of the drug that they could comfortably tolerate. By giving the subjects control as to the amount of drug to be injected and by the constant recording of vital signs, we insured the safety and confidence of the volunteers. Likewise, progressive administration of the drugs mimics the actual pattern of marihuana use, since it is most frequently inhaled until the user decides that he has reached his desired level of 'high'. Variable times of placebo injection were used ranging from 15 to 25 min, and the subjective ratings were always base line indicating that there were no placebo responses under our experimental conditions.

Results. After the placebo injection, Δ^9-THC was infused at the rate of 0.2 mg/min (0.92 ml/min) until the subject decided that he had achieved his desired level. Administration of cannabinol and cannabidiol at this rate of infusion was ineffective, and, therefore, the rate of injection was increased to 1.2 mg/min (6.0 ml/min) for cannabinol and 1,78 mg/min (9.0 ml/min) for cannabidiol.

The Figure illustrates the results of these experiments. It can be seen that the initial perception of drug effect by the subjects occurred with a small amount of Δ^9-THC, a large amount for cannabinol, and cannabidiol did not produce a noticeable effect. This is also true for the amount of cannabinoid necessary to accelerate the heart over 25% of the basal rate. The total dose of Δ^9-THC tolerated by the subjects was relatively small and produced in every instance intense psychological and physiological effects. Thus, subjects invariably reported never having been so 'high' before by smoking either marihuana or hashish. In contrast, the total dose of cannabinol infused was large, and the subjects never asked for the infusion to be terminated. At the end of the experiment they reported their experience as mild and enjoyable, and they stated that they had been 'higher' previously with either the smoking of marihuana or hashish. Cannabidiol at the large dose infused did not produce any psychological or physiological effects.

In conclusion, contrary to the results obtained in the Rhesus monkey, we have found that cannabinol is capable of producing a marihuana-like 'high' although the doses necessary for it are several orders of magnitude larger than those of Δ^9-THC. This finding indicates the need for caution in extrapolating results obtained in animal experimentation to man[3].

Resumen. Se hizo un estudio comparativo de la actividad del Δ^9-tetrahidrocannabinol, cannabinol, y cannabidiol en producir efectos similares a la marihuana cuando son inyectados i.v. a humanos. Estas substancias son los componentes predominantes de la marihuana o del hashish. Se encontro que a las dosis inyectados cannabidiol no tiene ninguna potencia, y que cannabinol es capaz de producir efectos tipicos de la marihuana, aunque a dosis varias veces mas grandes que las del Δ^9-tetrahidrocannabinol.

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Effect of Calcium and Temperature on Histamine Release from Pig Lung by Compound 48/80[1]

Histamine is released when mast cells are treated with compound 48/80, or sensitized and challenged with a specific antigen. When rat peritoneal mast cells are used as the model system, both types of histamine release have several features in common. The release occurs without any obvious disruption of the mast cell membrane[2], requires extracellular calcium[3], and is completely inhibited by cooling to 5 °C[4]. Calcium ions are also required for the anaphylactic release of histamine from chopped guinea-pig lung[5], human leucocytes[6], and rabbit basophil leucocytes[7]. In view of the importance of histamine in allergic reactions and its consequent effect on bronchial smooth muscle, it seemed appropriate to see whether 48/80 induced histamine release from chopped lung was dependent on calcium and was affected by low temperatures. This study shows that histamine release by compound 48/80 from pig lung is not dependent on the presence of extracellular calcium and is only partially inhibited by lowering the temperature to 4 °C.

Materials and methods. Tyrode buffer pH 7.4 was freshly prepared from stock solutions at the beginning of each experiment and contained (mM) NaCl 136.7, KCl 2.6, $MgCl_2$ 0.49, $NaHCO_3$ 0.9, NaH_2PO_4 0.29, glucose 5.55. Calcium was added as required in concentrations given in the text. Compound 48/80 was obtained from Burroughs Wellcome Co. (USA) Inc., Tuckahoe, New York. Pig lung was obtained from a local abbattoir and placed in regular or calcium free Tyrode immediately. Each experiment was performed on a single lung. Tissue preparation and histamine extraction were carried out as described previously[8,9]. In all experiments 0.5 g of chopped lung tissue was incubated in Tyrode buffer in a total volume of 5 ml. All incubations were performed in triplicate. Incubations at low temperatures were conducted in the refrigerator. Reagent blanks, tissue controls and an internal histamine standard curve (0.2–1.0 µg histamine base) were also incubated simultaneously. Histamine was determined by the fluorimetric method of

