Biochemical Pharmacology, Vol. 18, pp. 1529–1530. Pergamon Press. 1969. Printed in Great Britain

PRELIMINARY COMMUNICATION

Sensitivity to insulin *in vitro* is morphine-dependent in muscle of chronically morphinized rats

(*Received* 13 *January* 1969; *accepted* 22 *February* 1969)

IN EXPERIMENTS analogous to those previously reported of our work with adrenal hormones,[1–4] we find that the rate of glucose-uptake by isolated diaphragm from chronically morphinized rats, unlike that of diaphragm from normal rats, is not changed by the addition of insulin *in vitro*. Sensitivity to insulin is restored, however, when morphine is added to the incubating medium.

Morphine, like insulin, increases the rate of glucose-uptake by normal diaphragm, but it decreases the rate of uptake by chronically morphinized diaphragm.[1, 2] When allowance is made for this latter effect of morphine, our experimental results (Table 1) show that the effect of insulin in the presence of

TABLE 1. EFFECTS OF INSULIN AND MORPHINE ON ISOLATED DIAPHRAGM OF NORMAL AND CHRONICALLY MORPHINIZED RATS

State and (No.) of rats	Glucose-uptake (mg/100g wet tissue/hr)			
	Control	Experiment	Difference	
		+ insulin		
Normal (10)	203 ± 21	345 ± 30	+142 ± 28	($P < 0.001$)
CM (8)	230 ± 8	229 ± 10	− 1 ± 8	
		+ morphine		
Normal (20)	187 ± 24	274 ± 20	+ 87 ± 22	($P < 0.001$)
CM (15)	235 ± 24	159 ± 25	− 75 ± 18	($P = 0.001$)
		+ insulin		
		+ morphine		
Normal (6)	163 ± 4	344 ± 10	+181 ± 10	($P \ll 0.001$)
CM (10)	237 ± 7	309 ± 16	+ 72 ± 16	($P < 0.002$)

Hemi-diaphragms were incubated at pH 7·4 and 37° for 1 hr in an oxygenated, modified[8] Krebs–Ringer-phosphate (2·0 ml) containing glucose (0·15%) ± insulin (0·1 unit/ml) ± morphine (final concentration, $7{\cdot}7 \times 10^{-4}$ M). In each experiment half the excised diaphragm served as control for the other half to which drug and/or hormone was added. Decrease in glucose content of the medium was determined by a glucose oxidase method[9] and the results are tabulated as Means ± S.E. CM = Chronically morphinized, rats which had received daily injections of morphine (30 mg/kg body weight) for 6 weeks. No rats received either food or drug within a period of 24 hr before the experiment.

morphine on the chronically morphinized diaphragm is comparable with that of insulin alone on normal diaphragm.

There is evidence that the cell membrane is the site of action of morphine in effecting changes in the properties of muscle associated with sensitivity both to hormones and to the ionic composition of the medium.[3–6] The present experiments support this evidence, and they further support the view that addiction to morphine is a result of an induced dependence upon the drug for the hormonal control of metabolism.[7]

Acknowledgements—We thank the Nuffield Foundation and Hong Kong Government, the University of Hong Kong, and the China Medical Board of New York for grants in support of this work.

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