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Influence of (–)3-Hydroxy-N-Propargyl-Morphinan on the Respiratory Depressant Action of Codeine

The works of UNNA¹ and FROMHERZ and PELLMONT^{2,3} on the antagonizing effect of allylmorphine and of allylmorphinan ((–)3-hydroxy-N-allyl-morphinan = Levalorphan = Ro 1-7700, Lorfan®) on the respiratory depression produced by morphine, has given scope for further tests with new morphinan derivatives such as (–)3-methoxy-N-allylmorphinan (Ro 1-7687), (–)3-acetoxy-N-allylmorphinan (Ro 1-7929) and (–)3-hydroxy-N-propargyl-morphinan (Ro 1-7780). HUGGINS et al.^{4,5}, FROMHERZ and PELLMONT³ and RAUSCH et al.⁶ have reported the antagonizing effect of allylmorphinan against codeine and other morphine analogues.

H. HOFMANN and E. HOFMANN^{7,8} reported the action of Ro 1-7780 on O₂ uptake by the eggs of *Psammecinus microtuberculatus* under the influence of opiates. Ro 1-7780 possesses a definite but milder antagonizing effect on morphine. In view of these observations, it has become of interest to study the effect of Ro 1-7780 on the respiratory

depressant action of codeine in rats. Rats weighing about 200 g have been used and the respiratory rate, volume and blood pressure were recorded simultaneously under urethane narcosis, while testing with codeine and Ro 1-7780. Intraperitoneal injection of 150 mg/kg codeine phosphate caused death through respiratory depression following gradual reduction in respiratory volume and rate. Administration of 1.5 mg/kg Ro 1-7780 i.p. resulted in an increase in both respiratory volume and rate, but

¹ K. UNNA, J. Pharmacol. exp. Ther. 79, 27 (1943).

² K. FROMHERZ and B. PELLMONT, Exper. 8, 349 (1952).

³ K. FROMHERZ and B. PELLMONT, Arch. exp. Path. Pharmacol. 218, 136 (1953).

⁴ R. A. HUGGINS, W. G. GLASS, and A. R. BRYAN, Proc. Soc. exp. Biol. Med. 75, 540 (1950).

⁵ R. A. HUGGINS, W. G. GLASS, and A. R. BRYAN, J. Pharmacol. exp. Ther. 101, 19 (1951).

⁶ J. RAUSCH, J. SZEGI, I. SZLAMKA, and J. NAGI, Acta physiol. Acad. Sci. hung. Suppl. 14, 45 (1958).

⁷ H. HOFMANN and E. HOFMANN, Arzneimittelforsch. 7, 95 (1957).

⁸ H. HOFMANN and E. HOFMANN, Wiss. Z. Friedrich-Schiller-Univ. Jena 6, 285 (1956/57).

