Brit. J. Pharmacol. (1961), **17**, 305–309.

STRESS-INDUCED BLOCK OF MILK EJECTION

BY

R. R. CHAUDHURY,* M. R. CHAUDHURY AND F. C. LU

From the Food and Drug Directorate, Department of National Health and Welfare, Ottawa, Canada

(*Received August* 23, 1961)

A simple method has been described by which the action of drugs on the stress-induced block in milk ejection can be investigated on lactating guinea-pigs. Reserpine, meprobamate and chlorpromazine when administered to the lactating mother at various periods before suckling reduced the block in milk ejection caused by the stress. Dibenamine and dichloroisoprenaline did not affect in any way the stress-induced block. It is suggested that the stress-induced block in milk ejection is probably a nervous block and not mediated through adrenaline.

It has been known for a long time that fright or nervousness inhibits proper feeding of infants and milking in lactating animals. Ely & Peterson (1941) demonstrated marked inhibition of milk ejection in frightened cows, and Newton & Newton (1948) described inhibition of milk ejection caused by fear, embarrassment and anger in a lactating subject. It has been demonstrated that intravenous administration of adrenaline or stimulation of the sympathetic areas of the hypothalamus blocks the milk-ejection reflex (Cross, 1953, 1954). Cross (1955) has produced the stress-induced block of milk ejection in lactating rabbits and studied the mechanism of this block. The present concept appears to be that the adrenaline released in stress may block milk ejection by its vasoconstrictor action on the mammary myoepithelium. This peripheral action of adrenaline has been well demonstrated (Cross, 1953). It is, however, possible that the adrenaline released in stress may prevent the release of oxytocin and also that there may be other factors concerned in the psychological block of milk ejection. The effect of drugs on the stress-induced block of milk ejection does not appear to have been investigated in experimental animals. In this investigation the effect of some of the tranquillizers and two adrenergic nerve blocking drugs on the milk-ejection reflex in stress has been studied on the lactating guinea-pig.

METHODS

Guinea-pigs were bred in the animal house and the litter of each guinea-pig reduced to two for purposes of the experiment. Experiments were carried out from the third to the tenth day after birth of the litter. The two young guinea-pigs were separated overnight from the mother and weighed next morning before suckling. They were placed with the mother for 5 min, at the end of which period they were weighed again. When the weight gain of the

* Post-doctoral Fellow of the National Research Council of Canada.

litter was constant on several mornings the mother was turned and tied on its back on the day of the experiment and the two pups allowed to feed for 5 min. They were weighed at the end of the 5 min and then allowed to feed for a further 5 min in the cage in normal surroundings. After 5 min suckling without any stress the lactating guinea-pig was given an injection of 50 m-u. oxytocin and the two pups allowed to feed for a further 5 min. It was observed in the experiments that the weight of the litter after 5 min of uninhibited suckling was not further increased by allowing them to feed again after the injection of oxytocin into the mother. This indicated that there was full milk ejection when the litter were allowed a 5-min feeding in the cage after 5 min of "stress" feeding. The block in the milk ejection has been expressed as a percentage block where the total weight gain of the litter after both "stress" and "normal" feedings on any day has been taken as 100% milk yield. It was observed that this 100% milk yield was similar in amount to the milk yield on the earlier control days. Drugs were administered to the lactating mother at various intervals before the stress-induced block in milk ejection, and the % inhibition of the stress-induced block after administration of the drugs was determined. The lactating guinea-pigs were not used for administration of a second drug until there were three to four days' control readings of milk yield after the administration of the first drug.

To ensure that there would be adequate milk in the mammary glands of the guinea-pig prolactin 5 u. was injected into the mother on alternate days in the evening. It had previously been determined that prolactin, even in large doses, did not have any action on the milk-ejection reflex.

The drugs used were: reserpine, meprobamate (Wallace Laboratories), chlorpromazine hydrochloride (Schering Research Division), dibenamine (Merck), dichloroisoprenaline, and oxytocin. In another series of experiments the effect of the following drugs on normal milk ejection in the guinea-pig was investigated: antidiuretic hormone, adrenocorticotrophic hormone, prolactin, and adrenaline hydrochloride. All the above-mentioned drugs except meprobamate were administered intraperitoneally to the lactating mother. Meprobamate was administered orally to the mother as a suspension in 0.5% methylcellulose.

