Stress-triggered Changes in the Adrenal Medullary Cells Structure and Function in the Rat

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Abstract

Objective: Previous authors provided electrophysiological evidence for selective activation of epinephrine or norepinephrine-secreting adrenal chromaffin cells. However, the corresponding histological changes in the adrenal chromaffin cells were not described.
To provide histological and biochemical evidence that different sympathetic preganglionic neurons regulate epinephrine and norepinephrine secretion.

Methods: Male Wistar albino rats weighing 220-250g were subjected to stress inducing experiments including insulin-induced hypoglycemia, acute exposure to cold and acute hemorrhagic hypotension. The fine structure of adrenomedullary cells was examined; their catecholamine contents and volume fractions were measured.

Results: Insulin injection was followed by gradual and progressive depletion of epinephrine storing granules with no effect on norepinephrine granules, acute exposure to cold produced a response consistent with activation of norepinephrine secreting chromaffin cells, while acute hemorrhagic hypotension produced activation of both epinephrine and norepinephrine cells, all these morphological changes were accompanied by corresponding changes in the catecholamine content of the adrenal gland as well as in the volume fractions of epinephrine and norepinephrine cells.

Conclusions: In the presence of similar nerve endings on the epinephrine and norepinephrine chromaffin cells, the above results suggest the presence of different adrenal sympathetic preganglionic neurons that regulate epinephrine and norepinephrine secretion.

Keywords: Adrenal, Catecholamines, Epinephrine, Norepinephrine, Preganglionic sympathetic neuron.

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Introduction

The ability of the adrenal medulla to secrete epinephrine and norepinephrine depends upon both neural and hormonal factors[1]. The secretory process, per se, is under direct neural control. It is triggered by impulses from sympathetic cholinergic nerves that terminate adjacent to the adrenal chromaffin cells [1,2,3,4]. The efferent sympathetic innervation of the adrenal gland has been the subject of several investigations[5,6,7].

However, less attention has been paid to the existence of separate preganglionic

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innervation. Several lines of evidence have suggested that the two populations of adrenal chromaffin cells are regulated by distinct preganglionic sympathetic nerves to the adrenal medulla .

First, Edwards et al.[8] described distinct sympathetic preganglionic neurons (SPNs) innervating epinephrine and norepinephrine cells in the cat. Second, certain stimuli in the rat such as hypoglycemia produce increased secretion of epinephrine[9,10,11,12,13,14]. In contrast, acute cold exposure in the rat results in a preferential secretion of norepinephrine [14].

In the present study we sought to provide histological and functional evidence for the independent regulation of epinephrine and norepinephrine chromaffin cell secretion by stress- inducing experiments including hypoglycemia, acute exposure to cold and hemorrhagic hypotention in the rat.

Materials and Methods

Experiments were performed on male wistar albino rats weighing 220-250g. They were obtained from the closed colony of the medical school animal house- Jordan University.

Animals were fed rat pellets and water ad libitum and housed under a cycle of 12 h light and 12 h darkness. The animals were randomly assigned to each of three groups. Group 1 were subjected to insulin hypoglycemia, group 2 were acutely exposed to cold and group 3 were subjected to acute loss of blood as described below. The number of animals used in each group are shown in tables 1-4.

Group 1

Animals were starved for 20 hours, with free access to water prior to the subcutaneous injection of either insulin (10 I.e. /100 gm body weight) or 0.9% sodium chloride. Animals were anesthetised in pairs by means of sodium pentoarbitone at 1, 2 and 3 hours following these injections and the three procedures described below were performed.

Determination of blood serum glucose level

Blood was withdrawn from each of these two rats into heparinized syringes and plasma glucose was determined according to Teller's method[(15)].

Assay of adrenal catecholamines

The right adrenal gland of each animal was excised, trimmed of connective tissue and then homogenized using a telfon homogenizer in one milliliter of a mixture of 1.0M perchloric acid and 40mM sodium metabisulphite containing 5 nmol 3,4-dihydroxybenzylamine as an internal standard. The homogenate was centrifuged at 30000 rpm at 4˚C for 20 minutes and the supernatant stored at -80˚C.

