EFFECTS OF SUCCINYLCHOLINE AND RELATED SUBSTANCES ADMINISTERED INTO THE MEDIAL PREOPTIC AREA ON THE LOCAL EEG, BODY TEMPERATURE, HEART RATE, GALVANIC SKIN RESISTANCE AND BIOGENIC AMINES

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Summary : Succinylcholine (Sch) which is a cholinergic neuromuscular blocker has been known to occasionally lead to episodes of malignant hyperthermia in swine and humans. In order to find whether it producces any hyperthermic effects through action on medial preoptic area, experiments were carried on by administering intracerebrally the chemical into the medial preoptic area through an in-dwelling cannula-cum-electrode in the free moving rat. The changes in body temperature and the local EEG were studied. For comparison purpose, the effects of carbachol, atropine and phenylephrine were also studied. Further, in the curarized state of no muscular activity, the effect of SCh on the preoptic area was again tested and also the changes in the other autonomic parameters of heart rate and galvanic skin resistance (GSR) were studied. It was observed that SCh given into preoptic area caused a clear hyperthermic effect. The effect was countered by prior administration of atropine into the site. After SCh the local EEG changed into a high amplitude slow wave format. The heart rate was not altered but the GSR increased by two-fold. Carbachol caused a rise in body temperature, heart rate and also GSR. SCh also caused a reduction in noradrenaline content of the hypothalamus by 23% while no change in dopamine and serotonin occurred. Serotonin increased by 28% in the brainstem with no change in the other amines. Septum showed an increase of noradrenaline and dopamine contents by 40% and 25% respectively. Keeping in view the monoaminergic connections and thermoregulatory role of the preoptic area, one may postulate that SCh could inhibit the warm sensors and the controls of the dual sympathetic mechanism which normally leads to an increase of sudomotor activity and a decrease of vasomotor activity, the inhibition resulting in rise of body temperature.

Key words : muscle relaxants thermoregulation malignant hyperthermia

INTRODUCTION

A constant body temperature is maintained by a wide variety of physiological and behavioural responses and the hypothalamus is one of the primary integrative and controlling structures in thermoregulation. Certain hypothalamic neurons, especially those in the preoptic region and anterior hypothalamus (PO/AH) are temperature sensitive and

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change their firing rates when the hypothalamic temperature is altered (6). Other structures endowed with thermoregulatory and thermosensitive mechanisms are septum, posterior hypothalamus, midbrain, pons, medulla and the spinal cord. PO/AH is important in that it plays the role of a sensory integrator of thermal information and high Q_{10} and low Q_{10} pools of thermosensitive neurons have been located here.

A change in peripheral temperature elicits appropriate thermoregulatory responses (6). Thus, a decrease in peripheral temperature causes metabolic heat production, bringing into play either shivering or non-shivering thermogenesis. Skin blood flow is also altered by cutaneous vasomotor tone bringing about vasoconstriction when there is a decrease in temperature. An increase in temperature causes the evaporative heat loss mechanism to operate and panting and sweating are the common physiological responses. The vasomotor tone is again altered leading to vasodilation and thereby increased heat loss.

Several chemical substances have been found to exert effects on body temperature when administered intracerebrally. Thus compounds belonging to the class of adrenergic, cholinergic, serotonergic, histaminergic (23), purinergic, opioidergic (7), GABAergic and peptidergic (5) as well as the ionic milieu are all known to influence the temperature homeotasis. However, there is a lot of controversy and debate over inconsistent experimental findings which create problems in determining the role played by a specific substance in thermo-regulation. Variations in effects are attributed to species differences route of administration, drug dosage and also the ambient environmental temperature.

It is well known that most of the biogenic amine containing neurons are localised in the brainstem and innervate the forebrain by the ascending axons. It has been shown that the medial preoptic area contains substantial quantities of noradrenaline and dopamine (35) both of which appear to be contained in terminal fibres (34). These fibres are thought to originate from discrete NA and DA cell groups that lie caudal to medial preoptic area (3). The A11 cell group is assumed to innervate certain hypothalamic nuclei also (2). Dopaminergic cells have been found in the lateral edge of the arcuate and periventricular (A12 cell group) (9), and a smaller cell group (A14) is formed by a few cells in the periventricular preoptic nucleus (2, 3).

The medial preoptic area catecholamine mechanisms have been implicated in the control of thermoregulation (8,11). It has been shown that the NA innervation of the medial preoptic area is derived from A1 and A2 cell groups of the medulla whereas the A14 cell group is responsible for the DA innervation (10).

