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Ventromedial hypothalamic mediation of sucrose feeding induced pain modulation

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Abstract

Electrophysiological and behavioural studies suggest a modulatory role of ventromedial nucleus of the hypothalamus (VMH) in nociceptive behaviour. Lesion of the VMH produces hyperalgesia and a greater preference for sucrose solution. Hyperalgesia is also produced by sucrose feeding. To explore specifically the contribution of glucoreceptor neurons of the VMH in the mediation of sucrose-fed hyperalgesia, 2-deoxy-D-glucose (2-DG, antimetabolite of glucose) was slowly albeit continuously infused (1 μl/h for 7 days by microinfusion pumps) into the VMH of adult male rats. Simultaneously, the rats underwent tests for their nociceptive responses in control and sucrose-fed states. The tests for nociception, namely, tail flick latency (TFL), thresholds of tail flick (TF), vocalization during stimulus (SV), vocalization after discharge (VA) were recorded at 0500 h. The tests were repeated after 6, 12, and 48 h in 1 M saline (control group) and 2-DG (experimental group) microinfused rats. Rats were presented with sucrose (20%) solution for 48 h at 0500 h ad libitum in addition to food pellets and tap water. Infusion of 2-DG per se in the VMH led to hypoalgesia (in threshold of TF, SV, VA) while feeding sucrose for 6–12 h per se led to hyperalgesia (in TFL, threshold of SV and VA). Sucrose feeding to 2-DG rats, however, attenuated the hypoalgesia of 2-DG as well as the hyperalgesia of sucrose feeding. The results suggest that the VMH glucoreceptor neurons probably modulate sucrose mediated phasic pain responses.

Keywords: 2-DG microinfusion in VMH; Nociceptive behaviour; VMH pain control; VMH glucoreceptors; Sucrose-fed hyperalgesia

1. Introduction

Feeding and nociceptive behaviour are both modulated by opioids (Blass et al., 1987; Dum et al., 1983; Kaufman et al., 1988; Morley et al., 1983; Schoenbaum et al., 1989; Segato et al., 1997) and are recently reported to be closely related (Frye et al., 1993; Kanarek et al., 1997). Ingestion of fats, polycose, and sucrose has an immediate calming and antinociceptive effect in rat pups (Blass et al., 1987), human infants (Bucher et al., 1995; Lewindon et al., 1998), as well as in human adult models (Mercer and Holder, 1997). On the other hand, ingestion of either sucrose or drugs inducing hyperglycemia has been reported to lead to hyperalgesia (Frye et al., 1993; Schoenbaum et al., 1989). The direction of change in pain level is closely correlated with the duration of ingestion rather than to the concentration of sucrose (D'Anci et al., 1996).

The modulatory role of palatable food such as sucrose on nociception may be an attribute of its hedonic qualities directly (Kanarek et al., 1997) and/or indirectly through their action on endogenous opioid peptides in the hypothalamus (Dum et al., 1983; Kaufman et al., 1988; Morley et al., 1983). Lesion of the ventromedial nucleus of the hypothalamus (VMH) leads to finickiness in the choice of food for high carbohydrate (Teitelbaum, 1955) and high lipid diet besides an altered sensitivity to noxious stimuli viz. hyperalgesia to both phasic as well as tonic pain stimuli (Mathur et al., 1995; Turner et al., 1967).

Hypothalamic VMH and lateral area (LHA) intricately control feeding behaviour (Anand and Brobeck, 1951; Hetherington and Ranson, 1940) and have recently been implicated in the nociceptive behaviour (Sikdar and Oomura, 1985). The VMH and LHA exert their influence predominantly by the glucoreceptor and glucose-sensitive neurons contained in it. Both glucose and opioid peptides (morphine, β-endorphin and enkephalins) reciprocally inhibit the glucose-sensitive LHA neurons and excite the VMH glucoreceptor neurons directly (Ono et al., 1980; Oomura et

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al., 1967, 1986). It therefore, appears that these glucose-responsive neurons possibly possess the ability to exert influence on both nociceptive and feeding behaviours (Sikdar and Oomura, 1985).

