ELECTROPHYSIOLOGICAL CORRELATES OF DIURNAL FEEDING RHYTHM DISRUPTION IN RATS

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(Received on June 29, 1981)

Summary: Electrical activity was recorded simultaneously from Ventromedial (VMH) and Lateral Hypothalamus (LH) in chronically prepared rats before and during one hour gustation tests as also during and after food intake in Group I (*ad lib* feeding) and Group II (3-hour food schedule) animals. The VMH/LH activity designated as Response Ratio (RR) was calculated and gave a better index of the food related behaviour. The basal RR was higher in Group I as compared to Group II rats but the response to glucose and saccharin ingestion showed a differential pattern of decrease after glucose intake in Group I and an increase in Group II. By contrast, on saccharin intake, Group I showed an increase. RRs after food intake did not show a significant change in both Group I and II rats.

Key words: VMH/LH activity gustation response ratio hypothalamus

INTRODUCTION

The dual neural control over oral intake is now widely accepted. It is shown that the increase in the activity of lateral hypothalamus (LH) initiates and sustains eating (1,2,5, 11), whereas the increase in activity of ventromedial hypothalamus (VMH) leads to cessation of feeding (8,14,21). The reciprocal relationship between LH and VMH is also shown (29,30,38). Further investigations have indicated that VMH is involved in long-term regulation of nutritive state (16,32) and the LH activation is known to be "Pleasant" (28). In addition rhythms in hypothalamus (25) and oral intake (7,8,19,20) are known. However, the studies relating hypothalamic activity with intake in unrestrained animals are lacking. Again, though it is known that the feeding rhythms in rat are easily disrupted by meal-time restriction (13,33) the hypothalamic activity changes which may accompany it are not known and hence it has been undertaken in the present investigation.

MATERIALS AND METHODS

Two groups of adult rats of either sexes housed in individual cages were used. Gr I rats were on *ad lib* feeding. Gr II rats were adapted to 3 hr food schedule (9.15–12.15 hrs) for a period of 3–4 months. The body weight (bw), and food and water intake of rats were observed daily. One hour single bottle tests were conducted between 8.00 to 9.00 hrs for both the groups for a period of 3–4 months. Solutions of glucose, saccharin, sodium chloride, and quinine sulphate, were used for gustatory tests. After adaptation of feeding schedules and gustatory tests, the animals were prepared for the electro-physiological investigations. Stereotaxically-directed monopolar stainless steel electrodes, insulated excepting at tip (tip diameter and length 0.1 mm each), were chronically implanted one in VMH and the other in LH. The third electrode fixed on the skull surface served as indifferent electrode. After 3–5 days of post operative rest, the electrical activity from VMH and LH of unrestrained Gr I and Gr II rats was recorded with ink-writing dynograph, both during gustatory tests as well as during and after the availability of food. The recordings were obtained at regular intervals of 5, 15, 30 and 60 min during the solution tests, whereas the recordings after the availability of food were obtained at regular intervals of 1 hr each. The "after food" recordings were obtained from 9.15 hrs to 18.00 hrs in Gr I rats and from 9.15 hrs to 15.00 hrs in Gr II rats. The placement of electrodes was histologically verified after the conclusion of electrophysiological investigations.

RESULTS

On the disruption of diurnal feeding rhythms though the calorie intake and the bw of Gr II rats showed decrease initially as compared to Gr I rats, after 3–4 months of adaptation the bw of Gr II rats (224±6.5 *gms*) was similar to bw of Gr I rats (226±9.2 *gms*) inspite of their decreased calorie intake (17.5±0.44 Cal/100 *gm* bw) as compared to the intake of Gr I rats (19.2±0.61 Cal/100 *gm* bw). After such long period (3–4 months) period of adaptation to feeding schedules, electrophysiological invesitigations were initiated.