Catecholamine analysis was performed by high performance liquid chromatography (HPLC) according to the method described by Kent and parker[(17)]. The supernatant was diluted 1:100 with 0.1 M perchloric acid and aliquots of 100 µl were injected into HPLC system .This comprised a 5 µm ODS reverse-phase ion-pair column attached to an electrochemical detector incorporating a glassy carbon electrode, set at 1 namp/v, at a potential of 0.54 v. Mobile phase buffer comprised 12% methanol in 0.1 M-NaH_2PO_4, 1.2 mM $CH_3(CH_2)_4SO4Na$ and 0.1 mM EDTA, adjusted to PH 3.6. The peak areas corresponding to epinephrine and norepinephrine were integrated with reference to those of an internal standard in each sample and the final concentration of epinephrine and norepinephrine expressed in nmol per adrenal.

The final concentration of epinephrine and norepinephrine was expressed in nmol per adrenal.

Electron microscopy of adrenomedullary tissue

The animals were anesthetized and fixed by cardiac perfusion with a buffered saline solution followed by 2% gluteraldehyde in 0.1 M cacodylate buffer at PH 7.4.

The left adrenal gland of each animal was cut with a razor blade on random axes into parallel slices approximately 1 millimeter thick, fixed for 2 hours and processed as 3-4 tissue blocks for araldite embedding. Sections 1μm thick were cut on a Reichert ultramicrotome. The thin sections were mounted on 200 mesh copper grids, stained with lead citrate and examined with a Philips 300 electron microscope.

Stereology

Volume fractions (Vv) of adrenal medullary tissue components, including epinephrine and norepinphrine cells were estimated by point counting (Weibel 1979)[2,6]. Electron micrographs at a magnification of 4200 and calibrated with a carbon grating replica were used. They were taken from randomly selected areas from sections cut from each of the tissue blocks derived from a single adrenal gland. A test grid, for which the area per point was 3 cm^2, was applied for each micrograph. The number of intersctions over each tissue component was counted and the volume fractions of epinephrine and norepinephrine cells were calculated.

Group 2

Animals were anesthetized by an intraperitoneal injection of sodium pentobarbiton (60mg/kg)[7], then the four limbs were fixed on a wooden board and kept at 5˚C for 2 hours. After that the animals were sacrificed and the right adrenal gland was excised and processed for assay of adrenal catecholamines as above. The left adrenal gland was processed for electron microscopy as above.

Group 3

Animals were anesthetised by an intraperitoneal injection of sodium pentoborbiton(60mg/kg) [7] polyethylene catheter was inserted into the tail artery for hemorrhage. Rats were bled rapidly so the mean arterial pressure fell to approximately 50mm Hg within 2 minutes. Additional amounts of blood were withdrawn to maintain arterial pressure at that level for 6 additional minutes, then the animals were sacrificed and the right adrenal gland was excised and processed for assay of adrenal catecholamines as above. The left adrenal gland was processed for electron microscopy as above.

Statistical analysis

The results were analyzed using student's t test. Level of significance was considered at $P<0.05$. The data were presented as mean ± standard error of the mean (S.E).

Results

Response of blood serum glucose levels to insulin administration

The blood serum glucose levels of control rats are distributed between 100 and 144 mg% with a mean value of 123 ± 5 mg% (table 1). The blood serum glucose levels of insulinized animals dropped below the control value (table 1). The rate of blood serum glucose decline being greatest within the first hour (**31 ± 1.2)** and becoming less between one (**28 ± 2.0)** and three hours (**14 ± 0.6)**.