RESULTS

Stress caused a block in milk ejection in all 10 experiments when the 10 lactating guinea-pigs were allowed to nurse their litter while being tied down on their backs. The % block caused by stress varied from 33% to 100%. A further 5-min suckling in the cage immediately afterwards indicated that the milk-ejection reflex had been restored. The litter gained their usual increase in weight. Fig. 1 shows the daily increase in weight of two litters. The weight increase when the mother nursed for 5 min under conditions of stress has been shown. There was a block in milk ejection in both experiments and this block disappeared when the litter were allowed to feed in the cage. In four experiments the lactating guinea-pigs received an injection of 50 m-u. oxytocin intraperitoneally immediately prior to being tied down on their back and nursing the litter. The litter gained their normal increase in weight in these experiments and there was no block in the milk-ejection reflex. This indicated that the block in milk ejection caused by tying the mother down on her back was not caused by mechanical or postural factors but was in fact due to a lack of effective circulating oxytocin. Table 1 shows how different drugs affect the block in milk ejection caused by stress.

Adrenaline, when administered to the lactating mother in a dose of 5 to 10 μg, always caused a block in the milk-ejection reflex and this block was not prevented by prior administration of dibenamine to the mother.

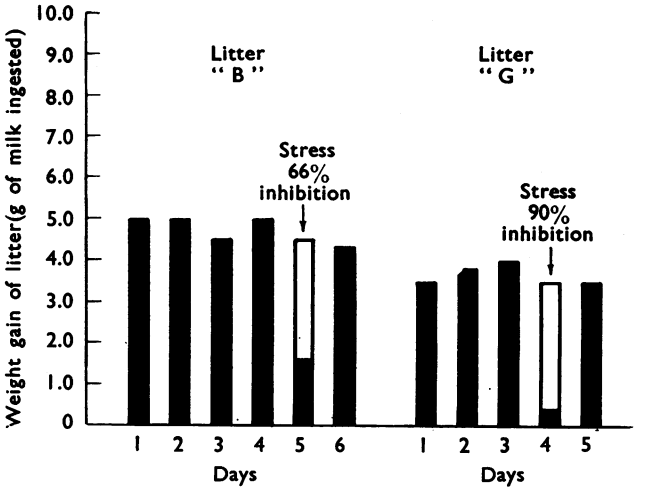

Fig. 1. The action of stress on the milk-ejection reflex in two lactating guinea-pigs. Stress was produced on the fifth and fourth day respectively. Shaded columns indicate the weight gain after 5 min suckling. Blank columns indicate the weight gain of the litter when they were allowed to feed for 5 min in normal surroundings following the stress.

Experiments were performed where adrenocorticotrophic hormone (20 u.) or antidiuretic hormone (10 m-u.) was administered to the lactating mother just before normal suckling. These drugs, which are released in stress, did not cause a block in milk ejection.

TABLE 1

PERCENTAGE BLOCK IN MILK EJECTION IN LACTATING GUINEA-PIGS

Stress	Stress after reserpine 250 μg/kg intraperitoneally 18 hr prior to suckling	Stress after meprobamate 200 mg/kg orally 30–40 min prior to suckling	Stress after chlorpromazine 2·5 mg/kg intraperitoneally immediately prior to suckling	Stress after dibenamine 200 mg/kg intraperitoneally 2 hr before suckling	Stress after dichloro-isoprenaline 10 mg/kg immediately prior to suckling
60·0	50·0	0	20·0	66·0	100·0
100·0	33·0	10·0	40·0	60·0	66·0
33·0	37·0	20·0	33·0	75·0	100·0
100·0	75·0	0	60·0	66·5	45·0
91·0	37·5	15·0	66·0	100·0	33·0
66·0	60·0	33·0	30·0	50·0	48·0
60·0	33·0				
75·0	35·0				
100·0	40·0				
75·0	37·0				

DISCUSSION

One of the purposes of this communication is to describe a simple method whereby the action of drugs on the stress-induced block of milk ejection can be studied. The guinea-pig responded to stress in a similar way every time and the milk yield after 5 min suckling was also relatively constant on different days in these litters. The results with the tranquillizing drugs indicate that reserpine, chlorpromazine and meprobamate all reduced the stress-induced block of milk ejection. In two experi-

ments meprobamate prevented the block. Reserpine could not be administered at a dose higher than 300 μg/kg because it was toxic to the guinea-pig, while chlorpromazine at a dose higher than 3.0 mg/kg itself blocked the normal milk-ejection reflex as in the rat (Chaudhury, 1961). Cross has also observed that chlorpromazine abolishes the stress-induced block of milk ejection in the rabbit (personal communication). It had been hoped that perhaps some of the tranquillizers would prevent the block in the reflex and others would not, and that this might give some indication of the site of action of this blocking phenomenon. However, this did not happen. As the investigation was not meant to be a study of the comparative merits of the tranquillizers no statistical evaluation of the three tranquillizers has been performed.