Recordings from VMH and LH of both Gr I and Gr II rats obtained before and at regular intervals (5,15,30 and 60 min) during 1 hr of solution intake are shown in Fig. 1 and 2. In Fig. 3 are shown the recordings obtained before and at regular intervals of 1 hr each after the food was given to Gr I and Gr II rats. The electrical activity in any recording session was first computed as frequency/min (Table I). Then the ratio of the frequency of the activity in VMH to that of in LH (VMH activity/LH activity) was calculated and designated as "Response Ratio" (RR). The RRs before and at different intervals during the intake of solutions are shown in Table II whereas Table III shows the RRs before and after food was given to Gr I and Gr II rats.

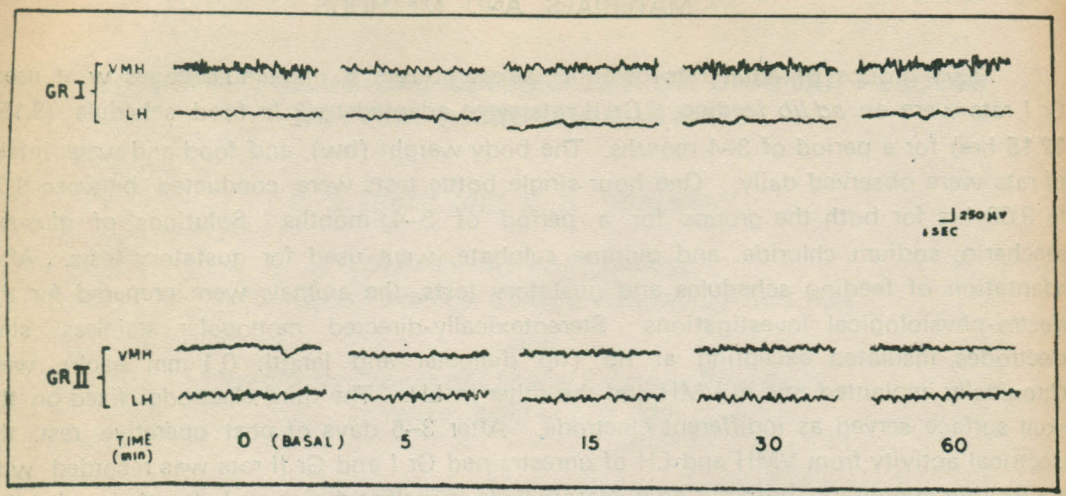

Fig. 1 : Recordings of hypothalamic (VMH and LH) activity of Gr I & Gr II rats before (0 time) and at regular intervals (5,15,30 and 60 min) during glucose intake.

The basal RR (1.34±0.14) of Gr I rats (Table II) one or two minutes before initiation of solution test was significantly higher as compared to that of Gr II rats (0.70±0.04). On ingesting glucose solution the RR of Gr I rats decreased at all recording intervals. However, the decrease was not significant excepting for the decrease at 5 min interval (0.74±0.04).

TABLE I : Hypothalamic activity (wave freq ± SE/min) changes in rats (Gr I and Gr II) during solution intake.

Group	*Solution*	*Hypothalamic area*	*Min*				
			0	5	15	30	60
I	Glucose	VMH	158.3±24.6	190.8±19.6*	245.7±18.7	219.7±12.3	196.0±21.8
		LH	216.4±21.7	256.1±17.1	224.2±59.2	231.7±19.2	223.8±32.5
II	Glucose	VMH	83.5± 6.1	117.6± 7.9*	123.4±4.1*	129.6± 3.4*	101.6± 9.8
		LH	118.1± 7.5	106.4±12.9	102.8±10.2	97.0±17.4	108.4± 7.9
I	Saccharin	VMH	258.3±24.6	221.0±46.6	211.9±34.6	223.8±14.2	266.2±52.2
		LH	216.4±21.7	148.3±25.9*	155.2±14.1*	141.4± 9.9*	131.9±14.9
II	Saccharin	VMH	83.5± 6.1	115.0± 3.2*	84.4± 5.9	122.1± 6.5*	87.9± 5.1
		LH	118.1± 7.5	106.6± 6.1	142.5± 2.9*	117.4± 7.7	142.5± 7.1*

*$P < 0.05$
Activity at '0' time taken as control.