However, the involvement of the VMH glucose-responsive neurons in the mediation of alterations in nociceptive behaviour related to sucrose ingestion has not been investigated. The present study was designed to explore the involvement of glucose-responsive VMH neurons in the mediation of sucrose-induced modulation of phasic pain. It was proposed to prohibit the use of glucose specifically by these neurons while the rat ingested sucrose ad libitum and simultaneously underwent tests for responses to noxious stimuli. The objective of inhibition of glucose utilisation by these glucose-responsive neurons in the VMH was achieved by a continuous microinfusion of antimetabolite analogue of glucose, 2 deoxy-D-glucose (2-DG) (Wick et al., 1957) for several days, while the nociceptive responses were recorded in sucrose-fed and control state of the rat.

2. Method

2.1. Animals

Twelve male Wistar rats weighing between 180 and 215 g were individually housed on a 14:10 h light:dark cycle. They had access to tap water and laboratory food pellets (Golden Seeds, India) ad libitum. The food and water intake were recorded daily at the same hour while the body weight was recorded weekly. The nociceptive tests in the sucrose-fed state were conducted in both the groups of rats after they received an additional bottle of freshly prepared sucrose solution (20%) ad libitum at 0500 h, which was withdrawn after 48 h. Whenever sucrose solution was provided, its intake was recorded at the end of 6, 12, and 48 h. Ethical guidelines were followed in accordance with the committee for research and ethical issues of IASP and Institute.

Six rats received surgical implant of microinfusion pumps (Alzet, model 2001) containing 2-DG (experimental group). These pumps were filled with 2-DG (12.5 μg in 0.25 ml of 0.9% sterile saline; Sigma, USA) before implantation. They are designed to infuse slowly albeit continuously at a constant rate of 1 μl/h for a week. An equal number of rats received the implants of pumps containing 1 M sterile saline (control group).

2.2. Surgical procedures

Following anaesthesia with ketamine hydrochloride (50 mg/kg, ip; KETMIN, Themis Chemicals, India) animals were positioned in stereotaxic apparatus (David Kopf, USA) with incisor bar at 5° below the intra-aural line. The tip of the cannula attached to the microinfusion pump was implanted in the VMH. The coordinates for the VMH as per Paxinos and Watson rat brain atlas were 2.8 mm posterior to bregma, 0.5 mm lateral from mid-sagittal suture and 9.5 mm ventral from the dorsal surface of the brain (Paxinos and Watson, 1982). The cannula was firmly fixed on the skull by screws and dental cement. The other end of the cannula was fitted to the prefilled microinfusion pump, which was implanted subcutaneously at the back.

The wounds were stitched, antibiotic cream was applied locally, and an intramuscular injection of tetracycline was given. The rats were allowed to recover.

DAY	1	2	3	4	5	6	7
Hours after Ist pain test			0 06 12		48/0 06 12		48
Activity	Surgery	Recovery	↓Pain test ↓	Rest	Pain test ↓ ↓	Rest	Pain test
Grou ps	Saline				*Sucrose***	****	*
	2DG infused				*Sucrose***	****	*

Fig. 1. Figure depicts experimental plan. After implantation of cannula tip in the VMH of the microinfusion pump located at the back, the basal nociceptive responses were tested at 0500 h. They were repeated after 6, 12, and 48 h under control and sucrose-fed states on post-implantation days 3 and 5, respectively. The arrows depict the test session, * depicts the availability of sucrose to the rats.

2.3. Experimental plan

On post-implantation day 3, each rat was tested for responses to both, the electrical and thermal noxious stimuli at 0500, 1100, and 1700 h on that day and again after 48 h at 0500 h. The duration of each test session was 1 h. This test schedule was repeated on day 5,when the rats received sucrose solution (20%) ad libitum after 0500 h test (Fig. 1). They had access to sucrose solution for 48 h. To check for the patency of the infusion assembly, leakage, etc., the pumps were filled with 2% pontamine blue on the eighth day, under anaesthesia (ketamine 50 mg/kg). The rats were allowed to recover. They were sacrificed after 24 h under deep anaesthesia. The brains were perfused and preserved for histological verification of the cannula site as well as for the extent of dye spread and leakage, if any.