With this knowledge in view, the medial preoptic thermoregulatory area of the rat was chosen as the site for experimental manipulation with the muscle relaxant succinylcholine (17, 22) which some times acts as a trigger in bringing about abrurpt onset of episodes of malignant hyperthermia in swine (15, 17, 19, 22) and humans (30, 36). Succinylcholine is equated to two molecules of acetylcholine joined together and has action at cholinergic junctions (12).

MATERIAL AND METHODS

Adult male Wistar rats of the Institute colony in the weight range of 280-330 g were used. Initially groups of male and female rats of the same age were monitored continuously from morning 9 : 00 a.m. to evening 8 : 00 p.m. for fluctuations in the rectal temperature during a day. Temperature was monitored using the Telethermometer model TA 41 and inserting the YSI probe 402 to a depth of 7 cm in the rectum. During the brief period of temperature measuremet, the animals were restrained by holding in the hand. The female rats showed a higher body temperature than male rats. Both groups showed a nadir around 2:00 p.m. of about 0.7°C from the basal value as measured at 9:00 a.m. and a peak around 6:30 p.m. (Fig. 1). All experiments were carried out between 9:00 a.m. and 12:00 noon during which period temperature fluctuations of the animals were hardly 0.1°C. For, estimation of biogenic amines also, the animrals were sacrificed between 9:00 and 10:00 a.m.

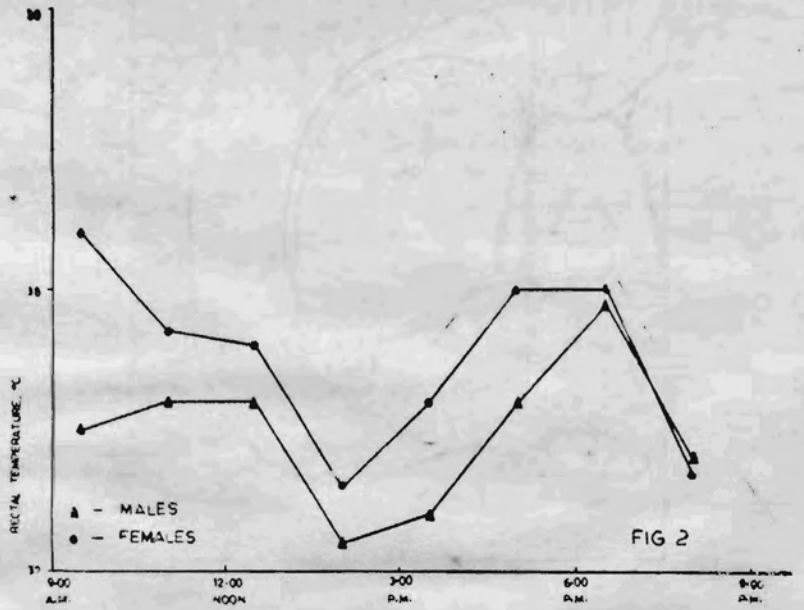

Fig. 1 : Rectal temperature in groups of Male and Female rats during the day.

Male rats were preatropinized and anaesthetised with pentobarbitone sodium given i.p. at a dose of 45 *mg/kg* body weight. Using the rat stereotaxic atlas of Pellegrino and Cushman (29) chronic implantations were done in the medial preoptic area with bipolar electrodes each consisting of an insulated injection needle joined to a 30 gauge insulated wire to have the dual facility of recording the local EEG of the thermoregulatory area and also injecting drugs. The insulation material used was a 10% W/V of polymethyl-methacrylate in chloroform (21). The reference electrode was placed on the cerebellar epiosteal surface. Preoptic-hypothalamic EEG with the bipolar electrode and monopolar recording with reference to surface electrode was recorded. The coordinates of the placements approximately were AP=7.8mm, H=8mm and L=1mm (Fig. 2). The connula was kept patent by placing a stillete inside it. The anchor screws and the cannula were fixed to the calvarium by using dental cement.