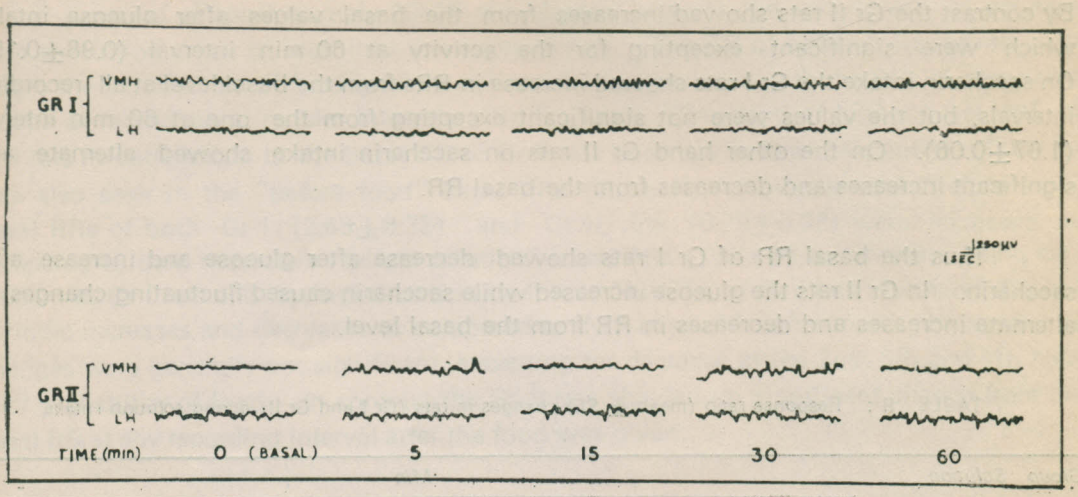

Fig. 2 : Recording of hypothalamic (VMH & LH) activity of Gr. I & Gr II rats before (0 time) and at regular intervals (5,15,30 and 60 min) during saccharin intake.

