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THE POTENTIAL ROLE OF THE ADRENAL MEDULLA IN HEMODYNAMIC RESPONSES DURING GABA ACTIVATION OF RAT AREA POSTREMA

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ABSTRACT

The goal of this study was to investigate the potential role of the adrenal medulla in the multiple cardiovascular alterations that occur during activation of GABA(A) subtype in the area postrema. Blood pressure, heart rate, renal, iliac blood flows and plasma catecholamines were monitored during nonaliter infusion of muscimol (10 nl/min/10min, 1ng/nl) in the area postrema of the rats. Responses in pentobarbital-anesthetized male Albino rats, either intact (CON) or acutely adrenalectomized (ADX), were compared. Muscimol infusion increased mean arterial pressure in a dose-dependent manner in CON, but in ADX group such pressor effect was significantly attenuated. Heart rate was not significantly affected by drug infusion in either group. Renal bed actively constricted with non-significant transient increase in renal blood flow in both groups. Iliac blood flow increased markedly in CON, but remained unchanged in ADX. Iliac resistance was increased significantly in both CON and ADX, but it was rapidly attenuated to control values in CON. Plasma catecholamine concentrations was significantly elevated by muscimol infusion. We conclude that activation GABA(A) subtype may augment sympathetic outflow to the adrenals causing catecholamine release that in turn produces iliac bed vasodilation, but renal bed vasoconstriction. In ADX, this dominant effect of adrenal sympathetic activation was acutely attenuated because of withdrawal of sympathetic vasomotor tone in these resistance beds.

INTRODUCTION

Anatomical connections of the area postrema that may be involved in cardiovascular regulation include its projection to the nucleus of the solitary tract (NTS), dorsal motor nucleus of the vagus (DMN), nucleus ambiguous (NA)[1], the lateral parabrachial nucleus (LPB)[2], and the ventrolateral medulla (VLM)[3,4]. These brain regions are major cardiovascular regulatory centers for central neural control of blood pressure and heart rate. The functional autonomic connections of the area postrema are capable of transducing both pressor[5,6,7,8] and depressor actions[9,10,11] as well as heart rate modulation [5, 7, 8, 11] depending upon the species and experimental conditions. In addition, there is evidence that the area postrema may be involved in both short term[7, 12,13,14] and long term[15,16] regulation of blood pressure. Moreover, the area postrema may participate in activation of the hypothalamic-pituitary-adrenocortical in response to an excitatory amino acid challenge and also during handling stress[17,18].

To date, the precise mechanism of either the pressor or depressor responses of the area postrema has not been extensively investigated, However, sympathetic withdrawal toward some vascular beds was reported[8,14]. Sympathetic withdrawal in some major vascular beds would tend to elicit depressor responses, revealing that pressor responses may occur if area postrema challange produced activation of adrenal medullary sympathetic outflow.

In the current investigation, the effect of $GABA_{(A)}$ activation by direct nano-injection of the $GABA_{(A)}$ agonist, muscimol, into the area postrema on mean arterial pressure, heart rate, renal and iliac blood flows, and calculated renal and iliac vascular resistances in pentobarbital-anesthetized rats was studied. The present study evaluated the relative adrenal sympathetic contribution to the changes in cardiovascular parameters that occurred during $GABA_{(A)}$ activation by comparing the responses during drug infusion in intact control rats (CON) with those obtained from acutely bilaterally-adrenalectomized rats (ADX). Plasma levels of endogenous catecholamines were also measured after muscimol in control and bilaterally adrenalectomized rats.

MATERIALS AND METHODS

Animal preparation:

Three groups of male Albino rats (n=5, each group, 300g/rat, obtained from the National Research Center, Cairo, Egypt) were anesthetized with pentobarbital (30 mg/kg, i.p.). An arterial catheter (tapered PE-50 tubing) was inserted into the femoral artery. Another venous catheter was inserted into the femoral vein for drug delivery, if needed, or blood withdrawal at the end of the infusion period. Following catheterization, one group underwent bilateral adrenalectomy (ADX), the other group served as intact controls (CON). An identical laparotomy procedure exposing the adrenals was performed for each rat in CON and ADX groups.