The depth EEG was recorded from a free moving animal using the Nihon-Kohden 13 channel EEG machine. Before injecting a drug, a control recording was taken after injecting 1 µl of isoosmolar buffer, the solution used for dissolving the drug. The pH

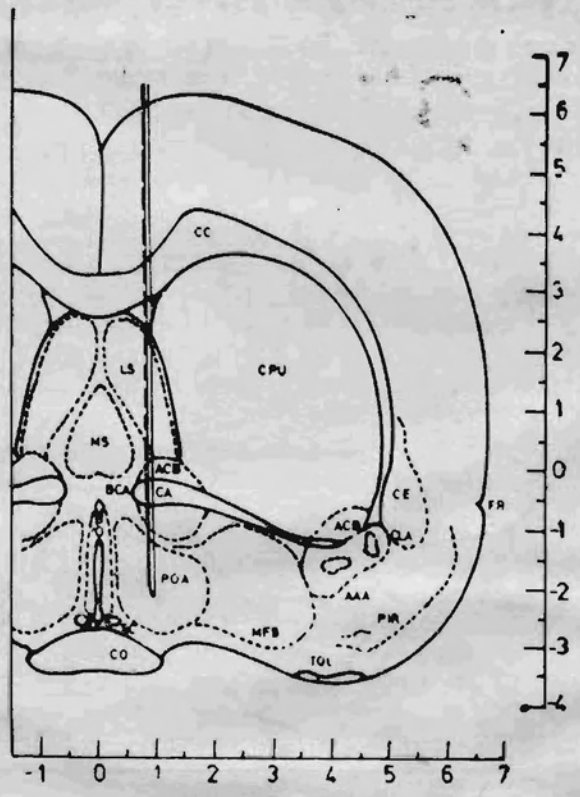

Fig. 2 : The intra-cerebrally implanted cannula-cum-electrode is illustrated in position. POA : medial preoptic area.

was adjusted to 7.2 and the solution was warmed to body temperature before injecting. The power spectral quantification of the EEG was also obtained on-line with the help of a computer.

Autonomic parameters of heart rate and galvanic skin resistance (GSR) were recorded on a Grass or a Beckmen polygraph machine, after curarizing the animal by injecting flaxedil ip (40 *mg/kg*). The animal was maintaind on artificial respiration. Heart rate was recorded by fixing silver electrodes on the limbs.

Biogenic amines were estimated using the Amberlite CG-50 column chromatography and thereafter estimating the amines spectrofluorometrically. An ethylene-diamine condensation method was used for estimating NA ad DA whereas opthalaldehyde was used for developing the fluorophore for serotonin. The method adapted was that of Ogasahara *et al.* (27) with the packing column height being reduced to 4.2 cm.

Animals were sacrificed by cervical dislocation one hour after the administration of the drug intracerebrally, when the core temperature had changed. The heads were dropped into chilled 3% perchloric acid containing 0.2% EDTA and 0.2% ascorbic acid. The skull was chipped off and the areas of hypothlamus, septum and brainstem were dissected, weighed and further processed for the determination of the amines. Control animals were injected with the same volume of isoosmolar buffer and they showed no change in rectal temperature after 1 hr. The control animals were also sacrificed and processed at the same time. The values were calculated from standard graphs and expressed as *ng/g* of fresh tissue.

Verification of injection site : Upon completion of the experiment in some animals 1 µl of 0.5% bromophenol blue dissolved in isoosmolar buffer was injected, so as to check the location site of the cannula and the extent of perfusion. After 1 hr the animals were anaesthetized with ether and 40 *m1* of saline was given intracardiac. This was followed by 40 *ml* of formal saline (10% V/V). The head was decapitated and left overnight in formal saline. The skull was chipped, brain removed and then left in buffered formalin. Hand cut sections were then taken and histology compared. The sections revealed the site of the cannula tip just below the anterior commisure and 1 *mm* laterel to midline in the region of the medial preoptic area.

Chemicals : Succinylcholine, carbachol, phenylephrine, atropine sulphate, noradrenaline, dopamine, 5-hydroxytryptamine, o-pathalaldehyde were purchased from SIGMA Chemical Co., Missouri. All other chemicals were of analar grade purchased locally from B.D.H. or S.D.S. Isobutanol and ethylenediamine were redistilled before use. Triple distilled quartz distilled water was used for all solutions.

RESULTS

Succinylcholine effects in a free moving animal : A normal hypothalamic EEG, both bipolar and monopolar were taken in a free moving animal in various behaviour states with particular interest being given to the quiet wakeful state of the animal. Rectal temperature was noted. EEG was taken following the injection of 1 μl isoosmotic buffer intracerebrally and 20' later 1 μl of succinylcholine (3 $\mu g/\mu l$) was given intracerebrally. Injection of isoomotic buffer caused no change in EEG or in rectal temperature. However, after the injection of succinylcholine there was a marked change in EEG pattern from a mixed frequency of (8–10 Hz) and low amplitude (50-100 μv) type to a slow wave (3-5 Hz) and high amplitude (200-300 μv) format (Fig. 3A).

