Effect of tonic pain on schedule specific feeding behaviour

Suman Jain, Rashmi Mathur, Ratna Sharma* & Usha Nayar**
Department of Physiology, All India Institute of Medical Sciences, Ansari Nagar, New Delhi 110029, India
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Food deprivation produces analgesia. This response is reversed i.e. pain sensitivity is lowered, when the food deprived rats are fed. In the present study the effect of chronic pain on the motivation to get food, in food deprived rats, was observed. In ten rats the effect of formalin and morphine plus formalin on the motivation to get food was studied. Injection of formalin significantly ($P < 0.01$) decreased the number of lever presses from $450 \pm 30$ to $225 \pm 25$. However, after injecting morphine the effect was reversed. The present study shows reduced internal drive to procure food by the food deprived animals, when they were under chronic pain. The effect was blocked by morphine, suggesting the role of opioids in modulating the motivation for getting food.

Food deprivation result in stress induced analgesia\(^1\). This analgesia is attenuated by injecting naloxone\(^2\), indicating the involvement of opioids in this analgesia. Further, it has also been shown that endogenous opioid systems modulate the food intake. Central injections of opioid peptides increase food intake\(^3\) in rats, while opiate antagonist decreases food intake\(^4\). Feeding, on the other hand, has been shown to have different effect on the pain than food deprivation. Feeding raises the pain sensitivity in the food deprived animals, whereas, food deprivation lowers it\(^1\). McGivern and Bernston\(^1\), thereby, suggested that the effects of food deprivation on pain sensitivity are related to the hunger state of an animal. This also shows that there exists a complicated relationship between feeding behaviour and pain. This relationship is further complicated by a study in which it was shown in fed humans, that in conditions where tonic pain follows trauma or disease, the food intake is reduced\(^5\). However, what happens to the food intake, after feeding the animals that were food deprived following induction of pain, remains to be studied. In the present study the effect of tonic pain on the motivation to get food (reward) in previously food deprived animals was observed.

Adult male wistar rats weighing between 200 and 300 g, were used for the study. They were housed in an animal room having controlled room temperature ($26^\circ\pm2^\circ$C) and lights on from 05:00 to 19:00 hrs. Water was available to them ad libitum.

Behavioural tests

(a) Formalin test — Each rat was conditioned in the restrainer for 30 min. They were then injected with 5% sterile formalin solution (50 $\mu$l) subcutaneously into the plantar surface of the hindpaw. The formalin was not injected into the forepaw, which is routinely done, as the animal was to use forepaws for pressing the lever. In a pilot study the pain rating obtained in the hindpaw injected animals was found to be comparable with forepaw injected animals. The pain related behaviour was quantified by using a four-point scale as described by Dubussion and Dennis\(^6\). The behaviour of the animal was observed for 10 min.

(b) Food intake — The procedure used for food deprivation is as follows. The rats were initially deprived of food for 5 hr. They were then deprived of food for 10, 15, 20 and finally 23 hr. On the last day of deprivation, they were also given food pellets used in the Skinner, along with the normal routine food pellets. This was done to familiarize the rat with the new variety of food pellets. The rats had access to ad libitum food for only one-hour i.e. between 13.00 and 14.00 hrs, at the same time, everyday, till the observation period. The rats were then magazines trained to press the lever and get the food (food pellet of 4 mg weight) as reward in the Skinner box. Each lever press resulted in the delivery of one pellet (CRF, continuous reinforcement schedule). In the experimental sessions, the rats were run on CRF for 10 min and the number of lever presses made was recorded.

Experimental design — All the ten rats were initially trained to press the lever and get the reward. In the first session, the rats were allowed to press the
lever and get the reward, without any intervention. In the second session, on the next day, 5% formalin was injected into the plantar surface of the hindpaw, and the rat was allowed to press the lever. On the third day, in the third session, morphine (3 mg/kg, i.p.) was given 30 min before formalin injection. The number of lever presses made in all the sessions, during the observation period of 10 min, was recorded.

Analysis of data — The number of pellets delivered in a session was converted into grams to calculate the total food intake in a session. Wilcoxon signed rank test was then used to find out the significant difference, if any, between the number of lever presses and food intake, amongst the three groups.

After 5% of formalin injection, the rats initially licked their hindpaw (score 3) for approximately 5 min, and then tucked its hindpaw (score 2) for the rest of the time with lever pressing intermittently. When morphine was injected 30 min before formalin injection, the rat for initially 5 min was intermittently lifting its forepaw or was grooming (score 1). Later for the rest 5 min it was moving freely on all forepaws (score 0).

In the first experimental session, the rats pressed the lever $450 \pm 30$ times during the 10-min of observation period. This was equivalent to a total food intake of $1.8 \pm 0.5$ g. Following formalin injection, the rate of lever press decreased significantly ($P < 0.01$) to $222 \pm 25$. The total food intake following formalin injection was $0.85 \pm 0.5$ g. However, preinjecting the formalin injected rat with morphine, restored the lever presses and the food intake to the basal value of $405 \pm 40$ and $1.75 \pm 0.6$ g respectively. The results indicate attenuation of the motivation to get food reward in food deprived rats when under pain.

Acute exposure of animals to many experimental stressors induces significant analgesia. Animals exposed to inescapable shock, rotation, food deprivation and other stressors display temporary analgesia. Acute administration of 2-deoxy-D-glucose (2DG) which induces gluocapration produces analgesia in dose dependent manner. Food deprivation inducing analgesia is also well reported. This analgesia is blocked by naloxone, indicating the role of opioids in food deprivation induced modulation of nociceptive behavior. Morphine induced antinociception is decreased with long term intake of palatable nutritive solutions, but is not affected by long term intake of a non-nutritive sweet saccharin, protein or vitamin solutions. Intake of palatable carbohydrates and fats has been shown to enhance morphine induced analgesia. They also modulate mu and kappa opioid receptor mediated analgesia. All these studies indicate a complex relationship between food (especially carbohydrates) and pain. Further injection of opioids also alters the food intake. Central injections of opioid peptides decrease food intake, while, opioid antagonists reduce it. The food intake is also decreased in humans who are under chronic pain. The present study shows that when the animal is under chronic pain, the motivation to procure food is reduced. The observed reduction in the food intake was blocked by morphine, indicating the role of opioids. This suggests that opioids can not only modulate the food intake of the fed animals, but also the motivation to procure food in food deprived animals is altered. It is difficult to pinpoint the exact relationship between food and pain. However, it has been shown that morphine decreases cerebral glucose utilization in a number of limbic and forebrain regions. Decreased glucose availability to ventromedial nucleus of hypothalamus (VMH) is known to inhibit the glucosensitive neurons present in the area, which results in feeding. Therefore, it seems that the endogenous opioids play a relatively specific stimulatory role in feeding.

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