

The involvement of corticosteroids in the supersensitivity produced in the rat anococcygeus muscle by morphine withdrawal or reserpine

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In the rat anococcygeus muscle morphine withdrawal reveals an unusual type of super-sensitivity similar to that produced by corticosterone and characterized by an increased maximum response to different agonists (Gibson & Pollock, in press). Since morphine withdrawal increases the secretion of corticosteroids (Sloan, 1971), this study investigated the possibility that morphine-induced supersensitivity might be caused by endogenous corticosteroids released during withdrawal.

Groups of male Wistar rats (300-400 g) received either morphine (50 mg/kg, i.p. daily for nine days), morphine (50 mg/kg, i.p. daily for nine days) and metyrapone (50 mg/kg, i.p. daily for nine days), which inhibits the synthesis of corticosterone (Bowman, Rand & West, 1968), metyrapone (50 mg/kg, i.p. daily for nine days) or saline (0.9% w/v NaCl; 2.5 ml/kg daily for nine days). These rats were weighed daily during treatment and withdrawal, when metyrapone treatment was continued. In addition, the possibility that reserpine (1 mg/kg, i.p. 20 h before death) might produce a similar supersensitivity by releasing corticosteroids (Safran & Vogt, 1960) was investigated in normal and adrenalectomized rats. The rats were stunned and killed by bleeding. The anococcygeus muscles were excised, suspended in oxygenated Krebs solution (37°C) and responses to acetylcholine and noradrenaline were recorded isometrically. For each agonist and tissue the maximum tension was measured, the dose-% response curve drawn and the pD_2 value (Ariens & van Rossum, 1957) calculated.

Metyrapone prevented the appearance of morphine withdrawal supersensitivity and also pre-

vented the weight loss, which normally follows morphine withdrawal (Akera & Brody, 1968). In tissues from intact rats reserpine produced a supersensitivity similar to that revealed by morphine withdrawal but had no effect in tissues from adrenalectomized rats.

These results suggest that the supersensitivity revealed in the anococcygeus muscle by morphine withdrawal is caused by corticosteroids, which also appear to be involved in the weight loss that follows morphine withdrawal. The supersensitivity produced by reserpine was similar to that described by Taylor & Green (1971) and quite unlike that produced by prolonged reserpine treatment, which did not affect the maximum response of the anococcygeus muscle (Gibson & Pollock, in press). The ability of reserpine to increase the maximum response of the anococcygeus muscle involves the adrenals and is probably mediated by the corticosteroids.

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References

- AKERA, T. & BRODY, T.M. (1968). The addiction cycle to narcotics in the rat and its relation to catecholamines. *Biochem. Pharmacol.*, **17**, 675-688.
- ARIENS, E.J. & VAN ROSSUM, J.M. (1957). pD_x , pA_x , pD_x values in the analysis of pharmacodynamics. *Archs int. Pharmacodyn. Ther.*, **110**, 275-299.
- BOWMAN, W.C., RAND, M.J. & WEST, G.B. (1968). In *Textbook of Pharmacology*, p. 859. Oxford, Edinburgh: Blackwell.
- GIBSON, A. & POLLOCK, D. Drug-induced changes in the sensitivity of the rat anococcygeus muscle. *Br. J. Pharmacol.* In press.
- SAFRAN, M. & VOGT, M. (1960). Depletion of pituitary corticotrophin by reserpine and by a nitrogen mustard. *Br. J. Pharmacol.*, **15**, 165-169.
- SLOAN, J.W. (1971). Corticosteroid hormones. In: *Narcotic Drugs Biochemical Pharmacology*, ed. Clouet, D.H., pp. 262-282. New York, London: Plenum.
- TAYLOR, J. & GREEN, R.D. (1971). Analysis of reserpine induced supersensitivity in aortic strips of rabbits. *J. Pharmacol. exp. Ther.*, **177**, 127-135.