Dibenamine, when administered in doses which block the pressor response to adrenaline, did not prevent the stress-induced block of milk ejection. It could not be administered at a dose higher than 200 μg/kg, as that altered the normal milk-ejection reflex. Dichloroisoprenaline, which has been shown to block the inhibitory actions of adrenaline (Powell & Slater, 1958), also did not prevent the stress-induced block of milk ejection when administered in doses up to 10 mg/kg before suckling. These results give no further support for the hypothesis that the stress-induced block in milk ejection is mediated through the release of adrenaline from the adrenals. Although adrenaline when administered to lactating animals causes a block in the milk-ejection reflex, it is possible that other mechanisms may be involved in the immediate emotional block of milk ejection. It has been observed that the ringing of the telephone or a knock on the door during suckling causes a momentary block of milk ejection. It is doubtful if adrenaline is released under these circumstances. It may well be purely a nervous inhibition mediated through a chemical transmitter.

Two other substances thought to be released in stress, adrenocorticotrophic hormone and antidiuretic hormone, did not block normal milk ejection in the lactating guinea-pig. They could not, therefore, be concerned in the stress-induced block of milk ejection. It would be interesting to investigate whether oxytocin is released in stress. Usually it is released whenever antidiuretic hormone is released and in larger quantities (Harris, 1955). If oxytocin is not released in stress, then this would be one of the few situations where oxytocin is not released but antidiuretic hormone is (Rydin & Verney, 1938). On the other hand, if oxytocin is released in stress it becomes difficult to explain the stress-induced block in milk ejection. Cowie & Folley (1957) have recently stated that the physiological and psychological factors which may inhibit the normal milk-ejection reflex are of great scientific and practical interest. It is hoped that further investigations will elucidate the mechanism by which the stress-induced block in milk ejection occurs.

We should like to thank the Endocrinology Study Section of the National Institutes of Health, Bethesda, for supplies of prolactin; Ciba Pharmaceutical Products Inc. of Canada for supplies of reserpine (Serpasil); Sandoz of Canada for supplies of oxytocin (Syntocinon); and Dr Slater of Eli Lilly for supplies of dichloroisoprenaline.

REFERENCES

CHAUDHURY, R. R. (1961). The release of oxytocin in unanaesthetized lactating rats. *Brit. J. Pharmacol.*, **17**, 297–304.

COWIE, A. T. & FOLLEY, S. J. (1957). Neurohypophysial hormones and the mammary gland in HELLER, H., *The Neurohypophysis*. London: Butterworth's Scientific Publications.

CROSS, B. A. (1953). Sympathetico-adrenal inhibition of the neurohypophysial milk-ejection mechanism. *J. Endocrin.*, **9**, 7–18.

CROSS, B. A. (1954). The hypothalamus and the mechanism of sympathetico-adrenal inhibition of milk ejection. *J. Endocrin.*, **11**, IV*P*.

CROSS, B. A. (1955). Neurohormonal mechanisms in emotional inhibition of milk ejection. *J. Endocrin.*, **12**, 29–37.

ELY, F. & PETERSON, W. E. (1941). Factors involved in the ejection of milk. *J. Dairy Sci.*, **24**, 211–223.

HARRIS, G. W. (1955). *Neural Control of the Pituitary Gland.* London: Arnold.

NEWTON, M. & NEWTON, N. R. (1948). The let-down reflex in human lactation. *J. Pediat.*, **33**, 698–704.

POWELL, C. E. & SLATER, I. H. (1958). Blocking of inhibitory adrenergic receptors by a dichloro analogue of isoproterenol. *J. Pharmacol. exp. Ther.*, **122**, 480–488.

RYDIN, H. & VERNEY, E. B. (1938). The inhibition of water diuresis by emotional stress and by muscular exercise. *Quart. J. exp. Physiol.*, **27**, 363–374.