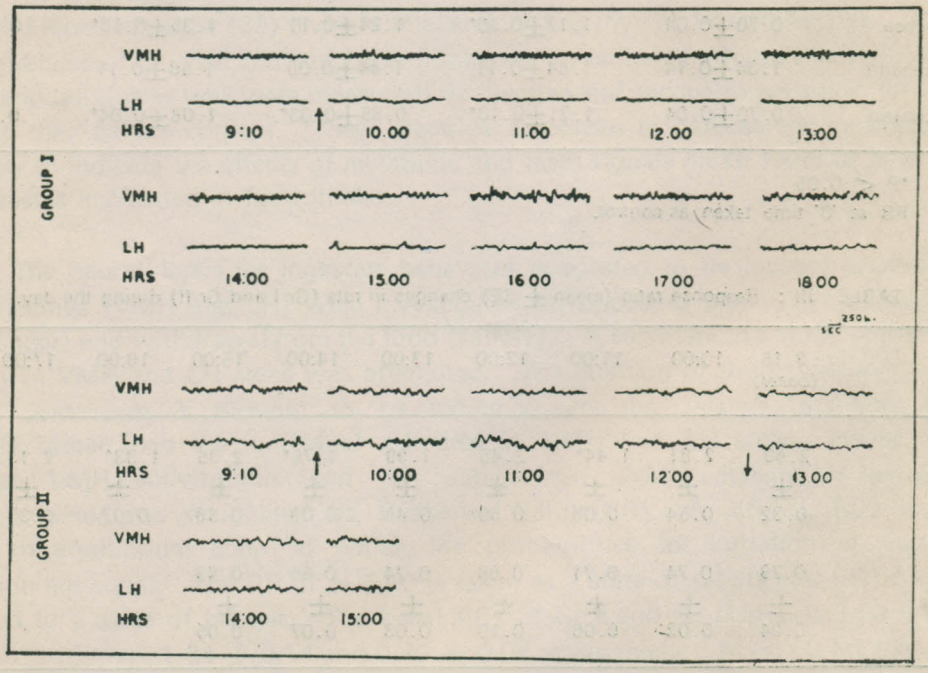

Fig. 3 : Recordings of activity in hypothalamic areas (VMH & LH) of Gr I and Gr II rats before and at regular intervals after food. The food was given at the mark ↑ for both Gr I and Gr II rats and taken out from Gr II rats at ↓ mark but not from Gr I rats.

By contrast the Gr II rats showed increases from the basal values after glucose intake, which were significant excepting for the activity at 60 min interval (0.98±0.15). On saccharin intake the Gr I rats showed increase in RRs from the basal level at all recording intervals, but the values were not significant excepting from the one at 60 min interval (1.67±0.06). On the other hand Gr II rats on saccharin intake showed alternate and significant increases and decreases from the basal RR.

Thus the basal RR of Gr I rats showed decrease after glucose and increase after saccharin. In Gr II rats the glucose increased while saccharin caused fluctuating changes of alternate increases and decreases in RR from the basal level.

TABLE II : Response ratio (mean ± SE) changes in rats (Gr I and Gr II) during solution intake.

Group	*Solution*	*Min*				
		0	5	15	30	60
I	Glucose	1.34±0.14	0.74±0.04*	1.20±0.23	0.96±0.24	0.95±0.14
II	Glucose	0.70±0.04	1.17±0.10*	1.24±0.11	1.35±0.18*	0.98±0.15
I	Saccharin	1.34±0.14	1.64±0.11	1.44±0.06	1.58±0.11	1.67±0.06*
II	Saccharin	0.70±0.04	1.21±0.13*	0.35±0.03*	1.08±0.04*	0.38±0.05*

*$P < 0.05$
RR at '0' time taken as control.

TABLE III : Response ratio (mean ± SE) changes in rats (Gr I and Gr II) during the day.

Time (hrs)	9.15 *(basal)*	10:00	11:00	12:00	13:00	14:00	15:00	16:00	17:00	18:00
Group I	2.69 ± 0.32	2.81 ± 0.54	1.44* ± 0.08	2.45 ± 0.50	1.99 ± 0.46	1.76* ± 0.09	2.35 ± 0.38	1.33* ± 0.07	2.13 ± 0.33	1.69 ± 0.41
Group II	0.79 ± 0.04	0.74 ± 0.02	0.71 ± 0.06	0.68 ± 0.10	0.74 ± 0.03	0.66 ± 0.07	0.83 ± 0.05			

*$P < 0.05$
RR at 9.15 hrs taken as control.

A period of approximately 10–15 min elapsed between the withdrawal of solution from and introduction of food into the cages of rats. The RR of either group of rats just before the introduction of food is taken as basal for comparisons with the RRs of respective groups of rats taken at regular intervals after the food. The trend of higher basal RR of Gr I rats in comparison to the basal RR of Gr II rats observed before the solution (Table II) was also seen in the "before food" basal RRs (Table II). However, the "before food" basal RRs of both Gr I (2.69 ± 0.32) and Gr II rats (0.79 ± 0.06) were increased as compared to their respective "before solution" basal RRs (Table II) the increase being significant in Gr I rats and not significant in Gr II rats. The RRs of Gr I rats after food showed periodic increases and decreases as compared to their basal RR before food. However, the changes were generally not significant, excepting for decrease at the 2nd, 5th and 7th hour after availability of food. In contrast the Gr II rats showed no significant change from the basal RR at any recording interval after the food was given.