Table 1. Blood serum glucose levels of rats following injection of physiological saline or insulin

Sacrifice time (n) (hours after injection)	Blood serum glucose (mg %)	
	Physiological saline	Insulin
0 (4)	123 ± 5.o	130 ±4 .5
1 (6)	130 ± 4.5	31 ± 1.2*
2 (5)	115 ± 4.2	28 ± 2.0*
3 (5)	126 ± 5.5	14 ± 0.6*

Results expressed as means ± S.E

n= number of animals, *P < 0.001

Cytological response of adrenomedullary cells to insulin administration

At the ultrastructural level, the chromaffin cells of rat contain two types of electro dense-core granules. The granules in epinephrine cells had a core which was less dense and usually less homogenous (fig.1). The core in the epinephrine cells was centrally located and was separated from the limiting membrane by electron-lucent space (fig .1).Granules in norepinephrine cells had a much more electron dense core which was eccentric in location (fig. 1). In response to the administration of insulin, the morphological changes which occur are associated with only the epinephrine cells. One hour following the injection of insulin (fig .2). The epinephrine cells presented a vacuolated appearance. These cells bore granules which were of greater size than normal and were mostly empty. The norepinephrine cells had an almost normal appearance. The depletion of epinephrine granules continued during the second hour and three hours after insulin injection (fig .3) there was absence of most storage granules in epinephrine cells.

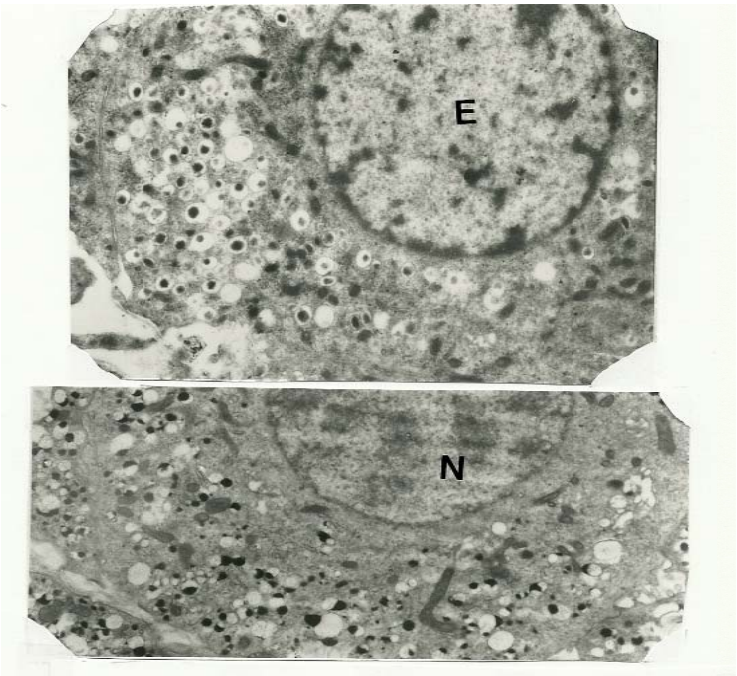

Figure 1: Control epinephrine (E) and norepinephrine (N) cells from animal which received subcutaneous injection of physiological saline. Note the difference in electron opacity of their secretory granules and the eccentric position of the content of N granules X11500

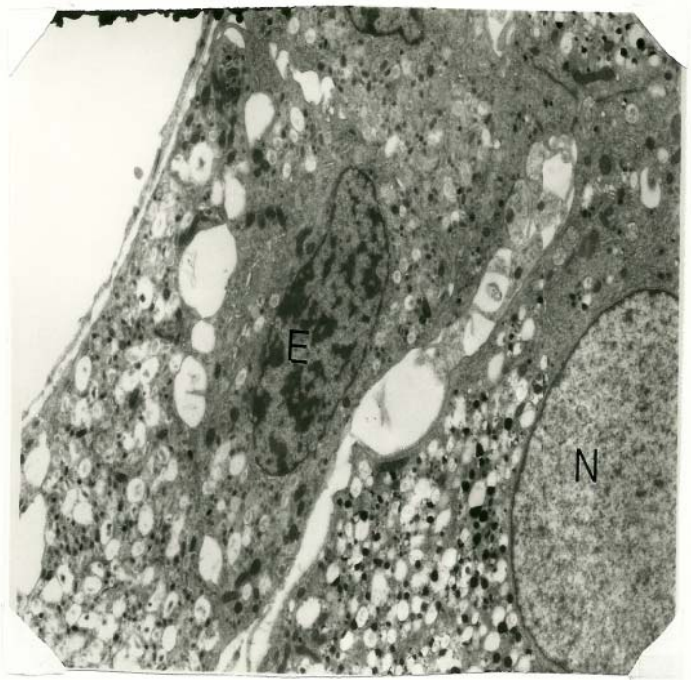

Figure 2: Epinephrine cell (E) (two hours post-insulin). Note the depleted storage granules and the presence of large vacuoles. The adjacent norepinephrine (N) cell with normal secretory granules X 10400

