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EFFECT OF AMINOGLUTETHIMIDE AND ADRENO-BLOCKING AGENTS ON MORPHINE-INDUCED HYPERGLYCEMIA

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Abstract—Morphine-induced hyperglycemia is completely suppressed in adrenalectomized rabbits. Phentolamine does not modify the effects of morphine. Aminoglutethimide and propranolol substantially reduce morphine-induced hyperglycemia which is partially mediated by β-adrenergic receptors.

Administration of morphine to laboratory animals induces numerous changes in carbohydrate metabolism. The effect of this narcotic on blood glucose levels is well known in man and in dogs and it is of interest that the hyperglycemic effect of morphine diminishes during the course of addiction and may even be reversed [1]. We particularly studied these changes because of their possible relations with the problems of drug dependence. The effect of morphine on blood glucose is a very complex phenomenon which is influenced by factors such as species, number and frequency of morphine doses and biological rhythms [2]. Until now, all experimental results show that the major cause of morphine-induced hyperglycemia is the release of adrenalin from the adrenal medulla. To attempt to clarify the role of adrenal secretions, we have used an inhibitor of steroidogenesis, aminoglutethimide, as well as the adreno-blocking agents, phentolamine and propranolol, in morphine-treated rabbits.

MATERIALS AND METHODS

Experiments were performed during May and June on Fauve de Bourgogne rabbits weighing 2–2.5 kg. Blood samples were taken from the marginal vein of the ear of 15 hr-fasted animals at 9 a.m. Morphine chlorhydrate (Chaix et du Marais) was injected intramuscularly at 10 or 20 mg/kg. Aminoglutethimide (Elipten, Ciba) was administered intraperitoneally at 120 mg/kg/day for 3 days before morphine injection. Phentolamine (Regitine, Ciba Geigy) at a dose of 1 mg/kg i.v. and propranolol (Avlocardyl Avlon) at a dose of 5 mg/kg i.p. were administered 30 min before morphine treatment.

Plasma glucose was determined by colorimetry [3] and glycogen by the method of Good *et al.* [4]. The activity of glycogen phosphorylase (α-1,4-glucan:orthophosphateglucosyltransferase) was measured with the technique of Sutherland [5].

Adrenalectomy was done under pentobarbital anesthesia. Results are expressed as means ± S.E.M. and P was determined by Student's *t*-test.

RESULTS

Effects of morphine on blood sugar in rabbits. The first dose of morphine caused a rise in plasma glucose. For a given dose, the amount of change varied with different animals, but the glucose level returned to normal 6 hr after injection. Plasma glucose determinations were made on a group of 24 rabbits. The values were 104 ± 3.8 mg per 100 ml plasma at time zero, 145 ± 9 mg 1 hr after an i.m. dose of 10 mg/kg of morphine ($P < 0.001$) and 106 ± 5.3 mg 6 hr after injection.

At the same time, morphine caused substantial glycogenolysis with significant activation of glycogen phosphorylase (Table 1).

Effects of morphine on blood sugar in adrenalectomized rabbits. Survival of adrenalectomized rabbits

Table 1. Effect of morphine on plasma glucose, liver glycogen and liver glycogen phosphorylase activity in rabbits

	Plasma glucose (mg/100 ml) (24)	Liver glycogen (g/100 g) (6)	Liver glycogen phosphorylase activity (μmole Pi/min/g) (6)
0 hr	104 ± 3.8	1389 ± 107	12.9 ± 0.7
1 hr following morphine	145 ± 9	344 ± 83	15.9 ± 0.9
	$P < 0.001$	$P < 0.001$	$P < 0.05$

Values are means ± S.E.M. The number of animals is shown in parentheses. Significance was determined by the Student's *t*-test.

Table 2. Effect of morphine (10 mg/kg) on plasma glucose in adrenalectomized rabbits

Glucose mg/100 ml plasma			
Before adrenalectomy	Effect of morphine after adrenalectomy	0 hr	1 hr
127	24 hr*	73	52
140	24 hr	125	110
	8 days	142	115
134	24 hr	85	108
	8 days	132	103
126	24 hr	89	92
132	8 days	123	120
117	24 hr	124	151
138	8 days	126	126

* Time between adrenalectomy and the first morphine injection.

was not long, 24–72 hr. To prolong the survival, it was usually sufficient to give a single injection of a very low dose of corticosteroids after the adrenalectomy. We thus obtained rabbits surviving more than 8 days following a single dose of 5 mg of cortisol. Table 2 shows that in adrenalectomized rabbits maintained with a single dose of steroids, morphine has no hyperglycemic effect. Only one animal presented a hyperglycemia similar to a normal animal.

Morphine requires intact adrenals to exert a hyperglycemic effect. Obviously, adrenalectomy does not allow conclusions as to the role of corticosteroids or catecholamines in morphine-induced hyperglycemia. To answer this question, rabbits were treated with a steroidogenesis inhibitor, aminoglutethimide, or with the adrenergic receptor blockers, phentolamine and propranolol.

Effects of morphine on rabbits pre-treated with aminoglutethimide. This inhibitor of steroidogenesis was administered for 3 days (120 mg/kg) and also 30 min before morphine (10 mg/kg) injection. Table 3 shows that in our experimental conditions aminoglutethimide greatly reduced but did not completely suppress the morphine-induced hyperglycemia.

Effect of morphine on rabbits pre-treated with phentolamine and propranolol. Fig. 1 shows that the α-blocker, phentolamine, when injected alone in low concentrations causes a significant durable rise in plasma glucose. It does not modify the effects of morphine. The β-blocker, propranolol, induced a slight but significant ($P < 0.02$) hypoglycemia. When injected together with morphine, it reduced but did not inhibit the morphine-induced hyperglycemia.