DISCUSSION

The investigation is intended to identify the electrophysiological basis for oral intake responses reported earlier (33) under normal and feeding rhythm disrupted states. The electrical correlates of glucose and saccharin intake are investigated (though behavioural intake of salt and quinine as well were measured) as glucose and saccharin are sweet for taste but differ in their calorie content. These electrical responses to glucose and saccharin intake are likely to indicate the effects of metabolic and taste signals on Gr I and Gr II and central mechanisms implicated in food intake.

The neural basis for ingestive behaviour suggested to be located primarily in the hypothalamus (VMH and LH) were investigated for opposing behaviours of readiness to eat (hunger) and withdrawal from the food (satiety). A simultaneous study of the electrical activity in VMH and LH areas was attempted. The position of the animal in the hunger-satiety continuum is thought to be indicated by the relative activities in VMH and LH, rather than the individual activities in VMH and LH areas. Hence the ratio between VMH activity/min and LH activity/min (VMH activity/LH activity) has been computed and designated as Response Ratio (RR). A RR of 1.00 is thought to be an equilibrium state in which the probabilities for initiation or cessation of ingestion are equal. The RR of > 1.00 is taken as a state of satiety and RR of < 1.00 is equated to a state of hunger. The basal RRs of Gr I and Gr II rats at 8.00 hrs (before solution test) were 1.34 ± 0.14 and 0.70 ± 0.04 respectively. At 08.00 hrs the Gr I rats had distended stomachs and were sleepy apparently due to their nocturnal feeding (20). They were temporarily disturbed when over head electrodes were connected to pen recorder and relapsed into sleep again. On the other hand, at 08.00 hrs the Gr II animals were

actively moving in their cages and frequently stood on their hind limbs to stare at the investigator. The basal RRs of Gr I and Gr II rats which indicated "satiation" and "hunger" respectively were therefore correlated well with their behaviour.

After glucose intake Gr I rats decreased their RRs, though not significantly, throughout the 1 hr period of observation (Table II). The decrease in RRs was due to decrease in VMH activity as well as to increase in LH activity, both of which were slight (Table i). The LH activity appears to be stimulated by specific signalisation pattern of glucose taste which has greater number of large spikes as compared to number of small spikes (14). Generally the taste information is known to project on to the LH via brachium conjunctivum (27) and prefrontal cortex (31). The activation of LH is known to be preferred by the animals for its "pleasant" aspect (16,28). Hence Gr I rats by periodical ingestion of glucose could have sustained the "pleasant" LH activation. On the other hand the VMH of Gr I rats on glucose intake showed reduced activity contrary to expectations based on earlier studies on glucose absorption (37) and glucose perfusion studies (3,4). However, the earlier perfusion studies (3,4) were conducted on anaesthetised animals which necessarily involves overnight starvation. The starvation leads to reduction in blood glucose levels and hence to reduction in VMH activity also (2). On perfusion with glucose the low basal VMH activity of over-night starved animals could have increased. The Gr I rats of present investigation in contrast were allowed to feed themselves during the night. It is reasonable to assume that the Gr I rats being nocturnal ingested large amounts of food during night (19) and had high blood glucose levels at 08.00 hrs and hence high basal VMH activity. Any rise in blood glucose level after oral intake of glucose (37) or after the sweet taste (23,24) was probably not sufficient to increase further the already high VMH activity. However, Gr I rats showed a slight decrease in VMH activity after glucose intake (Table I). This decrease may be a reciprocal response to the increased LH activity (29). Anyway the decreased RRs indicate that Gr I rats were "hungry" for glucose. This is supported by larger oral intake on glucose as compared to saccharin (33). In contrast to Gr I rats the Gr II rats showed increase in RRs after glucose (Table II). The increase was evidently due to the increase in VMH activity though the LH activity also showed slight increase. The Gr II rats were starved overnight and were thus similar to rats of Anand *et al.* (3,4) which showed increased VMH activity after perfusion with glucose. The increase in VMH activity of Gr II rats appears to be due to increased blood glucose levels resulting from the reflex release of bodily stores of glucose on orogastric stimulation with sweet taste (23,24) or the rapid absorption of glucose from the gut (37) or both. The sweet taste of glucose in addition may also be responsible for the slight increase in LH activity through its hedonic properties (16,28). Therefore, the increase in RRs of Gr II rats glucose, indicating a shift towards the state of "satiety" appears to be due to larger increase in VMH activity as compared to the slight increase in LH activity.

