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Effect of unilateral adrenalectomy on acute immobilization stress response in rats

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Objectives. The aim of the present study was to investigate the differential effect of unilateral adrenalectomy, right vs. left, in response to acute immobilization stress (IS) in rats.

Methods. Adult male rats were subjected to unilateral right or left adrenalectomy or sham operation (control). Two weeks later, the rats were sacrificed either immediately or 3 hours after IS exposure. Plasma samples were used for determination of catecholamines (CAs), adrenocorticotrophic hormone (ACTH), corticosterone (CORT), sodium, potassium, and glucose levels. After terminating the experiment, both or remaining adrenals were removed, weighed, and used for estimation of CAs and nitric oxide (NO) levels.

Results. Under basal conditions, either right or left adrenal kept all the tested parameters near to the control levels, except the adrenal weight and CAs content. These were significantly higher in the remaining right than left adrenal. However, the remaining right adrenal responded better to IS exposure than the remaining left one in the term of compensatory adrenal growth and plasma parameters which were all kept insignificantly different from those of IS intact group.

Conclusion. Our data indicate that the adrenal glands may substitute each other under basal conditions. However, the right adrenal seems to be dominant during exposure to acute immobilization stress.

Key words: adrenalectomy, catecholamines, immobilization stress, rat

The adrenal gland is an important peripheral hormone-secreting organ. It is a component of both the hypothalamic-pituitary-adrenocortical (HPA) axis and sympatho-adrenomedullary system (SAS) (Kim et al. 2009; Wood and Hammer 2011). The adrenal gland influences a number of processes during stress response and potently affects the immune system, glucose metabolism, electrolyte or water homeostasis, and cardiovascular functions (Riester et al. 2012).

The mammalian adrenal gland consists of two endocrine tissues of different embryological origin: the steroid-producing adrenal cortex and catecholamine-producing adrenal medulla, consisting of chromaffin cells. During adrenal gland organogenesis, close interactions between the two tissue types develop which are necessary for the differentiation, morphogenesis, and survival of the adrenals (Haase et al. 2011).

Postnatal deficiency of adrenocortical and adrenomedullary hormones induced by adrenalectomy leads to a profound hypoglycemia and hypotension in several species, including rats. Adrenal insufficiency also impairs the response to common physiological challenges, such as cold exposure, fasting, and exercise, with adverse consequences for morbidity and mortality in the long term (Fowden and Forhead 2011). This is of a considerable clinical importance because a person who has recently lost one adrenal gland function (for example through surgery) could be at high risk for any major

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operative procedure. In addition, the function of the remaining gland under such conditions might be very crucial. Unilateral adrenalectomy (UA) is performed not only to treat adrenal tumors but also as part of radical nephrectomy (Hafez et al. 2005).

The two suprarenal glands are not exactly similar at least in weight (Gerendai et al. 2009), which is reflected by the percentage of hormones secreted under different conditions. Only few studies are dealing with the morphological and pathological asymmetry of the adrenal gland (Toth et al. 2008). There might be body-side specific differences in adrenal functioning during both basal and stimulated physiological conditions. For example, an increased weight of the left compared with the right adrenal has been found under unstressed conditions in both rats and mice (Droste et al. 2007). Moreover, there is evidence from the same two rodent species for a body-side specific weight gain of only the right adrenal during prolonged voluntary wheel running (Droste et al. 2003; 2006; 2007) and a specific increase in the left adrenal weight has been described in humans who committed suicide (Szigethy et al. 1994; Dumser et al. 1998). Development of body-side specific differences in the reduction or loss of adrenal ACTH responsiveness between the left and right adrenals has also been reported (Reber et al. 2007).

The controversy about the presence of lateralization in suprarenal gland hormonal content and release under both normal and stressful conditions was the reason for this study. Either removal of the right or the left adrenal gland was included in the current study to determine whether one adrenal gland loose can be substituted by the other one under normal conditions as well as during acute stress exposure. If yes, will the response be different between the cases.

Materials and Methods

Animals. The study was conducted on 48 adult male rats, weighing (250-300 g). Rats were housed in wire mesh cages at room temperature with normal light/dark cycles (Kondo et al. 2013) and were left for two weeks after arrival from the supplier for acclimatization. Rats were fed by a standard diet of commercial rat chow and tap water *ad libitum* throughout the study (Popovic and Pajovic 2010). Experimental design was approved by The Laboratory Animals Maintenance and Usage Committee of Faculty of Medicine in Minia University.

All animal handling and operations were performed between 9:00 and 11:00 a.m. by the same person to diminish the influence of diurnal variations of hormonal levels (Adzic et al. 2009).