The high amplitude waves appeared as early as 5 min after the injection of the drug as brief bursts. The frequency of these bursts was more rapid by 20 min and by 1 hr after the injection of the drug long spells of these waves were seen. Such a pattern of the EEG was seen in both monopolar and bipolar hypothalamic recordings. There was also an increase in rectal temperature by 0.6°C. Injecting succinylcholine at double the dose (intracerebrally 6 μg) in a volume of 1 μl caused a further increase in rectal temperature of 1.7°C in 2 hrs. Eight hours after the injection of the drug, rectal temperature returned to normal.

Nature of succinylcholine-induced EEG waves : Typical high amplitude slow waves were also seen during the animal's sleeping behaviour. Although not much of variation was seen in frequency (4-6 Hz) during sleep or with drug the voltage pattern of the two was different. After the drug, the amplitude of the waves was of 220-340 μv whereas during sleep it was much higher (400-500 μv) (Fig. 3B).

Giving low frequency photic stimulation of 5 Hz prior to drug treatment caused synchronization and on the stimulation put off, an immediate desynchronization of the EEG pattern. whereas after drug treatment there was loss of the desynchronization effect on the high amplitude EEG pattern (Fig. 4).

Effect of succinic and acid choline chloride : In order to find out whether the EEG effect was due to succinylcholine as an entire moiety or its breakdown products, intracerebral injections of succinic acid or choline chloride were given in the same amount that wolud be present in the succinylcholine. After succinic acid injection there was no change in EEG or rectal temperature. However, after choline chloride the rectal temperature increased by 1.2°C but was not accompanied by any change in EEG pattern. Another cholinergic compound, carbachol when given intracerebrally caused the rectal temperature to increase by 1°C but there was no significant change in EEG pattern.