Hemodynamic measurements:

Direct pulsatile blood pressure was measured using a small volume displacement transducer (Telos medical corporation) connected to a Cardiomax II model 85 (Colombus Instruments) equipped with multi-channel universal recorder and a dual channel directional pulsed-Doppler flow interface. Heart rate was determined from the average of 5 R-R intervals or direct digital read out from the Cardiomax. Each animal was prepared for measurement of regional flows by securing miniature silastic flow probes (TMI Inc., Iowa City, IA) on the left renal, and the left common iliac arteries. Typically, flow probes were in place and the abdominal incision was closed within 20 min from the start of surgery. Relative blood flow velocity changes were monitored from the Doppler shift using the dual channel directional pulsed-Doppler flow interface. The correlation between blood flow velocity changes and relative blood flow changes has been verified by others[19]. Changes in vascular resistances were calculated from the simultaneously recorded changes in blood flow and changes in MAP caused by drug infusion. Percent changes in mean arterial

pressure and heart rate, blood flow and vascular resistance were calculated by expressing the change during muscimol infusion as a percent of corresponding data obtained before drug infusion.

Muscimol Infusion:

After hemodynamically preparing the rats, each rat was placed in a stereotaxic apparatus with its head flexed anteriorly downward 30 degrees from the horizontal plane between lambda and bregma. A dorsal cervical incision exposed the cisternum magnum. The atlanto-occipital ligament and membrane were removed simultaneously, followed by the inferior medullary velum. While viewing the region with a dissecting microscope, a glass micropipette, tip diameter 25 µm that is connected to the nanoliter infusion pump (WPI model A1400), was inserted 100 µm below the ependymal surface in middle AP and the drug was infused for the assigned dose and time. Two groups (CON and ADX) were infused with muscimol at a rate of 10 nl/min for 10min muscimol concentration was 1 ng/nl (20). Hemodynamic parameters were monitored in one additional control group, where equi-osmotic dose of saline to that of muscimol was infused for the same volume and time. Changes in flow velocity, blood pressure and heart rate were monitored simultaneously during drug infusion (10 minutes).

Measurement of plasma catecholamine levels:

At the end of the infusion period, 2ml of venous blood was withdrawn (from the femoral vein cannula) and placed in chilled 3 ml centrifuge tube containing heparin 6 IU/ml and 6 mg of the reduced from of glutathione (antioxidant). Blood samples were centrifuged at 3000 rpm for 5 min. Plasma was removed and immediately stored at 80°C for a maximum of 3 days. Catecholamines levels were determined using HPLC system (Kontron Instruments with dual pump, model 420) with electrochemical detector (ESA, model 5100A) equipped with an Altex ultrasphere C-18 reverse phase column. Two nanograms DHBA (3,4-dihydroxy-benzylamine, Aldrich Chemical CO.) were added to each known and unknown sample to serve as an internal standard. Epinephrine and norepinephrine were extracted on alumina with 70-90% recovery rates using standardized procedures published by Bioanalytical Systems, Inc., West Lafayette, IN (Application Note No. 14). Standard curves were constructed using purified epinephrine and norepinephrine obtained from Sigma Chemical Co. The sensitivity of the detector was 0.5 nA/V at a potential of 550 mV. The mobile phase consisted of 0.035 M KH_2PO_4, 0.015 M citric acid, 1.5 mM sodium octly phosphate, 2.0 mM Na_2EDTA and 10% ethanol, pH 4.85. The sensitivity of this HPLC method was 50 pg for both epinephrine and norepinephrine.

Statistical analysis:

All data are presented as experimental group mean ± standard error of the mean (SEM). Percent changes in mean arterial pressure, heart rate and blood flow are presented as a percentage of pre-infusion values. Vascular resistances were calculated coincident with related responses in mean arterial pressure and are each presented as a percentage of pre-infusion control. Differences between and among treatment groups were analyzed after 2-Way ANOVA, using the LSD post hoc procedure (PC ANOVA software program, Human Systems Dynamics, Northridge, CA).