Adrenalectomy. Adrenalectomy was performed according to the method described by Sfikakis et al. (2008) and Malendowicz et al. (2009). In brief, each rat was anesthetized using a ventilated plexiglas chamber filled with ether vapor. Under clean aseptic conditions, the hair was shaved from the abdomen and a single longitudinal skin incision was made in the midline of abdominal wall. The skin was then retracted laterally. A midline abdominal incision was made and the abdominal wall was retracted. The adrenal gland (either the right or the left one) was gently exposed and ligation of its vessels was done using a silk thread (3/0) and the gland was excised. Glands were examined histologically to verify their complete removal. Finally, the abdominal wall and skin were closed separately by interrupted sutures with local application of antibiotic (Dermatocin). The same procedures were done in control (sham operated) rats. Both right and left adrenal glands were exposed but not manipulated. Rats were returned to their cages and recovery from anesthesia was monitored. The surgical wound was cleaned daily with Betadine and local antibiotic (Dermatocin).

Experimental groups. Rats were randomly divided into the following groups (8 rats each): 1) Control (C) group: rats were subjected to sham operation and two weeks later were sacrificed; 2) Right adrenalectomy (RA) group: rats were subjected to right adrenalectomy and then sacrificed two weeks later; 3) Left adrenalectomy (LA) group: rats were subjected to left adrenalectomy and then sacrificed after two weeks; 4) Immobilization stress (IS) group: each rat was immobilized on a wooden board by fixing the four limbs with surgical tapes to a specially prepared metal mounts according to Nostramo et al. (2012) for 3 hours and then sacrificed; 5) RA + IS (RAIS) group: in which rats were subjected to right adrenalectomy and two weeks later each rat was subjected to IS before being sacrificed; and 6) LA + IS (LAIS) group: rats were subjected to left adrenalectomy and two weeks later, each rat was subjected to IS and then sacrificed.

Sample collection and chemical assays. At the end of the experiment and just before being sacrificed, all rats were anesthetized by light ether anesthesia. Blood samples were obtained by cardiac puncture, collected in tubes containing heparin as anticoagulant and then centrifuged at 3000 rpm for 15 min in a cooling centrifuge (Hettich centrifuge). The supernatant plasma was then collected in labeled Eppendorf tubes and stored at -20°C for estimation of the following parameters:

- Catecholamines (CAs), epinephrine (E), norepinephrine (NE) and dopamine (DA) were measured spectroflurophotometrically as previously described by Ciarlone (1978) using spectroflurophotometer (Shimadzu RF-5000, Japan).
- Adrenocorticotrophic hormone (ACTH) was measured using ELISA kit (DRG international Inc., USA) (Ganong et al. 1974).
- Corticosterone (CORT) was measured using spectroflurophotometer as previously described (Mattingly et al. 1962).
- Glucose, sodium and potassium were measured by enzymatic colorimetric method using commercial kits (Biodiagnostic, Egypt) following manufacturer's instructions.

After collection of blood samples, animals were sacrificed immediately by decapitation. Either the remaining or both suprarenal glands (according to experimental groups) were removed. Each gland was trimmed of surrounding fat and tissues. To prevent possible dehydration, cleaning of the gland was performed on filter paper saturated in 0.9% NaCl solution (Sfikakis et al. 2008). Finally, each gland was weighed and then stored at -80°C for determination of:

- Adrenal CAs content spectroflurophotometrically as previously described by Ciarlone (1978).
- Adrenal nitric oxide (NO) content by enzymatic colorimetric method using commercial kits (Biodiagnostic, Egypt) following manufacturer's instructions.

Statistical analysis. All the data were expressed as means ± standard errors (mean ± SEM). Data were analyzed using one-way analysis of variance (ANOVA) with repeated measurements. All the statistical analyses were performed using general linear model procedure (SAS Institute Inc., NC, USA, 2003). Significant differences among groups were detected using Duncan's multiple rang test (1955) with a value of $p \leq 0.05$ considered statistically significant.