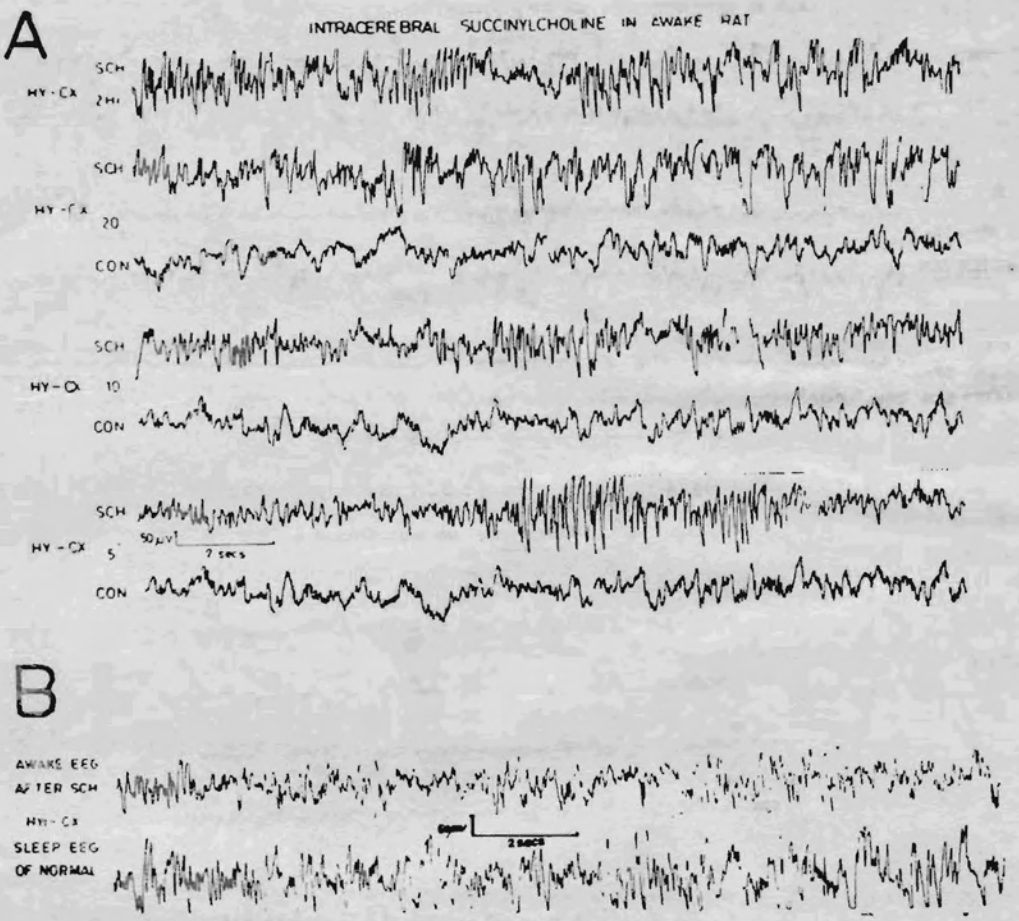

Fig. 3 : A : Pairs of EEG traces recorded from the preoptic area against distant indifferent electrode. In each pair one (CON) is without drug effect, and the other is after 5 or 10 or 20 min or 2 hrs after the drug effect. For the 2 hrs both traces are the SCh effects.
B : SCH effect compared to normal sleep pattern.

It has been reported that under certain circumstances, sympathetic agonists trigger what appear to be episodes of malignant hyperthermia in susceptible swine (14). Alpha agonists were more effective as a trigger than beta agonists and phenylephrine was demonstrated to initiate malignant hyperthermia (18). Phenylephrine when injected ip caused no change in rectal temperature at ambient temperature (32). However, when given intracerebrally (4 μg), 15' prior to succinylcholine there was a greater increase in rectal temperature than with succinylcholine alone (1.3°C). The preoptic EEG pattern did not show any change with phenylephrine alone but after succinylcholine the high amplitude slow waves appeared (Fig. 5).

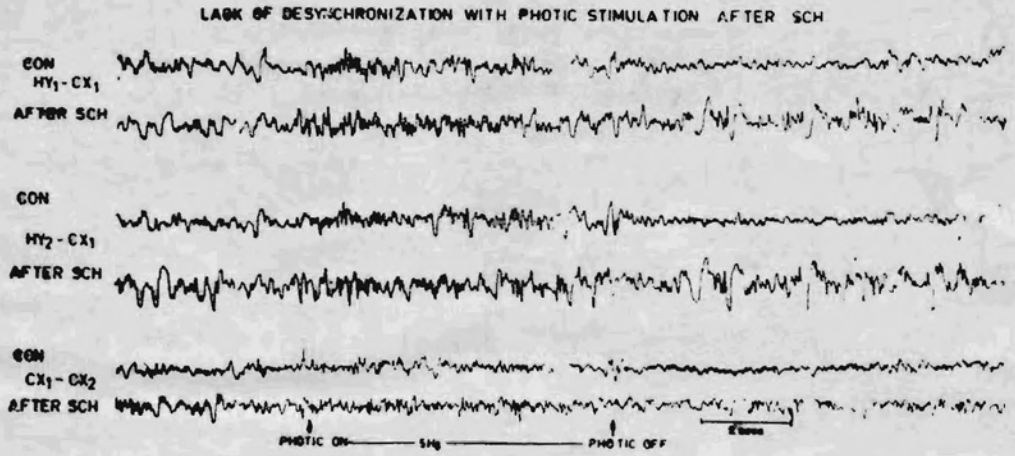

Fig. 4 : CON : Control ; SCH : succinylcholine.

