The data suggest that the dog is a suitable animal for evaluating duration of action of synthetic corticotrophins. Its size, large blood volume and ease of handling are also convenient for this type of study where serial samples are required. With as few as 2 dogs per group the difference in duration of action of any dose of tetracosactide and the two higher doses of 41,795-Ba was readily apparent. Furthermore, although within group variations in absolute cortisol levels obscured significant dose response relationships at any given time interval, dogs treated with 41,795-Ba showed clearcut dose-duration effects with time.

We conclude that 41,795-Ba stimulates a 2- to 4-fold more prolonged secretion of cortisol than does tetracosactide in the dog.

[6] Acknowledgements: We thank D. KARAFFA and J. CHINNERY for expert technical assistance.

Zusammenfassung. Die Bestimmung der Plasma-Konzentration von Cortisol in ovariectomierten Hunden, welche mit intravenösen Gaben von β-Corticotropin-oktadekapeptid (CIBA 41,795-Ba) oder Tetracosaktid vorbehandelt worden waren, ergab die interessante Tatsache, das in beiden Fällen die Cortisolkonzentration gleich stark erhöht war aber im ersten Fall die Erhöhung unter dem Einfluss von CIBA 41,795-Ba zwei- bis viermal länger erhalten blieb als nach Behandlung mit Tetracosaktid.

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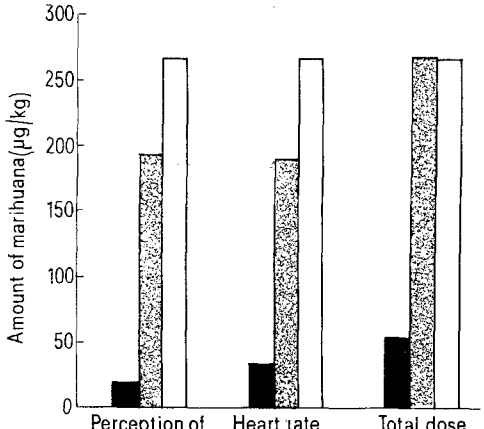
A Comparison of the Pharmacological Activity in Man of Intravenously Administered Δ^9-Tetrahydrocannabinol, Cannabinol, and Cannabidiol

The pharmacological activity of many of the chief constituents of marihuana have been systematically investigated in the Rhesus monkey by MECHOULAM et al.[1]. They found that Δ^9-tetrahydrocannabinol (Δ^9-THC) and Δ^8-tetrahydrocannabinol were active, and cannabinol, cannabidiol, and other cannabinoids present in the plant were not active. The development of a preparation to administer cannabinoids i.v. to man (PEREZ-REYES et al.[2]) has made it possible to make a comparison of the pharmacological activities and relative potencies of Δ^9-THC, cannabinol, and cannabidiol.

Method. 21 normal, paid, male volunteers were i.v. infused with Δ^9-THC, 6 with cannabinol, and 6 with cannabidiol. The preparation we have developed is a microsuspension of 10 mg of either of the cannabinoids in 50 ml of 25% salt-free human serum albumin. We have found that the amounts of cannabinoids can not be exceeded without inducing precipitation. Therefore, if different doses of these substances need to be infused, it is necessary to do so by changes in the rate of injection.



Drug		Perception of "high"	Heart rate acceleration	Total dose
Δ^9-THC $N=21$	mean	18.77	23.29	53.14
	S.D.	7.51	8.09	16.16
Cannabinol $N=6$	mean	194.41	189.59	269.56
	S.D.	41.11	103.01	39.78
Cannabidiol $N=6$	mean	>268.01	>268.01	268.01
	S.D.	–	–	22.38

Constituents injected i.v. to obtain certain specific effects. Since subjects varied in their body weight, all of the doses were calculated in terms of μg/kg of body weight. Figures indicated the mean values for the groups ± the standard deviation.

Subjects varied in their previous experience with marihuana from less than 1 cigarette/month to more than 5 cigarettes/week and were equally distributed in the groups. The subjects were hospitalized at the Clinical Research Unit of the North Carolina Memorial Hospital, Chapel Hill, N.C., and remained for 24 h until all the effects of the drugs had completely subsided. The heart rate was constantly recorded throughout the experiment by means of an Offner polygraph situated in a one-way screen room adjacent to the subjects' room.

To obtain the subjective evaluation of drug effects, that is of marihuana-like 'high', whether pleasant or unpleasant, we asked the subjects to rate themselves in a graph form provided for them. This rating was obtained at appropriate intervals for 6 h following drug administration. No specific instructions were given for these ratings, and each subject was free to utilize whatever criterion he wished for rating. We found that although there were variations in rating the magnitude of 'high', the pattern of the psychological experience in time was consistently similar.

Subjects were told that initially they would be i.v. infused with a drug-free solution (normal saline), and at some unspecified time, it would be replaced with the preparation containing either Δ^9-THC, cannabinol, or cannabidiol. The replacement of solutions without the subjects' awareness was possible because the Harvard constant infusion pump utilized for injection was located in the observation room. The subjects were instructed to report the moment they felt the action of the drug, that is the initial perception of marihuana-like effects, and to ask for the termination of the infusion as soon as they felt they had arrived at their desired level of 'high'. The volunteers were encouraged to receive the largest amount

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[2] M. PEREZ-REYES, M. C. TIMMONS, M. A. LIPTON, K. H. DAVIS and M. E. WALL, Science *177*, 633 (1972).

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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