2.4. Nociceptive testing

Responses to both thermal and electrical phasic noxious stimuli were recorded. Tail flick latency (TFL) to the former and thresholds for tail flick (TF), vocalization during stimulus and after discharge (SV, VA, respectively) to the latter were recorded. TFL was recorded by tail flick analgesia monitor (Omnitech, USA). Each rat was conditioned for 15 min in a Plexiglass, well-ventilated restrainer before starting the experiment (Narasaiah et al., 1995). The tail, after cleaning with spirit was kept over the trough containing a heating coil. The temperature was set at 45°C and the cut off latency at 30 s. The "on" switch activated both the heat source and the timer. As soon as the rat flicked its tail, the

timer was automatically switched "off" and the latency was noted (Ness and Gebhart, 1986).

The thresholds were assessed by applying AC electric current (Grass Stimulator S4-G, USA) through two needle electrodes inserted intradermally into the tail of the restrained rat. The needle electrodes were prepared from insect pins (00). The electrical stimulus (biphasic square wave pulses 40 Hz, frequency 1.5 ms duration and varying current strength for 200 ms) was applied to the tail. The current strength was increased in steps of 200 μA till the rat flicked its tail (TF). The threshold of electrical stimulus for eliciting SV was recorded similarly by further increasing the current strength (mA) gradually till the rat vocalized which was restricted to the period of stimulation. The VA was recorded by a still further increase in the current strength till the rat vocalized beyond the period of stimulation (Aimone et al., 1988).

2.5. Statistical analysis

The data was analysed by using paired *t* test for comparing the control with the sucrose-fed group and for 2-DG per se with 2-DG sucrose-fed group of rats. Unpaired *t* test was used for data analysis of control group vs. 2-DG group and sucrose-fed per se vs. 2-DG sucrose-fed group of rats. The food intake and body weight data of the pre-infusion with post-infusion state of rats was analysed using one-way ANOVA.

3. Results

3.1. Energy intake and body weight

In the experimental group of rats, the food intake before 2-DG infusion was 14.0 ± 1.26 g, which increased ($P < .001$) on 2 DG infusion days 3 and 4 to 19.33 ± 2.94 and 22.66 ± 5.27 g, respectively (Table 1). However, after sucrose feeding on 2-DG infusion day 5, it decreased to 17.00 ± 3.63 g. It further decreased on days 6 and 7. The rats ingested 9.8, 7.0, and 70.0 ml of sucrose at the end of 6, 12, and 48 h, respectively, thereby supplementing 7.8, 6.8, and 68.6 kcal.

Table 1
Food intake (mean ± S.D.) during 24 h

S. no.	Condition	Food (g)	Food (cal)
1	Pre-infusion	14.00 ± 1.26	50.4
2	Post-infusion day 1	8.83 ± 5.07	33.4
3	Post-infusion day 2	14.16 ± 3.8	54.0
4	Post-infusion day 3	19.33 ± 2.94***	72.0
5	Post-infusion day 4	22.66 ± 5.27***	82.8
6	Post-infusion day 5	17.00 ± 3.63	61.2
7	Post-infusion day 6	16.83 ± 4.73	61.2
8	Post-infusion day 7	16.83 ± 5.70	61.2

Food intake in the 2-DG-infused rats: The food intake increased significantly after infusion of 2-DG for 3 days. The sucrose solution was available on post-infusion days 5 through 7. The statistical analysis was done by one-way ANOVA, $F(3)$.

*** $P < .001$.

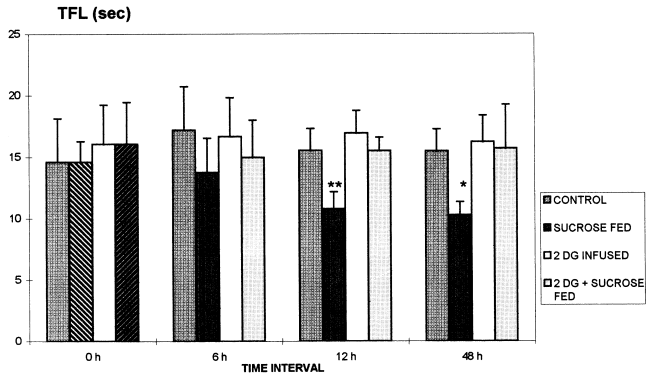

Fig. 2. Effect of sucrose ingestion on TFL of control and 2-DG microinfused rats. The control and 2-DG rats received sucrose after 0500 h. After ingestion of sucrose, the TFL of control rats decreased ($P < .05$) whereas that of 2-DG rats did not.