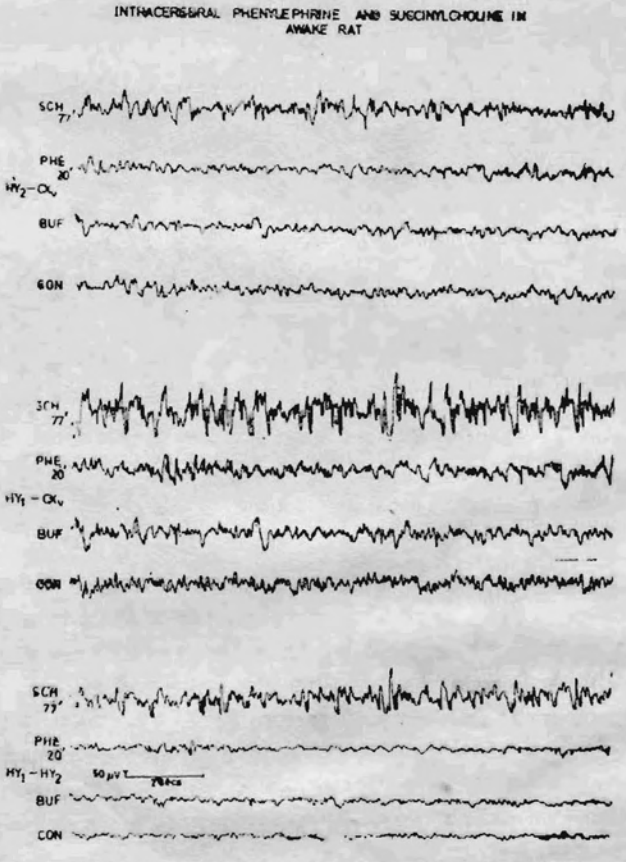

Fig. 5 : BUF : buffer solution; CON : Control without any injection; PHE : phenylephrine injection; SCH : succinylcholine.

The muscarinic antagonist, atropine sulphate (650 *ng*) when given intracerebrally prior to succinylcholine caused no change in EEG pattern. However, the increase observed in rectal temperature after succinylcholine was not seen and a decrease of 0.65°C was seen in the core temperature (Table I).

TABLE I : Changes in rectal temperature and EEG after intracerebral (preoptic area) injection of drugs in awake rats.

Drug treatment	*Change in rectal temperature* from baseline, °C	*Change in local EEG (preoptic area)*
Succinylcholine, 3 µg	0·5 ↑	High amplitude low frequency
Succinic acid, 1 µg	No change	No change
Choline chloride, 1.2 µg	1.1 ↑	No change
Carbachol, 250 *ng*	1.0 ↑	No change
Phenylephrine, 4 µg + Succinylcholine, 3 µg	1.3 ↑	High amplitude, Low frequency – Much later in onset
Atropine, 650 *ng* + Succinylcholine, 3 µg	0.65 ↓	No change

Drug effects in a curarized animal : In order to check the effects of the drugs on other autonomic parameters, the animals were curarized and maintained on artificial respiration. After curarization the rectal temperature decreased by about 0.6-0.8°C and drug effects were monitored from that as basal temperature.

After an intracerebral injection of succinylcholine there was an increase in core temperature by 0.5°C. There was no change in heart rate but there was a two fold increase in GSR. Injection of succinic acid caused no change in any of the parameters. However, injection of choline chloride caused a 1.5°C rise in rectal temperature, no appreciable change in heart rate and no change in GSR. Injection of carbachol brought about an increase in all autonomic parameters : 0.8°C rise in rectal temperature, heart rate increased by 30 beats/min and GSR showed an increase by 60 *kohms* (Table II).

Pattern of biogenic amine distribution after succinylcholine administration : Groups of control and experimental animals were sacrificed 1 hr after either administration of isoosmotic buffer solution to controls or succinylcholine to experimentals intracerebrally. Biogenic amines of noradrenaline, dopamine and 5-hydroxytryptamine were estimated in the areas of hypothalamus, septum and brainstem.

There was a decrsase in noradrenaline content of the hypothalamus by 23% with no change in dopamine and 5-HT. Septum showed an increase of NA and DA-contents by 40% and 25% respectively. 5-HT levels were increased by 28% in the brainstem with no change in the other amine levels (Table III).

DISCUSSION

The afferent and efferent connections of the medial preoptic nucleus have been demmonstrated by various methods, i.e., silver impregnation, Golgi impregnation, electron-microscopy, autoradiography, immunofluorescence and horse radish peroxidase (28). Afferent connections from the lateral septum to the medial preoptic nucleus has been shown to be via the medial forebrain bundle (1). While accounting the results of the drugs on the various autonomic parameters and EEG it becomes imperative to keep the neuroanatomical connections in mind and also the various nuronal models that have been proposed for temperature regulation (4,13,24).

Although succinylcholine in rats, given intracerbrally caused an increase in temperature and GSR and brought about high amplitude waves in the preoptic EEG, the rare type of precipitous rise (malignant) in colonic temperature as reported in swine and humans was not encountered. In humans, the syndrome has often proved to be fatal in spite of the symptomatic treatment given with dantrolene administration (16,18).

Once the heat production increases in the body, the heat dissipation pathways should become operative. The effective heat loss pathways would be (i) by a decreased vasomotor tone resulting in vasodilation and thereby heat loss; (ii) increased sudomtor activity so heat is lost via sweat mechanism; (iii) increased respiration resulting in panting and thereby evaporative heat loss; (iv) decreased thyroid activity, i.e., lowered a calorigenesis.