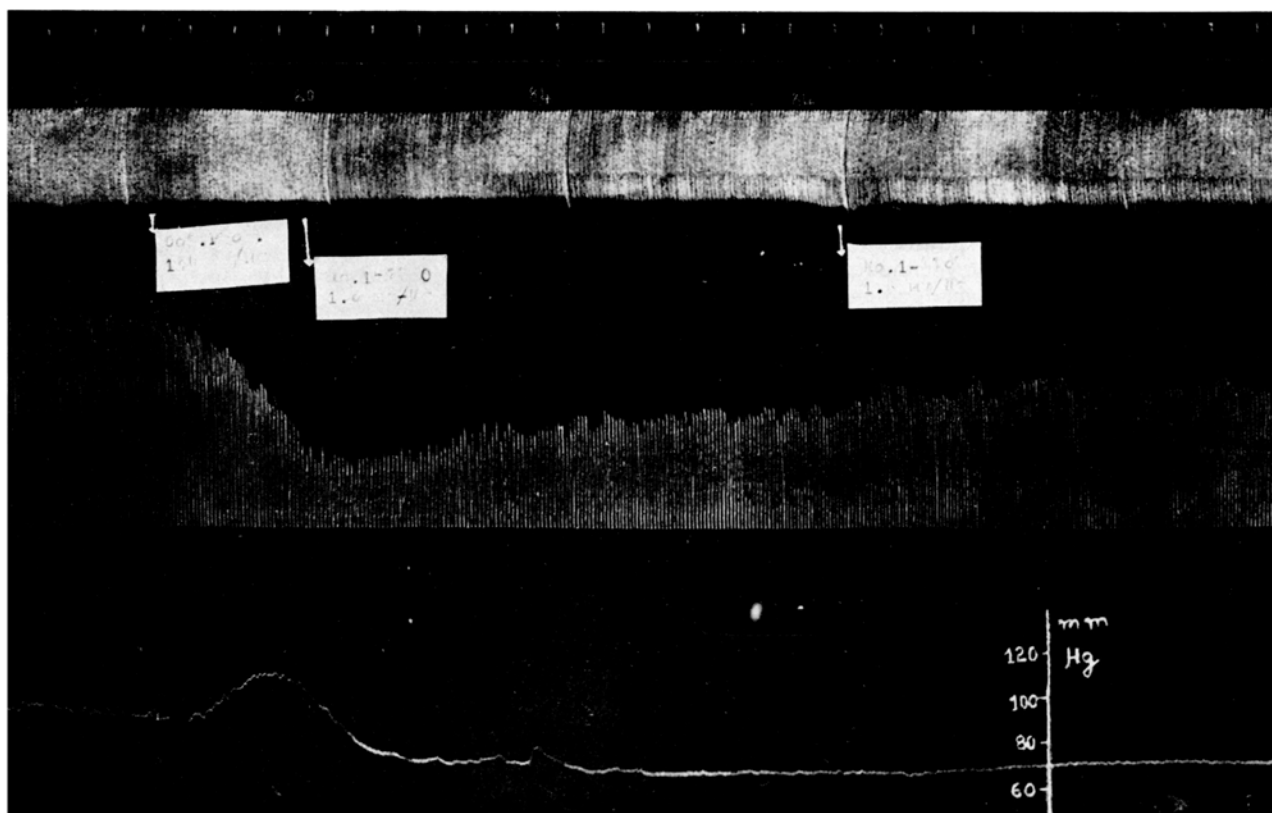


Fig. 1. Exp. No. 13; Dt. 2/2/1961; Weight of rat 220 g. Urethane 1.0 g/kg i.p.; Time recording/1 min; Values of resp. rate/1 min; Resp. vol./5 sec; Blood pressure in mm Hg; B.T. = Bronchial toilet. Expl. = After Codeine Phos. administration, two doses each of 1.5 mg/kg Ro 1-7780 given at intervals of 8 to 10 min restored only 66% of the original respiratory volume. 1st arrow 150 mg/kg i.p. Cod. phos., 2nd and 3rd arrows 1.5 mg/kg i.p. Ro 1-7780.