During the week when 2-DG was infused, the mean body weight gain was 7.28 ± 3.54 g, which was more ($P < .05$) than their own pre-infusion control value of 1.60 ± 5.58 g.

3.2. Tail flick latency

The pattern of TFL at different hours of the day did not vary either in control or 2-DG rats. The TFL of control rats at 1700 h and 0500 h (48 h) was 15.52 ± 3.22 and 15.47 ± 3.43 s, respectively. Sucrose feeding for 12 and 48 h (1700 and 0500 h) decreased it to 10.78 ± 3.8 ($P < .01$) and 10.26 ± 3.04 s ($P < .05$), respectively. Infusion of 2-DG did not vary TFL as compared to controls (16.93 ± 1.87, 16.22 ± 1.33 s at 12 and 48 h, respectively). Sucrose feeding to 2-DG rats did not reduce their TFL, unlike control rats (Fig. 2).

3.3. Threshold of tail flick

2-DG infusion increased the TF significantly ($P < .01$) to 0.12 ± 0.06 mA (1700 h) as compared to that in controls (0.05 ± 0.02 mA). Sucrose feeding per se did not alter the TF in control while sucrose feeding to the 2-DG rats decreased it to the control values (Table 2).

3.4. Threshold of vocalization during stimulus

The threshold of vocalization during stimulus increased to 0.23 ± 0.19 mA after 2-DG infusion and attained a statistical significance ($P < .01$) at 1700 h as compared to that in controls (0.09 ± 0.05 mA). The threshold of SV decreased ($P < .001$) after sucrose feeding for 6 and 48 h by both groups of rats. Sucrose feeding to the 2-DG group of rats returned the SV to control values while sucrose feeding to control rats reduced their threshold of SV (Table 2).

Table 2
Threshold of responses to phasic noxious stimuli in 2-DG-infused rats: effect of sucrose feeding (mean ± S.D. in mA)

Time (h)	Control	Sucrose fed	2-DG	2-DG + sucrose
Tail flick				
0500	0.08 ± 0.06	0.08 ± 0.06	0.09 ± 0.04	0.09 ± 0.04
1100	0.06 ± 0.02	0.04 ± 0.03	0.10 ± 0.06	0.08 ± 0.02 **
1700	0.05 ± 0.02	0.06 ± 0.03	0.12 ± 0.06[§§]	0.08 ± 0.02
0500	0.09 ± 0.08	0.05 ± 0.02	0.09 ± 0.04	0.08 ± 0.04
Vocalization during stimulus				
0500	0.10 ± 0.04	0.10 ± 0.04	0.18 ± 0.13	0.18 ± 0.13
1100	0.10 ± 0.05	0.04 ± 0.03***	0.30 ± 0.24	0.11 ± 0.05***
1700	0.09 ± 0.05	0.06 ± 0.03	0.23 ± 0.19[§§]	0.12 ± 0.03[#]
0500	0.14 ± 0.12	0.05 ± 0.02 **	0.20 ± 0.05	0.10 ± 0.04[#]
Vocalization after discharge				
0500	0.18 ± 0.2	0.18 ± 0.2	0.27 ± 0.20	0.27 ± 0.20
1100	0.16 ± 0.10	0.14 ± 0.1***	0.35 ± 0.23	0.13 ± 0.05
1700	0.16 ± 0.08	0.14 ± 0.08***	0.29 ± 0.17	0.19 ± 0.11
0500	0.20 ± 0.19	0.10 ± 0.06***	0.28 ± 0.27	0.13 ± 0.05

Effect of 2-DG infusion: the statistical analysis was done by paired and unpaired t test. All values are mean ± S.D.
** $P < .01$, comparison between control and sucrose-fed groups of rats.
*** $P < 0.001$.
[#] $P < .05$, comparison between 2-DG and 2-DG sucrose-fed rats.
[§§] $P < .01$, indicates comparison between control and 2-DG group of rats.

3.5. Threshold of vocalization after discharge

The threshold of VA also did not vary with the hour of the day (0.18 ± 0.02 to 0.16 ± 0.08 mA) in control rats. However, sucrose feeding for as early as 6 h reduced ($P < .001$) the threshold in control rats. On the contrary, the threshold was increased by 2-DG infusion and sucrose feeding reduced their threshold for eliciting vocalization after discharge to the control values (Table 2).