Differences between plasma catecholamine levels were tested for statistical significance using an unpaired Student's t test. $P \leq 0.05$ was considered a statistically significant difference in each comparison.

RESULTS

Percent changes in mean arterial pressure during muscimol infusion are shown in Figure 1 for both CON and ADX groups. Mean arterial pressure values obtained immediately before drug infusion were significantly different between CON and ADX groups, 126 ± 5 mmHg vs 91 ± 4 mmHg, respectively ($p < 0.002$). Muscimol infusion produced significant dose-dependent increase in mean arterial pressure in CON, but non-significant increase in mean arterial pressure in ADX. The responses of the two groups were significantly different from each other at 6, 8 and 10 min. Maximum percent increase in mean arterial pressure was 39.27 ± 6.25% in CON at 10 min and 12.6 ± 1.2 % at 4 min. in ADX. There was no significant difference in heart rate between groups before muscimol infusion. Heart rates did not change significantly during drug infusion at any dose tested in either group (figure 2). Infusion of saline into the area postrema during the time course of the experiment did not produce any significant changes in blood pressure or heart rate.

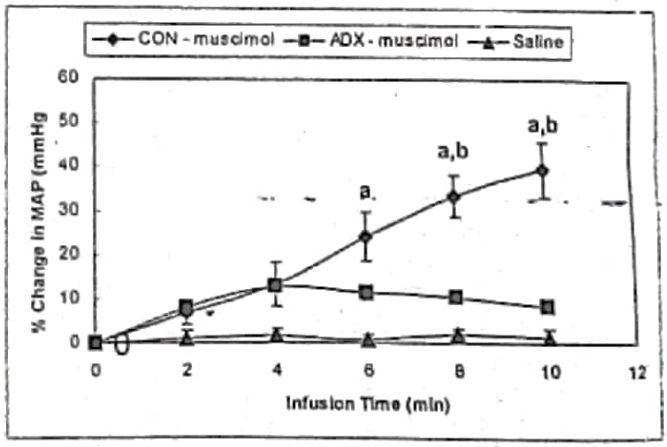

Figure (1): Percent changes in mean arterial pressure (MAP) during direct infusion of muscimol (10 nl/min/10min, 1 ng/nl) in area postrema of control (CON) and bilaterally adrenalectomized (ADX) male rats

[a] Indicates a statistically significant change from pre-infusion control values within treatments ($p \leq 0.05$).

[b] Indicates a statistically significant difference in MAP responses occurred between treatments at a given time ($p \leq 0.05$).

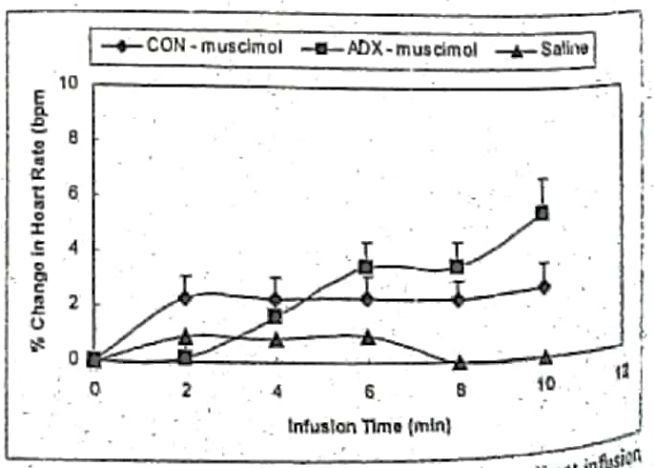

Figure (2): Percent changes in heart rate (HR) during direct infusion of muscimol (10 nl/min/10min,1 ng/nl) in area postrema of control (CON) and bilaterally adrenalectomized (ADX) male rats

Renal blood flow did not change significantly due to muscimol infusion in both CON and ADX groups (figure 3) despite the fact that mean arterial pressure changes were different. In contrast, iliac blood flow was increased significantly in CON at 6, 8 and 10 minutes (figure 5) but no significant changes in iliac blood flow in the ADX group could be detected.