Thus the hypothalamic activities of Gr I and Gr II rats indicated that whereas the former group was ready to ingest the later group was "satiated" on tasting glucose.

The saccharin-induced RRs in Gr I and Gr II rats (Table II) were in contrast to glucose-induced RRs. The Gr I rats showed increased RRs whereas Gr II showed alternate increases and decreases as compared to their respective basal RRs. The increase in RR of Gr I rats was mainly due to significant decreases in LH activity after saccharin though slight decrease in VMH activity was also responsible (Table I) The decrease in LH activity may be attributed to bitter after taste of saccharin (6,39) which is signalized by higher percentage of small spikes than the percentage in signal pattern of glucose (14) and the small spikes are shown to be related to bitter taste (6) The VMH activity of Gr I rats after saccharin also showed a slight decrease after saccharin. The simultaneous decrease in VMH and LH activities is difficult to explain. However, it is reported that mesencephalic reticular stimulation decreases the acitvity both in VMH and LH (10). Saccharin may be acting in a similar fashion and reducing the VMH and LH activity simultaneously. Anyhow the increased RRs after saccharin intake indicated that for Gr I rats the saccharin was not acceptable which was substantiated by behavioural ingestion of lowered intake on saccharin as compared to the intake on glucose (33). The Gr II rats in contrast showed periodical increases in VMH activity after saccharin intake (Table I). The increases in VMH activity appear to be due to reflex release of glucose from the bodily stores (23,24). As the anticipatory release of glucose was not reinforced by absorption from the gut after saccharin intake the VMH activity may have showed reversion to the basal level of activity. The reversion of VMH activity to basal level coincided with periodical significant increases in LH activity from its basal level (Table I). It indicates that the sweet taste signals of saccharin are "pleasant" for Gr II rats at least periodically. The bitter after-taste signals of saccharin (6,59) explained earlier as responsible for decreasing the LH activity of Gr I rats were ineffective on LH activity of Gr II rats. Probably they are suppressed (12, 36) by the Gr II rats in preference to sweet taste signals. Anyway the periodical increases and decreases in RRs of Gr II rats after saccharin may be the neural basis for behavioural intake of saccharin which was similar in amounts to that of glucose intake (33). The electrophysiological responses to saccharin, thus indicated that whereas for the Gr II rats the saccharin was acceptable atleast periodically, for Gr I rats it was not.

In short the hypothalamic responses of Gr I and Gr II rats were correlated well with their behavioural intake. Though the bws of Gr I and Gr II rats were similar their basal RRs as well as RRs to glucose and saccharin solutions were dissimilar. The RRs of Gr I rats showed their "readiness" to ingest glucose and "satiation" to saccharin. The RRs of Gr II rats showed almost the reverse. This indicates that *ad lib* feeding (Gr I)

predisposes the animal for calorie regulation whereas feeding rhythm disruption (Gr II) inclines it towards the sensory regulation of intake. The Gr I and Gr II rats of this investigation thus are similar to energy surfeit and energy deficit animals respectively of the model presented earlier (18) and subsequently reinforced (35).