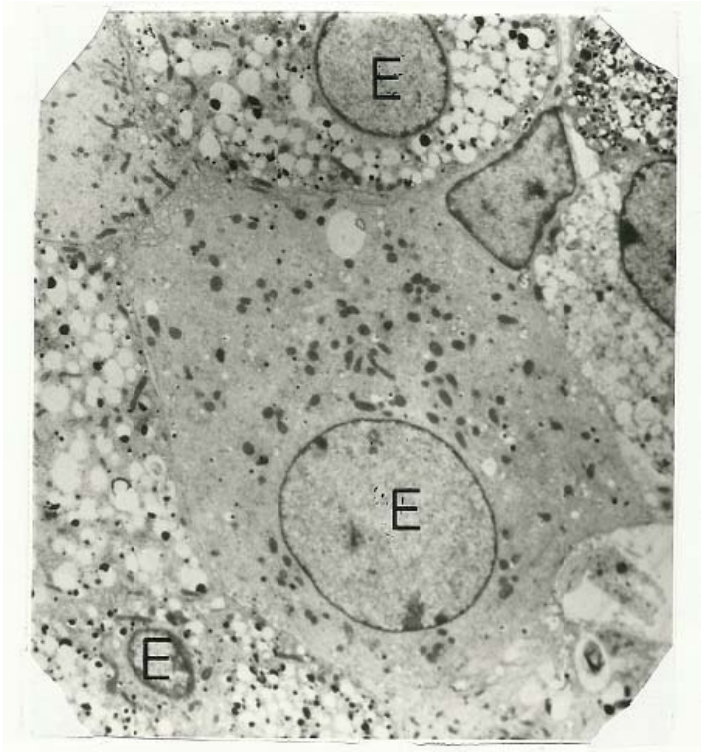

Figure 3: Epinephrine cell (E) (three hours post-insulin). Note the almost complete absence of epinephrine storage granules. The surrounding cells are markedly depleted E cells X 9800

Response of adrenal gland catecholamine content to insulin administration (table 2) Insulinized glands display a fall in epinephrine content with time following the administration of insulin. The lowest content was recorded three hours following insulin injection.

Table 2. Catecholamine levels of rat adrenal glands following injection of physiological saline or insulin

Sacrifice time (n) (Hours after injection)	Physiological saline		Insulin	
	Epinephrine	Norepinephrine	Epinephrine	Norepinephrine
0 (6)	108± 3.70	17.8± 1.6	113.00± 3.20	19.50±1.00
1(8)	98.00± 2.90	16.2± 0.9	81.00± 2.75*	17.30±1.20
2(6)	105± 2.80	16.8± 1.5	59.4± 2.10*	18.9±0.95
3(5)	102± 3.00	18.4± 1.1	32.52± 1.80**	20.10±1.10

Results expressed in moles per adrenal gland

Means ± S.E, n = number of animals,*P<0.05, **P<0.001

Table 3. Catecholamine levels of rat adrenal glands following acute cold exposure and acute hemorrhagic hypotension

Experiment (n)	Control animals		Experimental animals	
	Epinephrine	Norepinephrine	Epinephrine	Norepinephrine
1. Acute cold (6) exposure	120.00±4.40	21.00± 1.20	114.00±3.90	5.10±0.9*
2. Acute hemorrhagic (6) hypotension	112.00±3.80	19.50±1.33	40.00±1.80*	3.85±1.1*