Table 1
Lateralization of adrenal gland weight and catecholamines contents in the control non-stressed rats

Parameter	Control		p
	Right adrenal	Left adrenal	
Weight (mg)	26.1±1.32[b]	32.96±0.94[a]	**
E (μg/g)	485.03±0.61[a]	433.64±0.60[d]	***
NE (μg/g)	174.51±0.60[a]	144.43±0.60[c]	***
DA (μg/g)	54.54±0.60[c]	44.64±0.58[d]	***
NO (nmol/g)	74.68±0.83	73.48±0.82	ns

Data are expressed as mean ± SEM of 8 rats in each group. Means in the same horizontal row with different superscripts ([a, b, c, d]) are significantly different. **p<0.01; ***p<0.001; ns – not significant
E – epinephrine; NE – norepinephrine; DA – dopamine; NO – nitric oxide

Results

Variations in adrenal weight, CAs and NO contents in the right vs. left adrenals in the control non-stressed rats. As shown in Table 1, although the weight of the left adrenal gland was significantly higher (p<0.01) than that of the right adrenal gland, CAs including E, NE and DA contents/gm tissue were significantly higher (p<0.001) in the right than the left adrenal gland in the control non-

Table 2
The effect of right vs. left adrenalectomy on adrenal weights, catecholamines and nitric oxide contents

Parameter	C		RA remaining LT adrenal	LA remaining RT adrenal	p
	RT adrenal	LT adrenal			
Weight (mg)	26.10±1.32[d]	32.96±0.94[c]	41.43±0.89[b]	49.73±1.28[a]	***
E (μg/g)	485.03±0.61[a]	433.64±0.60[b]	434.70±0.89[b]	486.54±0.75[a]	***
NE (μg/g)	174.51±0.60[a]	144.43±0.59[b]	146.24±0.86[b]	176.26±0.86[a]	***
DA (μg/g)	54.54±0.60[a]	44.64±0.58[b]	45.25±0.86[b]	55.75±1.02[a]	***
NO (nmol/g)	74.68±0.83	73.48±0.82	74.61±0.87	74.78±0.75	ns

Data are expressed as mean ± SEM of 8 rats in each group. Means in the same horizontal row with different superscripts ([a, b, c, d]) are significantly different. ***p<0.001; ns – non-significant
C – control; RA – right adrenalectomy; LA – left adrenalectomy; RT – right; LT – left; E – epinephrine; NE – norepinephrine; DA – dopamine; NO – nitric oxide

stressed group. On the other hand, adrenal NO content did not differ significantly (p>0.05) between both glands.

Effect of unilateral adrenalectomy (right vs. left) on tested parameters under basal conditions.

Effect of right vs. left adrenalectomy on adrenal weight, CAs and NO contents. Table 2 shows that the weight of the remaining right adrenal in LA group was significantly higher than the remaining left adrenal in RA group as well as the right and left adrenals of the C group. Similarly, adrenal CAs contents (E, NE, DA) of the remaining right adrenal in LA group were significantly higher than the remaining left adrenal in RA group. However, no significant differences (p>0.05) were detected in the tested parameters between both adrenalectomized groups and their corresponding C groups (Table 2). As regards adrenal NO content, it was insignificantly (p>0.05) different in all experimental groups.

Effec t of right vs. left adrenalectomy on plasma CAs, ACTH and CORT levels. Data presented in Fig. 1 and Fig. 2 show that in either right or left adrenalec-

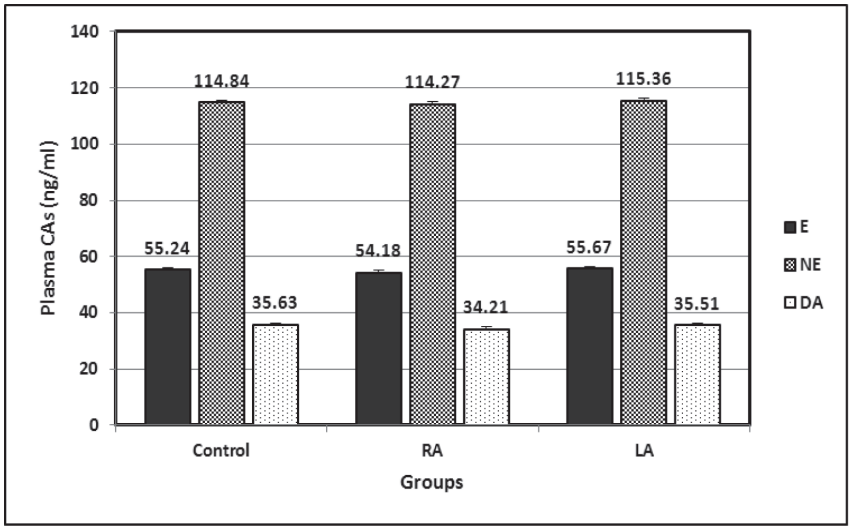

Fig. 1. Plasma catecholamines (CAs) levels in right vs. left adrenalectomized groups under resting conditions. Data are represented as mean ± SEM of 8 rats in each group.
RA – right adrenalectomy; LA – left adrenalectomy; E – epinephrine; NE – norepinephrine; DA – dopamine