In further extension of the studies, the electrical activities in VMH and LH of Gr I and Gr II rats were recorded before and at regular intervals of 1 hr after the food was given. The recordings of Gr I rats were obtained from 09.15 hrs to 18.00 hrs whereas recordings of Gr II rats were obtained from 9.15 to 15.00 hrs. The Gr I rats are known to become active and ingest food at about 18.00 hrs (20) and so the study was extended upto 18.00 hrs. The study of Gr II rats was terminated at 15.00 hrs, because the food was removed from Gr II rats at 12.15 hrs as stated earlier and it was assumed that post-absorptive period of 3 hrs was sufficient for effects on VMH and LH to be seen. The activity in VMH and LH recorded just before giving the food (9.15 hrs) was taken as basal for comparison with recordings obtained later. The basal RRs before food of Gr I rats (2.69 ± 0.32) and Gr II rats (0.79 ± 0.06) showed an increase over their basal RRs before solutions of 1.34 ± 0.14 and 0.70 ± 0.04 respectively. Whereas the "before food" basal RR of Gr I (2.69 ± 0.32) was significantly increased as compared to its "before solution" basal RR (1.34 ± 0.14), it was not so in Gr II rats. The increase in basal RRs of both groups of rats before food may be thought as due to stomach distension caused by solution intake which in its turn is known to increase the VMH activity (34). However, a large portion of 1 hr intake of glucose and saccharin solutions is ingested by both groups of rats in the first 5 min interval but not before food. Hence if increase in RRs is due to stomach distention, the increase in RRs at 5 min interval ought to be more than the increase at the end of 1 hr i.e. before food. Again if increase in RRs is distension-induced the Gr I rats with small sized stomach (13) and slower absorption across the intestine (37) as compared to Gr II rats ought to show a greater increase than that evidenced by Gr II rats in RRs recorded at 5 min interval after solution intake as contrasted with the "before food" RR. Contrary to expectations the reverse was shown (Table II). The Gr II rats showed at 5 min interval increased RRs (1.17 ± 0.10 after glucose and 1.21 ± 0.13 after saccharin) over their "before food" RR (0.79 ± 0.04), whereas Gr I rats at the 5 min interval showed RRs (0.74 ± 0.04 after glucose and 1.64 ± 0.11 after saccharin) which are less than their before food RR (2.69 ± 0.32). Therefore, it appears that the stomach distension is not the cause for increased basal RRs before food. It is possible that the increase in RRs before food may be due to long adaptation of Gr I and Gr II rats to their respective feeding schedules, which appropriately modulated their diurnal hypothalamic activities. This is suggested by the recent investigations on food and fluid intake (26, 35) which showed plasticity of hypothalamic neurons. Anyway, the recordings obtained at 1 hr interval before and after food from Gr I rats showed a

slow transition in LH activity from the low frequency at 9.15 hrs (70±2.8/min) to higher frequency at 18.00 hrs (138±1.9/min), whereas the activity in VMH did not show much deviation from the basal (Fig 3). This indicated that Gr I rats were slowly shifting towards the state of hunger in the hunger-satiety continuum as the evening approached. In contrast to these changes in RRs of Gr I rats, the Gr II rats showed no significant change from their basal RR of 0.79.±0.04 throughout the series of recordings (Table III). However, the VMH activity was slighly depressed and LH activity was approximately stable from 09.15 hrs to 12.15 hrs when the food was available to Gr II rats (Fig. 3). After the food was removed at 12.15 hrs, the VMH activity was slighlty increased. The rats showed RRs which were < 1.00 throughout the period of observation. It indicated that Gr II rats were hungry even after ingesting 17.5±0.44 cal/100 *gm* bw within 3 hrs.

In summary the electrical activities in VMH and LH of Gr I rats and their computed RRs indicated that Gr I rats were satiated and not inclined to eat during the light phase of light-dark diurnal cycle. However, at the approach of dark phase (18.00 hrs) the Gr I rats evidenced reduced RR which is an indication of inclination to eat. In contrast the electrical activities in VMH and LH as well as computed RRs of Gr II rats indicated that they were in constant "readiness" to eat.

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