

IMMOBILISATION STRESS INDUCED ANALGESIA IN DIABETIC RATS

AARTI SOOD MAHAJAN*, KRISHNA CHAKRABARTY,
TARUN KUMAR MISHRA** AND A. S. CHAKRABARTY

*Departments of Physiology and **Biochemistry,
Maulana Azad Medical College,
New Delhi - 110 002*

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Abstract : Stress is known to produce analgesia. The pain threshold is altered in diabetics. We studied the effect of 1 hr of immobilisation stress on pain threshold in male Wistar rats. The same effect was tested in streptozotocin induced diabetic rats.

The pain threshold of tail flick, vocalisation and vocalisation after discharge increased in the control group after the stress procedure. Significant analgesia was also obtained in diabetic rats, for flick and after discharge pain threshold. However the vocalisation threshold was not altered, probably due to the antagonistic action of glucose on opiate receptor at the level of brain stem.

Key words : STZ-streptozotocin
immobilisation

analgesia
diabetic rats

INTRODUCTION

Stress produces analgesia. This endogenous analgesia mechanism may be both opiate and non-opiate mediated (1-4). It is suggested that acute stress produced analgesia while repeated exposure, lead to adaptation, a manner similar to that seen for opiates (1). The activation of either mechanism may depend on the type of stressor and its other parameters.

Diabetes affects the pain threshold. Diabetic mice shows an increased latency to tail pinch behaviour which was abolished when xylocaine was injected, suggesting a nociceptive pathway (5). Streptozotocin

induced diabetic rats are less sensitive to the antinociceptive effect of morphine (6-9).

Foot shock induced analgesia was lower in diabetic mice and was completely blocked by μ receptor antagonist. Immobilisation stress has been found to increase the latency for escape responses and not the paw lick response in rats suggesting the involvement of endogenous analgesia mechanism in the affective and not the sensory aspect of pain (11).

Hence various stress parameters act differently in diabetic rats. Variations in the pain threshold have been observed. We

*Corresponding Author and present address: Department of Physiology, All India Institute of Medical Sciences, New Delhi - 110 029.

aimed to see the effect of one hour of immobilisation stress on the pain threshold in both normal and STZ induced diabetic rats. This effect was studied for tail flick, vocalisation, and vocalisation after discharge pain threshold, representing spinal, brainstem and hypothalamic responses.

METHODS

Twenty male albino wistar rats were used in the weight range 255-250 g. They were kept in separate cages and given food and water *ad libitum*. They were divided into two groups of ten each.

Experimental protocol

In group A, the rats were tested for pain threshold by placing steel electrodes in the middle of tail of rats. The electrodes were connected to a stimulator whose voltage was progressively increased till the three threshold of tail flick, vocalisation and vocalisation after discharge were reached (12-14). Three readings at interval of 15 min were taken for three days. The readings of the first two days were not taken into consideration as this time is required for the rat to get used to the restraining apparatus and experimental procedure. These should not be stressful (14). The average of readings of third day were taken as baseline values. The rats were exposed to immobilisation stress, for a period of one hour, using a plexi-glass restrainer which was adjusted according to the size of the animal.

They were tested for the three threshold again. Three set of readings were taken and their average was taken. In the second group B, first the baseline values were

recorded. Then STZ in dose of 50 mg/kg body weight was injected intraperitoneally (streptozotocin buffered with citrate at pH-4.5). Pain threshold were recorded on the fifth, sixth and seventh day. The average of three readings of seventh day were taken as the diabetic values. The response to immobilisation stress for a period of one hr was tested in the control group. All three thresholds were tested. Blood glucose was determined to confirm the diabetic state of the rats.

RESULTS

In group A immobilisation stress for 1 hr produced significant analgesia for all the three pain threshold tested (Fig. 1).

In the second group, the pain threshold increased when rats become diabetic (Table I). When these STZ induced diabetic rats, were exposed to immobilisation stress, there was a significant increase in pain threshold for the tail flick and vocalisation after discharge responses. The change observed for the vocalisation response was not significant after one hr of immobilisation stress (Table II).

TABLE I: Effect on diabetes on pain threshold.

	Baseline (n=10) Mean \pm SD	Diabetes (n=10) Mean \pm SD
TF	0.359 \pm 0.096	0.470 \pm 0.18
V	0.663 \pm 0.199	1.230 \pm 0.94*
AD	1.170 \pm 0.298	2.710 \pm 1.097*

TF - Tail flick; V - Vocalisation

AD - Vocalisation after discharge

All - value are in volts.

*Values significant P<0.05

TABLE II : Effect of stress on pain threshold (control and diabetic group).

	<i>Control (A)</i>		<i>Diabetes (B)</i>	
	<i>Without stress</i>	<i>With stress</i>	<i>Without stress</i>	<i>With stress</i>
TF	0.350 ± 0.09	0.618 ± 0.23	0.470 ± 0.18	0.755 ± 0.318
V	0.650 ± 0.19	1.293 ± 0.71	1.230 ± 0.94	1.816 ± 0.947
AD	1.870 ± 1.793	3.532 ± 1.829	2.710 ± 1.097	3.975 ± 1.519

TF - Tail flick;

V - Vocalisaion;

AD - Vocalisation after discharge;

All value are in volts

In control group A and for tail flick and after discharge in Diabetic group (B), change in pain threshold was significant ($P < 0.05$). In vocalisation of group B, change was not significant ($P > 0.05$).