4. Discussion

Sucrose feeding per se decreased the TFL, thresholds of SV and VA indicating a hyperalgesic response to phasic noxious stimuli except for TF. Secondly, microinfusion of 2-DG in the VMH led to an increase in thresholds of TF, SV, and VA, suggesting an analgesic response to phasic noxious stimuli. Thirdly, sucrose feeding to the 2-DG rats neither led to the hyperalgesia of sucrose feeding nor to the analgesia of 2-DG microinfusion. The study suggests a pivotal role of the VMH glucoreceptor neurons in modulation of sucrose induced nociceptive responses.

In the present study, the precise role of glucoreceptors in the VMH was studied by a slow, uninterrupted delivery of 2-DG in micro quantities at a constant rate of 1 μl/min for 7 days in the VMH. 2-DG is an antimetabolite analogue of glucose, which prevents glucose utilisation by the neurons. It competes with glucose for hexokinase substrate (as they are structurally similar) leading to an artificial scarcity of glucose in the neurons, thereby inhibiting the phosphohexose isomerase reaction and membrane transport. 2-DG was locally infused into the VMH to circumvent the stress-related effects observed on systemic administration, including marked glucoprivation, peripheral sympathoadrenal discharge, hyperglycemia, etc. (Brown, 1962; Himsworth, 1970; Wick et al., 1957).

Neurons that increase their activity on iontophoretic application of glucose are termed as glucoreceptor neurons (Oomura et al., 1969). Besides glucose, they also respond (decrease activity) to free fatty acids or insulin, further supporting the contention that levels of glucose, free fatty acid, and insulin are important intrinsic signals regulating feeding behaviour (Oomura, 1976). Surprisingly, they also respond to enkephalin/morphine with a similar latency, magnitude and dose effects, although the duration of morphine effect is double that of glucose (Ono et al., 1980). It appears from the above observations that the VMH and LHA glucoresponsive neurons are primarily involved in both, the motivation to eat and the nociceptive behaviour (Oomura et al., 1986; Sikdar and Oomura, 1985). Therefore, we proposed to target our investigations to explore the contribution of the VMH glucoreceptors in sucrose-fed nociceptive response.

The possible mechanism by which sucrose modulates pain is either indirectly through the taste or directly through its metabolic product viz. glucose (Kanarek et al., 1997). VMH glucoreceptors are in an advantageous position as they are in receipt of chemical sensory and neural information from the tongue as well as from the CSF (Shimizu et al., 1983). VMH contains glucose-responsive neurons mostly located near the center of the VMH (as demonstrated by HRP staining) and some of their dendrites extend towards the third ventricle (Ono et al., 1982). We designed experiments wherein the glucoreceptor neurons could not be activated by these physiological cues. We achieved this by local

continuous microinfusion of 2-DG for 7 days which arrests glucose utilisation by the neurons leaving them functionally inactive, while the animal has access to sucrose solution and its response to pain could be tested in an awake state.

Ingestion of sucrose for the moderately longer period of time (6 h) in our study led to hyperalgesia. This is in line with the study of Frye et al. (1993) wherein sucrose was fed for 5 h. They have also studied in rat model. However, they have fed their rats on a higher concentration of sucrose solution (32%) than ours (20%). Moreover, they have tested the nociceptive response (TFL) to only thermal noxious stimulus. Adult female rats were chosen by Frye et al. (1993) while we chose adult male rats. Our study shows hyperalgesia not only to thermal noxious stimulus, but also to electrical stimulation. The study suggests that the hyperalgesic response is probably a generalised one. D'Anci et al. (1996) have reported that calming and pain reducing properties of sucrose are not influenced by concentration or volume of sucrose ingested, therefore a difference in the sucrose concentration of Frye et al. (1993) and our study did not affect the direction of change in the nociception viz. hyperalgesia.

The action of sucrose is proposed to be mediated probably by the interaction between gustatory pathway and opioidergic system (Blass et al., 1987; D'Anci et al., 1996; Kanarek et al., 1997). Sucrose feeding produces analgesia followed by hyperalgesia. The first phase has a shorter duration wherein the β-endorphins are released immediately after sucrose ingestion resulting in a brief period of analgesia (Blass et al., 1987; Dum et al., 1983). The second phase of hyperalgesia, in response to continued sucrose consumption, has been hypothesised to be mediated probably by a gradual decrease in endorphin function, which is attributed to the extension of the refractory period following the initial activity (Schoenbaum et al., 1989). The mechanism of immediate analgesic effect of sucrose has probably drawn the attention of scientists and is therefore better understood than the late hyperalgesic effect.