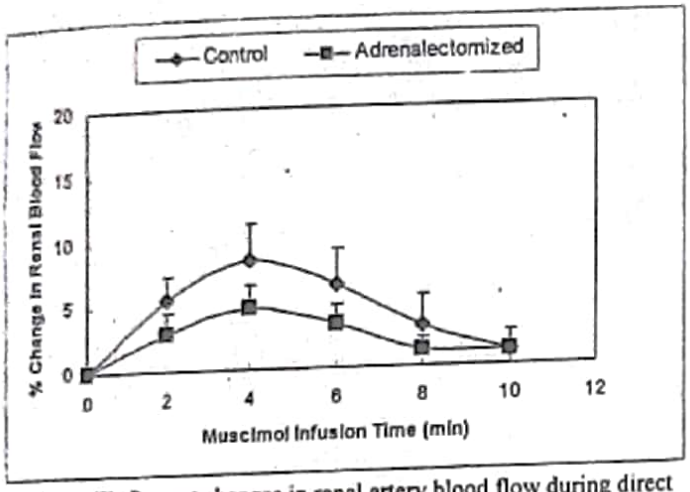

Figure (3): Percent changes in renal artery blood flow during direct infusion of muscimol (10 nl/min/10min, 1 ng/nl) in area postrema of control and bilaterally adrenalectomized male rats

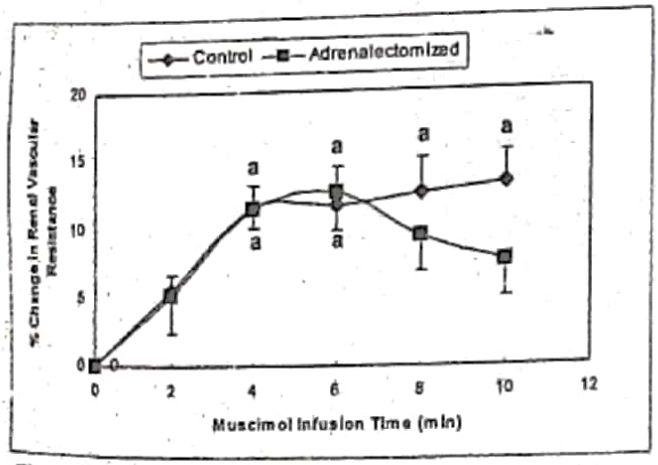

Figure (4): Percent changes in calculated renal vascular resistance during direct infusion of muscimol (10 nl/min/10min, 1 ng/nl) in area postrema of control and bilaterally adrenalectomized male rats
[a] Indicates a statistically significant change from pre-infusion control values within treatments ($p \leq 0.05$).

Calculated percent changes in renal and iliac vascular resistances are presented in Figures 4 and 6. In CON, renal vascular resistance (figure 4) was increased significantly in a dose-related manner starting at 4 min, while in ADX a transient increase in resistance occurred at 4 and 6 minutes of infusion. Both groups were not significantly different from each others. Iliac vascular resistances (figure 6) increased significantly in both groups, starting at 2 min, however it was rapidly attenuated in CON and returned to control values within 10 min of muscimol infusion. Iliac resistance in ADX continued to increase in a dose related manner.

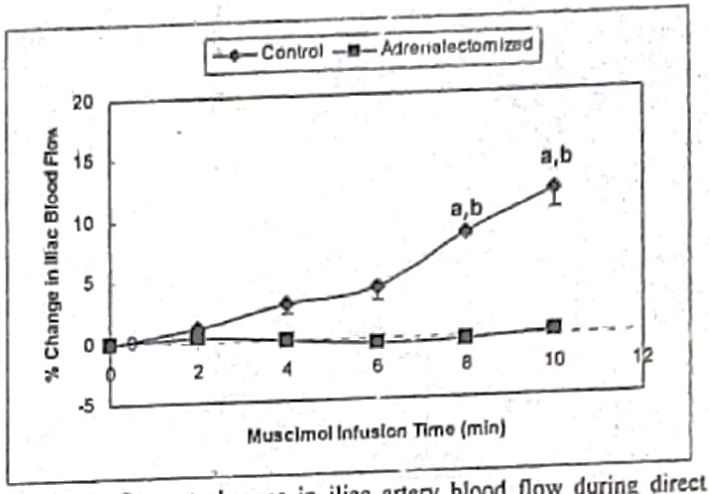

Figure (5): Percent changes in iliac artery blood flow during direct infusion of muscimol (10 nl/min/10min, 1 ng/nl) in area postrema of control and bilaterally adrenalectomized male rats.
[a]Indicates a statistically significant change from pre-infusion control values within treatments ($p \leq 0.05$).
[b]Indicates that a statistically significant difference occurred between blood flow responses between treatments at a given time ($p \leq 0.05$).