Results expressed in mole per adrenal gland

Means ± S.E, n = number of animals, *P<0.001

Table 4. Volume fractions, expressed as percentage, for the tissue components of the adrenal medulla

	Treatment			
	Control (physiological saline) n=	Insulin after 3h n=	Acute cold exposure n=	Acute hemorrhagic hypotension n=
Epinephrine cell	45.7±4.0	36.2±3.1**	43.0±3.8	35.3±3.5**
Norepinphrine cell	8.4±1.9	9.8±2.2	5.0±1.2*	5.9±1.7*
Interstintial tissue	25.3±2.7	29.5±3.0	26.4±2.5	28.8±2.5
Blood vessels	18.2±2.0	21.4±2.2	23.1±2.3	23.5±2.1
Nerve cells	2.4±0.6	3.1±1.0	2.5±0.9	3.1±1.1

values expressed as means (SEM). differs from control on Student's t test :**P < 0.01,

*P <0.05; all other comparisons not significant.

Response of adrenal gland catecholamine content to acute cold exposure and acute hemorrhagic hypotension (table 3)

Acute cold exposure resulted in a preferential stimulation of norepinephrine cells with a corresponding decrease in the adrenal content of this hormone, while acute hemorrhagic hypotension stimulated the secretion of both epinephrine and norepinephrine cells with a corresponding decrease in the adrenal content of both hormones.

Cytological response of adrenomedullary cells to acute cold exposure

In the response to acute cold exposure, the morphological changes which occur are associated with only the norepinephrine cells (fig.4). depletion of the norepinephrine granules was associated with the appearance of large empty vacuoles within the cytoplasm.

Cytological response of adrenomedullary cells to acute hemorrhagic hypotension

In response to this stressful condition depletion affected the secretory granules of both epinephrine and norepinephrine cells (fig.5) some of the latter cells showed marked decrease in the number of their secretory granules.

Discussion

The results of this study support earlier observations that a release of catecholamine from the adrenal medulla is associated with certain stress-inducing factors, and that different sympathetic preganglionic neurons regulate epinephrine and norepinephrine secretion[9,10,11,12,13,14].

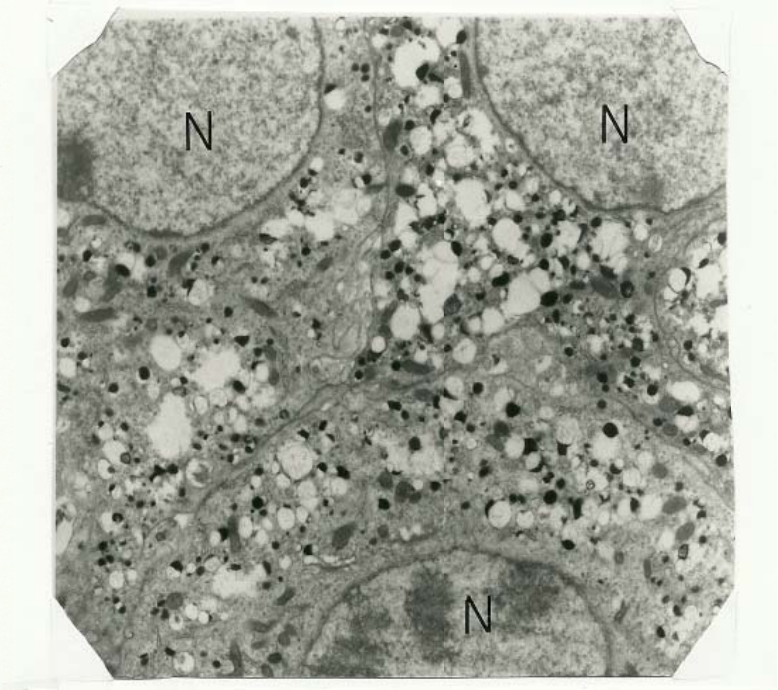

Figure 4: Parts of three norepinephrine cells N from animal subjected to acute cold exposure. Most of the storage granules appear empty and some are enlarged and appear as empty vacuoles X 12800