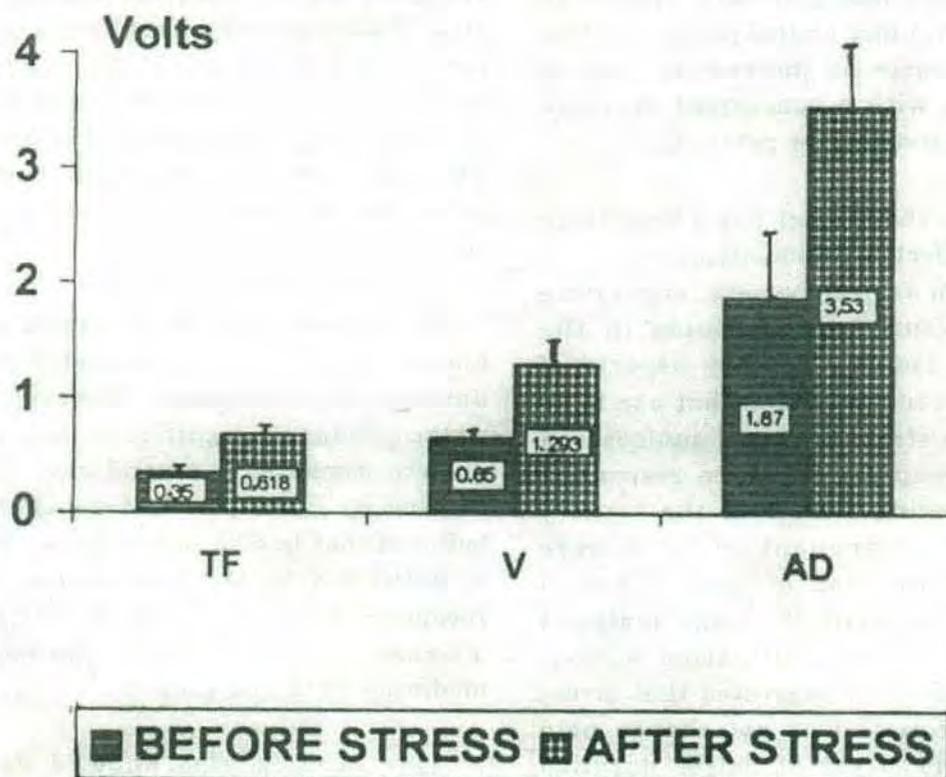


Fig. 1: Effect of stress on pain threshold in group A rats.

TF - Tail flick; V - Vocalisaion;

AD - Vocalisation after discharge. All comparisons significant ($P < 0.05$).

Blood glucose levels increased to 134.03 ± 18.58 mg% when compared to a group of ten normal rats (weight matched with values 77.51 ± 24.84 mg%)

DISCUSSION

Stress induces analgesia through specific activation of intrinsic pain inhibiting system which may be both opiate/non-opiate mediated (15). Analgesia by periqueductal stimulation and 2 deoxy glucose bear a close relationship to opiate, cold water swim and foot shock induced analgesia do not. The non-opiate mediated analgesia with components in hypothalamus and pituitary appear to involve hormonal and neural processes (16). Acute stress causes an increase in level of opiate peptides with a concurrent decrease in pain responsiveness in rats (17).

It has been shown that hypophysectomy blocked the effect of immobilisation stress in chronic pain responsiveness, suggesting the role of pituitary endorphins in the affective and not the sensory aspects of pain (11). However, we found that one hr of immobilisation stress produced analgesia in the control group for all three responses, thereby suggesting that both the sensory and affective component of pain were affected. The duration of immobilisation stress is also important. We found analgesia after one hr of immobilisation stress. However, it has been suggested that stress of shorter duration does not change pain threshold while stress of longer duration upto eighteen hrs produces profound analgesia (18).

STZ induced Diabetes is associated with a decrease in the neurointermediate pituitary lobe of betaendorphin (19). Thus stress may produce different responses in diabetic rats. STZ induced diabetes is a chronic stimulus to the hypothalamic pituitary axis (20). Diabetes itself is a stress in some diabetic rats known as reactive responders, with an increase in the basal level of epinephrine which is exaggerated in response to stress (21).

The effect of one hr of immobilisation stress was studied in STZ induced diabetic rats. We found that stress produces analgesia for the tail flick and vocalisation after discharge responses, but not for the vocalisation response. This could probably be due to the antagonistic action of glucose on opiate receptor at the level of brain stem. The duration of diabetes could also influence the response to immobilisation stress.

Foot shock induced analgesia has been known to be lower in diabetic mice and unresponsive to naloxone. However, one min swim produced significant analgesia in diabetic compared to control mice which was blocked by μ receptor antagonist (6). It is believed that in STZ induced diabetes, there is deficiency in the functioning of the μ receptors which leads to activation of an alternate endogenous analgesia mechanism mediated by δ receptor.

Our studies also showed decreased response of diabetic rats to immobilisation stress at the levels of brain stem.

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