The immediate effect is explained by most of the workers on the basis of an increase in the release and breakdown of β-endorphin. The hypothalamic concentration of β-endorphin decreases immediately (within 20 min) after the ingestion of sucrose (Dum et al., 1983). Antinociception induced by β-endorphin (administered intracerebroventricularly) is mediated by epsilon opioid receptors (Tseng et al., 1993). β-endorphins induce antinociception by the release of Met-enkephalin and subsequent stimulation of delta opioid receptors in the spinal cord via the activation of serotonergic and noradrenergic system (Tseng et al., 1980). Met-enkephalin is degraded rapidly by enkephalinase and aminopeptidase. The intrathecal injection of Met-enkephalin inhibits the tail flick response for 1–2 min and returns to basal value after 10 min, which explains sucrose fed immediate analgesic effect.

The mechanism for the late hyperalgesic effect of sucrose ingestion cannot be explained purely as for the early effect, but there is a possibility that repeated albeit interrupted ingestion of sucrose leads to a pulsatile release of β-endorphins and the consequent analgesia. This is possible, when the sucrose stimulus is paced such that there is sufficient time for its synthesis. However, with the passage of time, when the stimulus is more frequent, the limitation of synthesis process reduces β-endorphin levels. This may account for a further increase in the preference for carbohydrates, in our case for 'sucrose.' This was evident by a gradual increase in sucrose intake, since smaller quantities of opioids increase the preference for carbohydrates (Milano et al., 1988). The possibility of other mechanism cannot be ruled out as there are multiple opioid receptors located in the VMH (Finley et al., 1981).

There was an increase in TFL and thresholds of TF, SV, and VA indicating hypoalgesia in our rats following 2-DG microinfusion in the VMH. Electrical stimulation or activation of the VMH leads to analgesia (tooth pulp evoked response) (Rhodes, 1979), while lesion (electrolytic/GTG lesion) to hyperalgesia (TFL, TF, SV, VA, and tonic pain) (Mathur et al., 1995; Turner et al., 1967). However, both these procedures activate a heterogeneous population of neurons, thereby activating different sets of interneurons. Therefore, the results are difficult to explain in terms of specific neuronal involvement. This is further supported by iontophoretic glucose application to 43 neurons in the VMH. Only 24 neurons were excited while 19 were unaffected (Ono et al., 1980). In our experimental paradigm, 2-DG was specifically targeted to act on glucoresponsive neuronal population of the VMH. Intracarotid administration of 2-DG was undertaken by Desiraju et al. (1968). They reported a decrease in the activity of the VMH neurons only and no effect on neuronal activity of anterior, middle or posterior nuclei was observed. Conversely, iontophoretic application of glucose increases the glucoreceptor neuronal activity (Oomura et al., 1969) and 2-DG produces no distinct response (Oomura, 1976). This discrepancy is probably due to either insufficient quantity or time to exhibit the change. A decrease in activity of the VMH glucoreceptor neurons is associated with analgesia. In our 2-DG-infused rats, there was analgesia because 2-DG competes with glucose (Wick et al., 1957), which probably left the neurons functionally inactive.

It was surprising to observe the reversion of 2-DG analgesia to eualgesic state by sucrose ingestion. There are no previous reports to this effect, however, it may have been possible because 2-DG competes with glucose and arrests its metabolism, thereby decreasing its activity as discussed in previous paragraphs. It appears that sucrose ingestion leads to a greater availability of glucose in the VMH, which competitively gains entry into the neurons and counteracts the effect of 2-DG, thereby restoring normalcy and eualgesic state. Glucoreceptors were functionally left inactive (glucoprivation) by our 2-DG infusion and this is further supported by an increase in food intake and larger gain in body weight of our rats.

These observations support the contention that glucoreceptors in the VMH respond both to glucose and opioids vis-a-vis exert control on both feeding and nociceptive behaviour, and more interestingly, they also govern the sucrose ingestion-induced nociceptive behaviour.

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