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Effect of calcium and temperature on spontaneous and 48/80 induced histamine release from pig lung

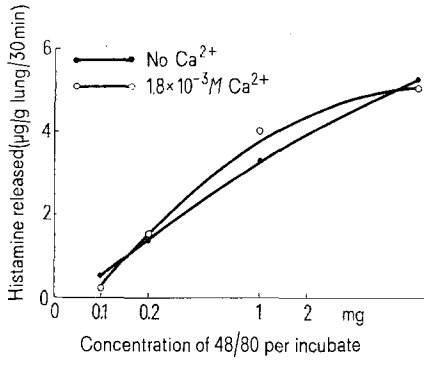
	Histamine released (μg/g lung/30 min) 37 °C		4 °C	
$[Ca^{2+}]$	Spontaneous	48/80 (2 mg)[a]	Spontaneous	48/80 (2 mg)[a]
0	1.21 ± 0.23 (4)	5.29 ± 0.57 (4)		
1.8×10^{-3}	1.11 ± 0.16 (3)	5.12 ± 0.67 (3)	0.83 ± 0.09 (3)	2.11 ± 0.28 (3)
1.8×10^{-2}	1.16 ± 0.29 (3)	2.79 ± 0.51 (3)		

Figures are means ± S.E.M. Figures in parentheses refer to number of experiments. [a]Corrected for spontaneous release. Average total histamine was 28.52 (16.2–41.5) μg/g lung, $n = 5$.

SHORE et al.[10]. The data are expressed as μg histamine base released per g wet weight of chopped lung.

Results and discussion. Compound 48/80 released histamine from chopped pig lung in a dose dependent manner both in the presence and absence of calcium (Figure). There was no difference in the amount of histamine released either spontaneously or with 48/80 in the absence or in the presence of 1.8×10^{-3} *M* calcium (Table). When the calcium concentration was increased to 1.8×10^{-2} *M* the amount of histamine released spontaneously and with 48/80 was inhibited (Table). The amount of histamine released in the presence of 1.8×10^{-3} *M* calcium was reduced when the incubation took place at 4 °C compared to that released at 37 °C (Table).

Histamine release from chopped lung by compound 48/80 differs from anaphylactic histamine release from this tissue in that the release has a longer time course[8], calcium is not required, and the release is not completely abolished by low temperatures. The concentration of 48/80 required for the minimum detectable amount of histamine release from chopped lung from several species is 2 to 3 orders of magnitude higher than that required for histamine release from rat peritoneal mast cells[8,11]. In contrast, the amount of antigen required to release histamine from sensitized mast cells and chopped guinea-pig lung is of the same order of magnitude[2,5]. It is thus possible that histamine release occurs by 2 mechanisms. 1. Release by low concentrations of 48/80 and in anaphylaxis is by a calcium dependent mechanism. 2. Release by high concentrations of 48/80 as required for chopped lung is by a different calcium independent mechanism. Thus histamine release from chopped lung by compound 48/80 may not be a useful model for the study of anaphylactic histamine release from this tissue.



Histamine release by various concentrations of 48/80 in the presence and absence of calcium. The data are corrected for spontaneous release.

Zusammenfassung. Es zeigt sich, dass die anaphylaktische Histaminausschüttung Calcium benötigt und bei niedriger Temperatur vollkommen gehemmt wird. Bei Zugabe der Substanz 48/80 erweist sich die dadurch hervorgerufene Histaminausschüttung als dosisabhängig und benötigt kein extrazelluläres Calcium. Die Reaktion wird bei niedriger Temperatur (4 °C) nur teilweise gehemmt. Sie kann daher nicht als zweckmässiges Modell für das Studium der anaphylaktischen Histaminausschüttung der Lunge angesehen werden.

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5-HT Hyperpolarization of Bullfrog Sympathetic Ganglion Cell Membrane

It is well known that the slow inhibitory postsynaptic potentials (slow IPSP) of sympathetic ganglion cells are produced by an activation of preganglionic nerve fibres, and that these potentials can be produced in the presence of nicotine or D-tubocurarine but are blocked by atropine[1,2]. A hyperpolarization of ganglion cells is produced by a direct application of acetylcholine (ACh) to ganglia, and the nature of this ACh hyperpolarization, which could be eliminated in a Ca-deficient Ringer's solution containing Mg, is essentially similar to that of the slow IPSP[2]. Thus, the slow IPSP does not seem to be produced by a direct action of ACh but rather by the action of some transmitter released from intermediating

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