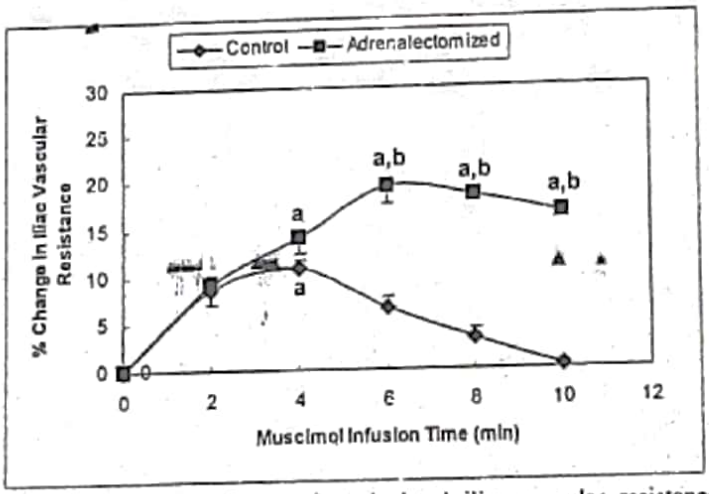

Figure (6): Percent changes in calculated iliac vascular resistance during direct infusion of muscimol (10 nl/min/10min, 1 ng/nl) in area postrema of control and bilaterally adrenalectomized male rats.
[a]Indicates a statistically significant change from pre-infusion control values within treatments ($p \leq 0.05$).
[b]Indicates that a statistically significant difference occurred between blood flow responses between treatments at a given time ($p \leq 0.05$).

Plasma epinephrine levels determined during muscimol infusion were significantly increased, 1.35 ± 0.4 ng/ml (CON group) when compared to either normal control values (0.06 ± 0.04 ng/ml, $p = 0.006$) or ADX group after muscimol infusion (0.16 ± 0.05 ng/ml). Plasma norepinephrine levels during muscimol infusion (CON group) was only significantly elevated (1.52 ± 0.48 ng/ml) when compared to normal control values (0.22 ± 0.06 ng/ml $P = 0.052$), untreated group. Muscimol infusion in ADX group caused marginal elevation (0.68 ± 0.15 ng/ml) in norepinephrine values when compared to normal control values (figure 7).

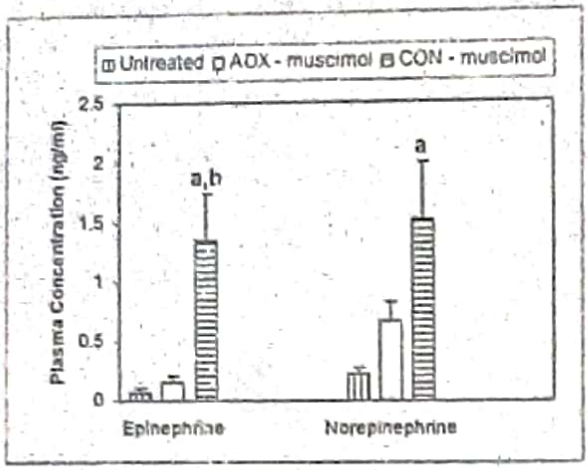

Figure (7): Plasma catecholamine levels from untreated control male rats (without drug infusion) and from control (CON) and bilaterally adrenalectomized (ADX) male rats during direct infusion of muscimol (10 nl/min/10min, 1 ng/nl) in area postrema

[a]Indicates a statistically significant difference between control untreated male rats and muscimol-infused control male rats ($p \leq 0.05$).

