

EFFECT OF GLUCOSE ON STRESS INDUCED ANTINOCICEPTION IN NORMAL MICE

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Abstract : Stress induced analgesia has been shown to utilise both non-opioidergic and opioidergic mechanisms. Earlier studies indicate that opioidergic analgesics exhibit corollary changes in blood glucose level. In this study, the changes in blood glucose level by swim induced stress and the influence of exogenous glucose administration on the stress induced antinociception were studied. Stress *per se* (both 30 sec and 3 min) did not modify the blood glucose level. However, exogenous administration of glucose reversed the stress induced antinociception in both non-opioid and opioid segments. Our results favour a role for glucose in stress induced analgesic activity.

Key words : swim stress stress-induced antinociception opioid
non-opioid blood glucose exogenous glucose

INTRODUCTION

Antinociceptive activity can be tested either in experimental models like thermal, chemical, mechanical assay or clinically using visual analog scale. However, the mechanism involved could be identified using more than one model. One of the possible mechanisms suggested for antinociceptive activity of agonist acting through opioidergic pathways is, the associated changes in blood glucose level in the body (1, 2). A recent study with α -2 adrenergic agonist such as clonidine which also elicits antinociception, independent of opioid pathways, indicated that the changes in the blood glucose level produced by

clonidine and its analgesic action can be dissociated (3). This finding corroborates the suggestion that only opioid analgesics show a relationship between changes in the blood glucose level and antinociceptive action. During stress, there is a possibility of changes in blood glucose due to energy utilisation. However, studies correlating stress induced antinociception involving (both non-opioid and opioid mechanisms) and the changes in blood glucose during stress if any, are not available to the best of our knowledge. Therefore, this study was designed primarily to identify such a correlation and subsequently to the relevance of such association to the mechanisms utilised in eliciting analgesic action.

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METHODS

Male Swiss albino mice (20–25 gm) were obtained from Central Animal House, JIPMER, Pondicherry and were housed in the departmental animal house with free access to food and water at room temperature (34–35°C).

Each animal was used once only. Forced swimming in water at room temperature (34–35°C) either for 30 sec (for non-opioid analgesic testing) or for 3 min (for opioid analgesic testing) was used as a stress (4). The animals were removed from water after the specified period of swimming, wiped with a dry cloth and a two minutes rest period was allowed between and of swimming and measurement of blood glucose and assessment of antinociceptive action (5).

Acetic acid (glacial, Sarabhai, Vadodara) induced writhing assay (6) was used to test the antinociception. It has been observed that in acetic acid induced writhing assay

morphine is more effective (ED_{50} 0.3 mg/kg against 10 mg/kg in thermal tests) with minimal nociception (7). Therefore this procedure was employed. Animals received 0.6% acetic acid (10 ml/kg) intraperitoneally and the number of writhing response was counted in the following 15 minutes period. A significant reduction in the writhing response as compared with saline (Core Parenterals, Ahmedabad) treated animals was considered as antinociceptive response.

The blood glucose was estimated in all the animals prior to exposure to stress and analgesic testing using AMES glucometer (Bayer's Diagnostic India Ltd., Vadodara). The blood was collected by the incision of the tail tip. The changes in the blood glucose were expressed as the percentage considering the initial blood glucose (estimated prior to the stress) as 100%.

In four groups of mice glucose (6 or 12 mg per mouse) was administered intraperitoneally. After 10 minutes of

TABLE I : Influence of stress and changes in blood glucose on the acetic acid induced writhings in mice.

Pretreatment (ip)	Treatment	Change in blood glucose	No. of writhings
None	Control	100.5 ± 4.9	24.4 ± 2.3
Saline	30 sec swim	94.2 ± 7.7	10.8 ± 2.3*
Saline	3 min swim	100.9 ± 8.1	5.4 ± 0.6*
6 mg glucose	30 sec swim	100.8 ± 8.9	27.0 ± 2.7†
6 mg glucose	3 min swim	92.8 ± 10.2	19.4 ± 4.7†
12 mg glucose	30 sec swim	106.4 ± 11.3	25.3 ± 3.1†
12 mg glucose	3 min swim	109.9 ± 7.4	26.0 ± 2.2†

The values represent Mean ± SEM; n=5

*P < 0.05 as compared with control

†P < 0.05 as compared with respective saline treatment value

glucose administration and after either 30 seconds or 3 minutes swim stress blood glucose was estimated. The influence of external glucose administration on the antinociceptive activity of the stress in these animals was tested as described earlier.

The data was subjected to statistical analysis ANOVA followed by Dunnett's "t" test.

RESULTS AND DISCUSSION

The animals subjected to 30 seconds and 3 minutes swim showed a significant antinociception when compared to control animals (Table I). The degree of antinociception was more after 3 minutes swim when compared to 30 seconds swim. However, there was no significant change in blood glucose level either after 30 sec or 3 min swim stress as compared to their initial values. Administration of glucose (6 or 12 mg) 10 min prior to swim did not significantly change the glucose level estimated before stress. However, it reversed the antinociceptive action induced by both 30 seconds and 3 minutes swim stress at both concentrations.

Drugs acting through opioid receptors are known to produce antinociception which is associated with hyperglycemia (2,3). On the contrary, drugs eliciting antinociception utilising mechanisms other than opioid exhibited no such correlation, rather exhibiting dissociation (4).

In this study, the antinociceptive activity to a varying degree elicited by 30 seconds and 3 minutes swim stress was confirmed. It has been observed that stress (30 seconds or 3 minutes) *per se* did not induce any change in the blood glucose. This observation is in contrast to those (2,3) where in opioidergic analgesic agents alter blood glucose level. This may be due to the low intensity of the stress employed which does not interfere with the acute glucose availability or utilisation in eliciting antinociceptive action. The second aim of the study was tested by pretreating the mice with glucose. Irrespective of the dose used, exogenous glucose administration has reversed the non-opioid as well as opioid segment of antinociceptive activity produced by stress. This observation tempts to suggest that stress induced antinociception is related to the glucose availability. This is in confirmation with our earlier observation wherein the control of clonidine induced hyperglycemia by glibenclamide potentiated antinociception elicited by clonidine (4). Though the results of the study shows that stress *per se* did not induce any significant changes in the blood glucose, a role for glucose in swim stress induced antinociception cannot be excluded since exogenous administration of glucose reverses the antinociceptive action. The finding that the non-opioidergic segment of swim (30 sec) stress induced antinociception is also reversed by glucose, indicates that at least in this assay model glucose plays a role in non-opioidergic and opioidergic antinociception.

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