Table 3. Effect of aminoglutethimide on morphine-induced hyperglycemia

	Glucose mg/100 ml plasma			
	0 hr	1 hr	3 hr	6 hr
Aminoglutethimide (9)	123 ± 3	125 ± 3	130 ± 3	124 ± 3
Morphine (8)	132 ± 4	179 ± 10 $P < 0.001$	182 ± 10 $P < 0.001$	147 ± 5 $P < 0.02$
Aminoglutethimide + morphine (9)	119 ± 4	137 ± 4 $P < 0.01$	145 ± 6 $P < 0.01$	133 ± 3 $P < 0.02$

Values are means ± S.E.M. The number of animals is shown in parentheses.

Significance was determined by the Student's *t*-test.

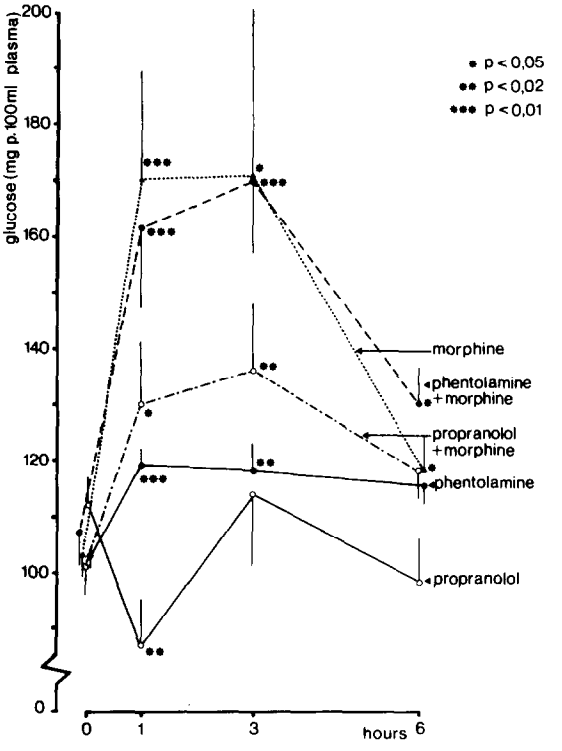

Fig. 1. Changes in plasma glucose levels induced by morphine, propranolol, phentolamine, propranolol + morphine and phentolamine + morphine. Each point represents the mean ± S.E.M.; P values are the probability based on the Student's *t*-test.

DISCUSSION

Under our experimental conditions, morphine-induced hyperglycemia is completely inhibited in adrenalectomized rabbits. Inhibition of steroidogenesis and the blockade of β-adrenergic receptors greatly reduces the effect of morphine. Phentolamine has no effect on morphine-induced hyperglycemia.

The rise in circulating glucose might be the result of hepatic glycogenolysis, stimulation of gluconeogenesis or a reduction in peripheral utilization. All three possibilities should be considered in morphine treated animals. Previous experiments have shown that morphine administration in rats and mice causes significant hepatic glycogenolysis [6], a substantial rise in lactate concentration of various tissues [7] and also a reduction in plasma free fatty acids [8]. It is well known that lactate and FFA directly or indirectly stimulate gluconeogenesis. In addition, various authors have shown that morphine modifies permeability to glucose at the cellular level [9, 10]. In rabbits, morphine-induced hyperglycemia requires the presence of intact adrenals as in dogs and cats [11] and

rats [12]. We have previously reported a stimulation of corticosteroid secretion by morphine in rabbits [13]: by blocking steroid synthesis with aminoglutethimide, a hyperglycemic factor is eliminated and morphine effects are reduced because corticosteroids facilitate gluconeogenesis and reduction in glucose utilization at the cellular level [14].

With regard to glycogenolysis, numerous reports have shown that it is usually the result of adrenal catecholamine secretion, particularly adrenaline. Authors have considered adrenaline to be responsible for morphine-induced hyperglycemia. The effect of the drug is central in origin and due to a sympathetic discharge of adrenaline from the adrenals [15, 16]. We have also published additional proof in a histological study of the rabbit adrenal medulla in which we found a rapid depletion of pheochrome granules in the medulla following morphine administration [17]. In support of the role of adrenaline in glycogenolysis, a significant rise in phosphorylase activity was found in morphinized rabbits. Recently, reports have tried to specify the α or β nature of adrenergic receptors involved in glucose metabolism in liver and muscle. With this object the authors have used the adrenergic blockers propranolol and phentolamine.

Under our experimental conditions it seems that α-receptors are not involved in the metabolic effects of phentolamine or morphine since when injected alone or in association, these substances always cause an equivalent rise in blood glucose.

Concerning the β-blocker, our results show that propranolol alone, causes a slight but significant ($P < 0.01$) hypoglycemia. The same effect has been observed in man [18, 19] and in dogs [20] under anesthesia. The hypoglycemia induced by propranolol in fasting rabbits can be explained in the same way as anesthetized subjects, by the effects of the β-blocker which reduces the availability of replacement substrate in an organism in which glucose stores are very limited. In addition, β-adrenoreceptor blockade by propranolol clearly reduces morphine-induced hyperglycemia in rabbits which proves that some of the effects of the narcotic are mediated by β-adrenergic receptors. The reduced hyperglycemia can be explained by an inhibition of lactate production in morphinized animals (unpublished data). It is known that lactate is a considerable source of glycogen. On the other hand, it is difficult to estimate the influence of β-blockade of hepatic glycogenolysis in the reduction of the morphine-induced hyperglycemia. The nature of the receptors mediating hepatic glycogenolysis is not clearly defined and at the present time we have no information about the nature of the receptors which mediate the effect of adrenaline in rabbits.

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