[b]Indicates a statistically significant difference between muscimol-infused control male rats and muscimol-infused bilaterally adrenalectomized male rats ($p \leq 0.05$).

DISCUSSION

In the current study, it was found that muscimol infusion directly into the area postrema increased mean arterial pressure in CON, without significant change in mean arterial pressure in ADX. This indicates a major role of the adrenals in the pattern of hemodynamic changes consequent to $GABA_{(A)}$ activation in rat area postrema. Further evaluation of regional circulations indicated that increases in mean arterial pressure in CON were accompanied by a more pronounced renal resistance increase. However, in ADX these resistances and blood pressure changes during muscimol infusion were largely attenuated. Remarkably, renal blood flow in both groups was not significantly altered, even though mean arterial pressure responses were different (attenuated in ADX).

Iliac blood flow was increased when mean arterial pressure increased during muscimol infusion in CON and did not change from control values after bilateral adrenalectomy. Iliac vascular resistance increased during muscimol infusion in both CON and ADX but rapidly attenuated in CON. This attenuation of iliac vascular resistance was probably due to β_2-adrenoreceptor action from circulating catecholamines. It is well known that β_2 adrenoreceptors have a higher affinity for epinephrine than do α_1 adrenoreceptors and are therefore the first to be activated as blood levels of epinephrine rise. This argument is supported by the finding of significantly elevated plasma epinephrine levels during muscimol infusion. Where epinephrine was significantly elevated when compared to norepinephrine levels. The iliac blood flow increases in CON were therefore caused by a combination of a decrease in resistance and during an increase in perfusion pressure. The observation that iliac vascular resistance returned to control (pre-infusion) values in CON and persisted in ADX suggests that muscimol infusion may directly cause significant sympathetic vasomotor withdrawal in the skeletal muscle bed. In CON, the lack of heart rate increases when plasma catecholamines were significantly elevated suggests activation of a vagal motor deceleration pathway and/or withdrawal of sympathetic cardiac accelerator activity during muscimol infusion. This indicates an active inhibition of the arterial baroreflex. Others have demonstrated that the area postrema can enhance the baroreflex control of sympathetic efferents to the kidney[3,8] and the heart[31].

This study demonstrated that patterning of mean arterial pressure and regional hemodynamics during muscimol infusion was significantly dependent upon the adrenals. The data indicated that elevated renal vascular resistance and attenuation of iliac vascular resistance in CON are caused not by increased sympathetic vasomotor activity but secondary to elevated circulating adrenal catecholamines. Adrenal sympathetic outflow does not necessarily parallel sympathetic outflow to other vascular beds because of the role of the medulla in compensating hemorrhagic[22,23] and hypoglycemic shock[23].

Muscimol infusion simultaneously promotes sympathetic vasomotor nerve suppression while powerfully stimulating adrenal catecholamine secretion. Although $GABA_{(A)}$ receptor activation has not been previously reported in rats to cause release of adrenomedullary catecholamines, activation of a major efferent projection site from the area postrema i.e. the lateral parabrachial nucleus in the pons has been reported to elevate plasma epinephrine and norepinephrine to levels similar to those we report for $GABA_{(A)}$ activation[24]. The net work of efferent and afferent projections of the area postrema could explain the excitatory effect produced by muscimol when directly infused to the area postrema. It is noteworthy that lesions of the lateral parabrachial nucleus block renovasoconstriction during hypothalamic stimulation[25] and the paraventricular hypothalamic nucleus also receives ascending projections from the lateral parabrachial nucleus[26]. Also, the parvicellular region of the hypothalamic paraventricular nucleus projects heavily to the area postrema[27], the rostral ventrolateral medulla[28] and to the spinal sites of preganglionic neurons innervating the adrenal medulla[29]. Other known connection by which the area postrema could affect the pattern of sympathetic efferent activity to the vasomotor neurons or to the adrenal medulla are related to the C_1 region of the rostral ventrolateral medulla[4,10] which projects directly to the site of preganglionic sympathetic neurons in the spinal cord and to the nucleus of the tractus solitarius, NTS[1,10,13,31,32,33]. This latter nucleus has connection that can either increase or decrease sympathetic outflow[3,32,33] also receives ascending projections from the lateral parabrachial nucleus[26].