Increased respiration as a means of heat loss would not be operative in the animals under study as (i) rats showing increased temperature with succinylcholine either showed no discomfort in the free moving state or (ii) wherein autonomic parameters were checked the animals were curarized and hence they were maintained on artificial respirations. As regards increased sudomotor activity to cause heat loss, there are varied reports about the presence of sweat glands in the rat (except on tail and paws) and therefore its operation to cause heat loss would not be very feasible.

Were the warm sensors to be activitated to cause heat loss, a concomitant decrease in GSR due to increase in sympathetic sudomotor activity would result and decrease in vasomotor activity of the skin, i.e. a dual sympathetic mechiansm would be played. In rats,

TABLE II : Changes in autonomic parameters after intracerebral (Preoptic area) injection of drugs in curarized rats.

Drug treatment	*Change in rectal temperature from base line, °C*	*Change in GSR from base line K ohms*	*Change in heart rate from base line baats/min*
Succinylcholine 3 μg	0.51±.07↑	61.8±9.8↑	No change
Succinic acid 1 μg	No change	No change	No change
Choline chloride 1.2 μg	1.5±0.32↑	No change	11±2.58↑
Carbachol 250 *ng*	0.88±.13↑	65.6±9.82↑	30.5±5↑

TABLE III : Biogenic amine concentration changes in different areas of the brain of SCh treated rats (*ng/g* fresh tissue).

Areas	*Control*			*Succinylcholine treated*			*Percentage cha*	
	NA	DA	5-HT	NA	DA	5-HT	NA	DA
Hypothalamus	954.6±30.9	599.1±18.8	1050.8±16	755.7±40.8	550.8±18.6	1073.2±33.7	23*↑	—
Septum	1038±19.1	1704.5±27.7	850±30.1	1457.6±85.5	2173.8±127.8	780.1±14	40↑	28↑
Ventral brain stem	327.6±14	171.1±41.6	619.7±22.5	329.8±16.8	176±52	793.4±10	—	—

administration of succinylcholine as well as with carbachol an increase in GSR was noticed. Therefore, one may postulate that succinylcholine could inhibit the warm sensors and controls of the dual sympathetic mechanism. Thus the temperature increase seen may be a consequence of the normal heat loss pathways not being operative, thereby resulting in heat retention.

So far there have been no reports on the EEG pattern of thermoregulatory areas during succinulcholine induced hyperthermia in swine or humans. Here, in rats a high amplitude low frequency EEG pattern in the preoptic areas is distinctly seen after succinylcholine administration.

However, seizures induced by hyperthermia have been observed in the rat pup (26). It has also been shown that in th 6 day old pups made hyperthermic, the EEG pattern is of a high voltage slow wave type (20). A similar pattern was observed in the rats treated with succinylcholine. Agonists which are known to act as a trigger in the development of the hyperthermic episode, likewise caused a greater increase in rectal temperature in rats when administered prior to succinylcholine. Although choline chloride caused a greater increase in rectal temperature it was without effect on the EEG format and possibly its mechanisms of action may be different to that of succinylcholine. Since succinic acid was without any effect it is possible that the effect of succinylcholine could be due to its *per se* effect than due to its breakdown products. Central nor-adrenergic pathways have been shown to integrate hypothalamic neuroendocrine and autonomic responses (31). In general, catecholamines cause a decrease in temperature whereas 5-HT elevates body temperature (25). Hypothalamus showed a decrease in noradrenaline levels after succinylcholine treatment with a concomitant increase in rectal temperature. Exposure of mice to a warm environmental temperature causes a depletion of the content of noradrenaline in the hypothalamus (33). Since noradrenaline generally decreases body temperature in order to counteract the increase in body temperature due to succinylcholine it may be possible that the noradrenaline content of the hypothalamus is getting depleted. In the medial preoptic area the A_1, A_2 and A_{14} groups of cells are known to supply the NA and DA content whereas the 5HT content of the hypothlamus is derived from the ascending serotonergic system of the brain stem. The increase in 5HT levels of the brain stem observed after succinylcholine treatment may also contribute to the increase in rectal temperature.

Thus, the drug succinylcholine, a routinely used cholinergic muscle relaxant seems to have significant effects on the preoptic EEG, rectal temperature, GSR and the amine levels of the hypothalamus and brainstem.

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