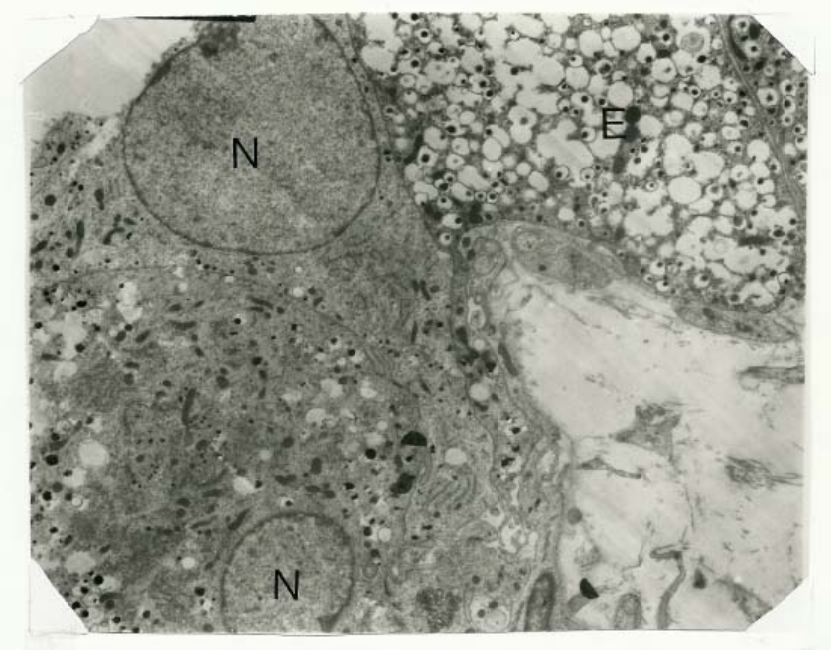

Figure 5: Parts of one epinephrine cells (E) and two norepinephrine cells (N) from animal subjected to acute hemorrhagic hypotension. Most of the storage granules of (E) cells appear as empty vacuoles. Note the marked decrease in the number of granules of (N) cells X 8400

Because electron–opaque granules characteristically present in the adrenomedullary cells are visual representation of the cells catecholamine content, an alteration in the vesicle morphology and/or population mirrors a change in gland catecholamine content.

The adrenal medulla is composed of two cell types, each exclusive of the other in the storage of epinephrine and norepinephrine. The histochemical method used in the present study[5,6] allows a distinction to be made between epinephrine and norepinephrine cells as a consequence of fixation of tissue in glutaraldehyde followed by post-fixation in osmium tetroxide. Progressive loss of the electron opaque core of the secretory granules and decrease in their number indicates depletion of the secretion of epinephrine and norepinephrine cells[5,6]. This being the case, we were able to correlate alterations in the fine structure of epinephrine and norepinephrine-synthesizing cells with alterations in the epinephrine and norepinephrine contents of the gland.

Morphological[16,17] and biochemical[18,19,20] studies have been conducted to evaluate separately the changes in these parameters following insulin administration.

In the present work the use of four endpoints i.e the three stress-triggered conditions, gland catecholamine content, adrenomedullary cell fine structure the volume fractions of epinephrine and norepinphrine cells, observed within the same animal, sets this investigation apart from earlier studies and allows a far more meaningful correlation to be made. The changes in the appearance of the catecholamine- storage granules and their

volume fractions and the associated changes in the catecholamine content in the present study, highly suggests that the medullary chromaffin cells secreting epinephrine and those that secrete norepinephrine are controlled by different descending and preganglionic pathways.

