Reversal of Hormonal Effects as a Result of Chronic Morphinization

Morphine accelerates the rate at which the rat diaphragm takes up glucose from synthetic media, to an extent comparable with the effect of insulin. With tissue from a chronically morphinized animal this acute effect of the drug is reversed, and the rate of glucose-uptake is retarded[1]. These effects of morphine are antagonized by hydrocortisone[2]. Hydrocortisone alone, in the concentration used for the experiments ($7{\cdot}7 \times 10^{-4}$ M) with morphine, has no significant effect on the rate of glucose-uptake by either normal or chronically morphinized tissue. We have confirmed this by additional experiments, and have concluded that the previously observed effects of the hormone in the presence of added morphine may be attributed entirely to a suppression by the hormone of the effects of the drug.

We now find, however, that hydrocortisone in lower concentrations has a marked and apparently direct effect on the glucose-transport mechanism. The effect on tissue from the chronically morphinized animal is the reverse of that on normal tissue. Following the experimental procedure previously described[2], we find that hydrocortisone, in concentrations of $3{\cdot}85 \times 10^{-4}$ M and below, strongly retards the uptake of glucose by diaphragm from normal rats, but accelerates its uptake by diaphragm from rats which had received daily injections of morphine sulphate (30 mg/kg body wt.) for 4–6 weeks. As previously emphasized[2], there is no significant difference between the normal and chronically morphinized rat diaphragm in the rates of glucose-uptake in the absence of added hormone or drug. Results are presented in Table 1.

Differences between normal and chronically morphinized rats in tissue response to adrenaline have also been observed in a study of the effects of hydrocortisone and adrenaline[3] analogous to that with hydrocortisone and morphine. There is a possible analogy here between the reversal of hormonal effects by morphine and the reversal of the effect of vitamin B_1 on yeast fermentation as a result of growth in the presence of cocaine[4,5], for, in both cases, reversal of the effect of the active substance is induced by chronic exposure to a drug which to some extent it resembles in chemical structure. The morphine molecule embodies both a steroid-like and an adrenaline-like structure and it is to be expected that the drug would interfere with the normal action of both types of hormone.

While we cannot as yet offer a full explanation for our observations, it would seem that, in the hormonal control of metabolic processes, a hormone or other active substance such as a hormone-simulating drug may either activate or inhibit a process according to its concentration relative to that of other active substances, and depending on the state of the tissue on which it acts, this latter factor being related to the established hormonal balance of the organism. There is ample evidence that morphine disrupts the normal hormonal balance so far as adrenal hormones are concerned[6,7].

Table 1. *In vitro* Effects of Hydrocortisone on Glucose-uptake by Diaphragm of Normal and of Chronically Morphinized Rats

	Glucose-uptake, mg/100 g wet tissue/h (Mean ± S.E.)			
	Control	+ Hydrocortisone ($7{\cdot}7 \times 10^{-4}$ M)	Difference	*t*-test
Normal rats (17)	205 ± 31	171 ± 34	−34 ± 81	N.S.
Chronically morphinized rats (12)	139 ± 28	134 ± 46	−5 ± 44	N.S.
		($3{\cdot}85 \times 10^{-4}$ M)		
Normal rats (6)	193 ± 41	52 ± 27	−141 ± 27	($P < 0{\cdot}01$)
Chronically morphinized rats (7)	228 ± 29	325 ± 35	+97 ± 35	($P < 0{\cdot}05$)
		($1{\cdot}92 \times 10^{-4}$ M)		
Normal rats (8)	253 ± 27	163 ± 26	−90 ± 30	($P < 0{\cdot}02$)
Chronically morphinized rats (8)	196 ± 25	276 ± 20	+80 ± 13	($P < 0{\cdot}001$)

Our observations lead us to suggest that morphine, directly as well as indirectly, induces a change in the tissues which are targets for hormonal action, somewhat in the nature of an adaptation to the changed hormonal balance, with the additional complication that morphine itself participates in that balance by virtue of its hormone-simulating properties. We suspect that, in this way, morphine induces a biological dependence in tissues which are sensitive to the adrenal hormones and that this is the basis of morphine addiction.

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HÆMATOLOGY

Inhibition of ADP-induced Platelet Aggregation by Substituted Amino-acids

Aggregation of platelets in the presence of adenosine diphosphate (ADP) appears to be important in hæmostasis and in the genesis of platelet thrombosis. There is evidence that this reaction is common to platelet clumping induced by a variety of stimuli, including collagen, adrenaline, long-chain fatty acids, and perhaps weak solutions of thrombin. Although this phenomenon is under investigation in many laboratories, the mechanism by which ADP causes platelet aggregation is largely unknown. Certain inhibitors of platelet clumping have been described (for example, inhibition of thrombin-induced platelet aggregation by heparin[1] or of ADP by adenosine[2]), and investigation of the inhibitory reaction has afforded some insight into the underlying process.

We have examined platelet clumping induced by ADP, using the turbidimetric technique of Born[3]. This reaction is strongly inhibited by certain substituted α-amino-acids, such as arginine methyl ester. Arginyl esters in which the α-amino group is also blocked, such as BAME, BAEE and TAME, are equally effective. The degree of inhibition varies with the concentration of the inhibitor. The inhibition becomes manifest immediately on addition of the substituted amino-acid and is not enhanced by incubation before addition of ADP, unlike inhibition produced by adenosine. Indeed, if the addition of the inhibitor is delayed until the maximum effect of ADP has been achieved, the platelet aggregates promptly disperse. Fig. 1 illustrates this phenomenon with benzoyl-arginine methyl ester (BAME); similar data have been obtained with other inhibitory agents in this family.

If the reciprocal of the velocity of platelet aggregation in platelet-rich citrate plasma is plotted against the reciprocal of the concentration of added ADP by the technique of Lineweaver and Burk[4], a straight line is obtained (Fig. 2, control) which intersects at the ordinate with a similar curve derived in the same manner by adding ADP to platelet-rich plasma in the presence of arginine methyl ester. Analogous curves may be derived with other concentrations of inhibitor and with other members of the family of inhibitors, and the lines characteristically con-