In similar context, activation of presynaptic serotonergic receptors ($5HT_3$), increased the excitatory glutaminergic input to the area postrema[30]. Also muscimol bilaterally infused into the caudal ventrolateral medulla (CVLM), to which the area postrema projects[3,4], produced similar pressor effect and increased vascular resistances[34,35]. However, inhibition of the rostral ventrolateral medulla (RVLM) or blockade of glutaminergic inputs by microinjections of muscimol decreased arterial pressure in control rats[35]. Similarly, microinjection of muscimol into the NTS produced a

significant increase in the baseline of mean arterial pressure, no changes in the baseline of heart rate and a reduction in baroreflex gain[36]. The participation of the area postrema in central mechanisms of adrenal medullary sympatho-excitation has not been previously reported in rats, but has been noted in an earlier study that muscimol produced similar hemodynamic effects that interact with NMDA receptors[20]. These data suggest a possible suppression of pathways from the area postrema to the NTS or VLM[37] which might, in turn activates the sympatho-adrenal arc.

It remains to be determined if the area postrema-adrenal medullary arc can be activated by chemical stimuli known to affect area postrema function, e.g., vasopressin[3,20] angiotensin[11,12,38] and excitatory amino acids[5,6]. In conclusion, the regional hemodynamic and pressor effects of $GABA_{(A)}$ activation by muscimol are largely dependent upon augmenting sympathetic outflow to the adrenal medulla. If so, this chemosensitive circumventricular organ could participate in adrenal medullary regulation in a variety of physiological states.

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الدورالمحتمل لنخاع الغدة فوق القظرية في تغيرات الدورة الدموية أثناء تحفيز المنطقة البوستريمية بحمض الجابا

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قسم الفارماكولوجى والسموم- كلية الصيدلة - جامعة الزقازيق- الزقازيق- مصر

تهدف هذه الدراسه إلي معرفة الدور المحتمل لنخاع الغده فوق القظرية في التغيرات المتعدده في الدوره الدموية أثناء تحفيز المنطقة البوستريمية بالجابا (أ). وقد تم ملاحظة التغيرات في ضغط الدم الشرياني ومعدل ضربات القلب وسرعة تدفق الدم الكلوي والوركى وكذلك تركيز أمينات الكاتيكول في مصل إلجرذان أثناء الحقن الدقيق لدواء الميوسيمول لمدة عشرة دقائق في المنطقة البوستريميه لذكور الجرذان البيضاء المخدره بمادة البنتوباربيتال في مجموعه ضابطه وأخري تعرضت للاستئصال الحاد للغده فوق القظرية.

وقد أدي الحقن البطئ للميوسيمول في المنطقة البوستريمية لزيادة ضغط الدم الشريانى معتمدا علي الجرعه الدوائية في المجموعه الضابطه ولكن هذا التأثير قد ضعف في المجموعه المستأصله ولم يتأثر معدل ضربات القلب بهذه المعالجة الدوائية في أى من المجموعتين . وقد زاد معدل تدفق الدم الكلوي بصوره بسيطه ووقتيه ، وقد زاد أيضا تدفق الدم الوركى بصوره واضحه في المجموعه الضابطه ولم يتأثر في المجموعه المستأصله. وقد زادت المقاومه الوعائية الوركيه في المجموعتين ولكنها سرعان مارجعت للمستوي الطبيعي في المجموعه الضابطه ، وقد أدي حقن الميوسيمول إلي زياده تركيز أمينات الكاتيكول في المصل.

مما سبق أوضحت هذه الدراسه أن تحفيز الجابا (أ) في المنطقة البوستيريمية أدي إلي مضاعفة التدفق السيمبثاوي للغده فوق القظريه والذي أدي إلي زياده ملحوظة في أمينات الكاتيكول والتى أدت بدورها إلي التوسع الوركي الوعائى والانقباض الكلوي الوعائى ، وقد إنعكس هذا التأثير في المجموعه المستأصله وإنسحب التأثير السيمباثاوي في هذه الأوعية .