Recently, Morison and Wei-Hua[21] reported that the sympathetic preganglionic neurons (SPNs) were excited by stimulation of the rosral ventrolateral medulla (RVLM) with either a short or long latency. The latter group of adrenal SPNs were remarkably insensitive to baroreceptor reflex activation but strongly activated by hypoglycemia indicating their role in regulation of adrenal epinephrine release. In contrast , adrenal SPNs activated by RVLM stimulation at a short latency were completely inhibited by increase in the arterial pressure but were unaffected by hypoglycemia and are presumed to govern the discharge of adrenal norepinephrine- secreting cells. However, these authors presented no morphological or quantitative changes in the adrenal medullary cells to support their results. It is of interest to note in the present study the gradual response of the epinephrine-storage cells to insulin-induced hypoglycemia which could be caused by stimulation of the long latency SPNs while the dramatic response to acute cold and hemorrhagic hypotension could be produced by stimulation of short latency SPNs. The acute response to hemorrhagic hypotension represents an acute activation of the baroreceptor reflex, a potent short term regulator of cardiac and vasoconstrictor sympathetic outflows that also has been shawn to modulate adrenal nerve activity in the rat.[22,23]

The results of the present study provide support to the existence of functional specificity at the level of SPN[24]. They also strengthen some of the recent progress in understanding the development of the chromaffin cells. Although a common sympathoadrenal progenitor cell for chromaffin cells (epinephrine and norepinephrine) and sympathetic neurons has been postulated, the glucocorticoid-rich medium that surrounds the chromaffin cells makes these cells able to synthesize both epinephrine and norepinephrine[25]. This is in contrast to sympathetic neurons which releases only norepinephrine[7]. Although the synthesis of epinephrine and norepinephrine is influenced by glucocorticoids, the secretory process in under neural control[24,25].

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تأثير الإجهاد الحاد على تركيب ووظيفة خلايا نخاع الغدة الكظرية في الجرذ

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الملخص

الهدف: باستخدام تجارب التنبيه الكهربائي الفسيولوجي لاحظ بعض الباحثين وجود خلايا عصبية في الجهاز العصبي المركزي متخصصة في تنبيه إفراز هرموني الأدرينالين والنورادرينالين من نخاع الغدة الكظرية كلا على حدة، ولم يقم هؤلاء الباحثون بوصف التغيرات في تركيب خلايا هذه الغدة نتيجة هذا التنبيه.

التحقق من وجود خلايا ودية ما قبل التشابك تنظم إفراز هرموني الأدرينالين والنورادرينالين بشكل مستقل وذلك باستخدام تجارب تظهر التغيرات في تركيب ووظيفة الخلايا التي تفرز هذين الهرمونين.

الطريقة: تم استخدام ذكر الجرذ الأبيض والذي يتراوح وزنه بين 220-250 غرام وقد تعرضت حيوانات التجارب للإجهاد الحاد بإحداث هبوط في تركيز سكر الدم وذلك بحقنها بمادة الأنسولين، أو بتعريض الحيوانات لدرجة حرارة متدنية، أو بإحداث نزيف حاد، وبعد قتل هذه الحيوانات تم فحص التركيب الدقيق لخلايا الغدة الكظرية، وكذلك كمية هرموني الأدرينالين والنورادرينالين في هذه الغدد.

النتائج: إن حقن الحيوانات بمادة الأنسولين أدت إلى تفريغ تدريجي للحبيبات التي تخزن مادة الأدرينالين من مخزونها، ولم يكن هناك أي تغير في الخلايا التي تخزن مادة النورادرينالين، بينما أدى تعرض الحيوانات إلى درجات حرارة متدنية إلى تفريغ الحبيبات المخزنة لمادة النورادرينالين، وأدى النزيف الحاد في الجرذ إلى تفريغ حبيبات الخلايا التي تخزن مادتي الأدرينالين والنورادرينالين، وقد رافق هذه التغيرات في تركيب الخلايا تغيرات في كمية الهرمون المخزن في كل غدة.

الاستنتاجات: في وجود نهايات عصبية متشابهة في التركيب على سطح الخلايا التي تخزن الأدرينالين والنورادرينالين فإن نتائج البحث تشير إلى وجود خلايا ودية قبل التشابك في النخاع الشوكي تنظم بشكل مستقل إفراز الخلايا التي تخزن الأدرينالين، وتلك التي تخزن النورادرينالين.

الكلمات الدالة: الخلايا اليفة الكروم، الأدرينالين، النورادرينالين، خلايا ودية ما قبل التشابك.