krebs buffer solution. The muscles were frozen in frigen 12 and solid CO_2 at fixed times after administration of the drugs. The frozen tissues were homogenized in 5% trichloroacetic

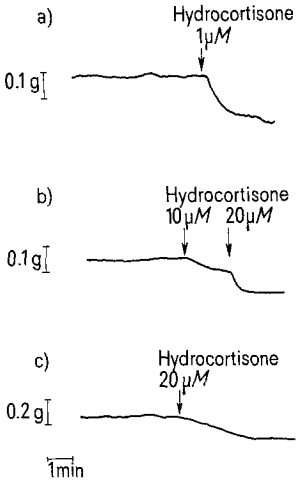

Fig. 1. The relaxing effect of hydrocortisone on different smooth muscle preparations with spontaneous tone. a) Segmental bronchi from humans. b) Tracheal rings from guinea-pig. c) Bovine tracheal muscle.

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