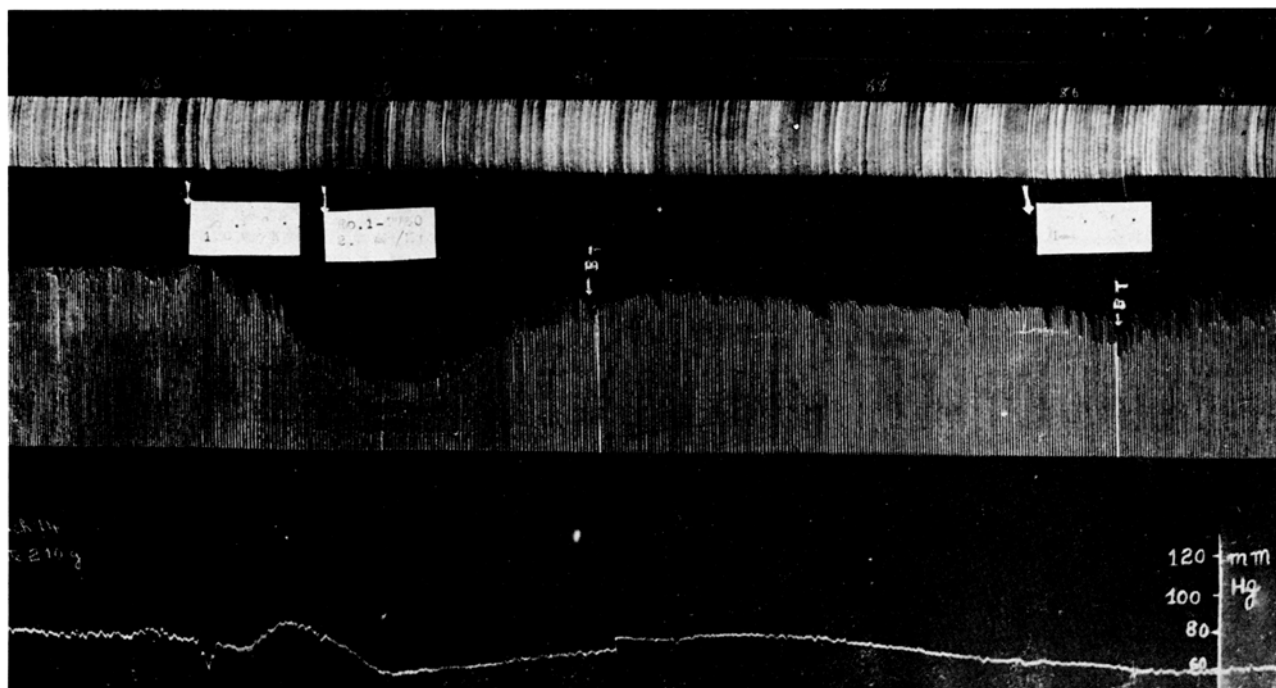


Fig. 2. Exp. No. 14; Dt. 9/2/1931; Weight of rat 210 g. Other items are as described under Figure 1. Expl. = Even a single dose of Ro 1-7780 adequately antagonized the action of codeine on the respiratory centre and raised the respiratory volume to 88 to 90% of the original. A second lethal dose of Cod. phos. injected after Ro 1-7780 shows no influence on respiration. 1st and 3rd arrows 150 mg/kg i.p. Cod. phos., 2nd arrow 2.0 mg/kg i.p. Ro 1-7780.

the original volume was not recovered. A second dose of 1.5 mg/kg Ro 1-7780 administered after 8 to 10 min increased the volume to 66% of the original. But a single dose of 2.0 mg/kg i.p. raised the respiratory volume to 88% of the original; still higher doses could not restore the original volume. Under the influence of Ro 1-7780, the respiratory rate usually recovered the values existing before codeine phosphate administration. In all the trials, the antagonist had to be administered to rats under the effect of codeine when the respiratory volume was reduced to 50% of the original, whatever the respiratory rate and blood pressure. Ro 1-7780 had no antagonizing effect when the volume became as little as 30 to 40% of the original. Another dose of codeine phosphate (150 mg/kg i.p.) injected even 20 min after Ro 1-7780 (2 mg/kg i.p.) did not show any influence either on respiration or on blood pressure. The influence of Ro 1-7780 on blood pressure was indiscriminate. Codeine phosphate lowered the blood pressure to about 60% of the original value. Administration of Ro 1-7780 brought about first a transient increase in blood pressure, and then, either maintained the levels under the influence of codeine, or

gradually increased the levels to 80 to 85% of the original. It may be concluded that (-)-3-hydroxy-N-propargyl-morphinan possesses the same influence as levallorphan⁹ in antagonizing the respiratory depression produced by codeine in rats, and that it should be administered in doses (2 mg/kg i.p.) twice those of levallorphan (1 mg/kg i.p.)¹⁰.

Zusammenfassung. Es wird festgestellt, dass Ro 1-7780 die atemdepressive Wirkung von Codein aufhebt. Die Dosis muss zweimal so gross wie die von Levallorphan sein. Das Dosisverhältnis zwischen Ro 1-7780 und Codein ist 1:50 bis 1:75.

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⁹ H. HOFMANN and H. BRÄUNLICH, in press.

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Macro-Radioautographic Localization of K⁴² and I¹³¹ in the Canine Kidney

The existence of the counter-current system in kidneys is based upon the fact that the concentration of some material is greater in the medulla than in the cortex and that this concentration increases from the basis toward the tip of papilla. This type of dislocation was proved in sodium (KRAKUSIN and JENNINGS¹, ULLRICH and JARAUSCH²), chlorides (GLIEMSTEDT³), urea (LEVINSKY and

BERLINER⁴), bromides (ANDRYSEK, SCHÜCK, and ANDRYSKOVÁ⁵), exogenous creatinine and aminoacids (ULLRICH and JARAUSCH²).

¹ J. B. KRAKUSIN and R. B. JENNINGS, Arch. Path. 59, 471 (1955).

² K. J. ULLRICH and K. H. JARAUSCH, Pflüg. Arch. ges. Physiol. 262, 537 (1956).

³ G. GLIEMSTEDT, Z. mikr. anal. Forsch. 52, 335 (1942).

⁴ N. C. LEVINSKY and R. W. BERLINER, J. clin. Invest. 38, 741 (1959).

⁵ O. ANDRYSEK, O. SCHÜCK, and J. ANDRYSKOVÁ, in press.