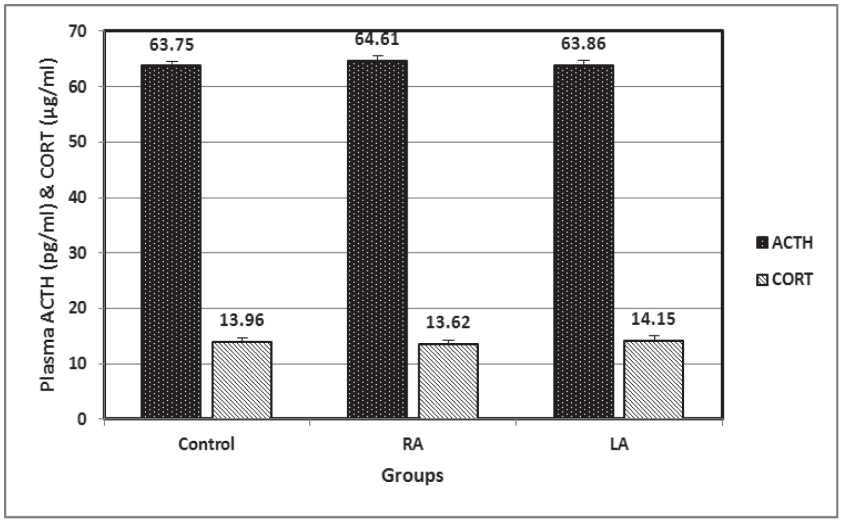

Fig. 2. Plasma adrenocorticotrophic hormone (ACTH) and corticosterone (CORT) levels in right vs. left adrenalectomized groups under resting conditions. Data are represented as mean ± SEM of 8 rats in each group.
RA – right adrenalectomy; LA – left adrenalectomy

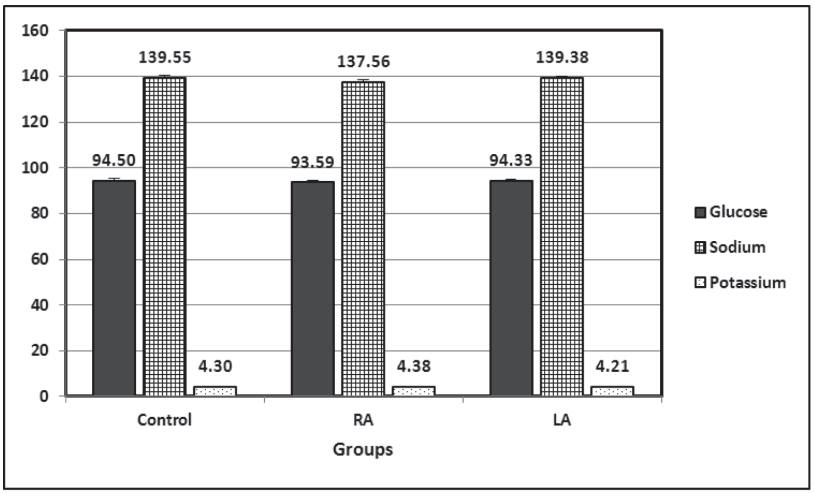

Fig. 3. Plasma glucose (mg/dl), sodium and potassium (mmol/l) levels in right vs. left adrenalectomized groups under resting conditions. Data are represented as mean ± SEM of 8 rats in each group.
RA – right adrenalectomy; LA – left adrenalectomy

tomized groups, plasma levels of E, NE and DA as well as ACTH and CORT were preserved nearly completely at the control level. Their levels were kept insignificantly different ($p>0.05$) from that of the control.

Effect of right vs. left adrenalectomy on plasma glucose, Na^+ and K^+ levels. Fig. 3 shows that in comparison with the C group, either right or left adrenalectomized groups showed insignificant differences in plasma levels of glucose, Na^+ and K^+ which were all kept near to those of the control group.

Effect of immobilization stress (IS) on tested parameters in different stress groups.

Effect of IS with or without adrenalectomy on adrenal weights, CAs and NO contents. IS did not significantly affect the weight of either adrenal gland, however, E and NE contents/g tissue were significantly lower while adrenal DA and NO contents were significantly higher than the corresponding C groups (Table 3). In the RAIS and LAIS groups, the remaining adrenal gland weight was significantly higher than that of its corresponding of the IS group. Adrenal E, NE, DA, and NO contents were not significantly different from the levels of the corresponding adrenal of IS group (Table 3). Comparing the results of RAIS vs. LAIS groups, the

Table 3
The effect of immobilization stress with or without adrenalectomy on adrenal weight, catecholamines and nitric oxide contents

Parameter	C		IS		RAIS	LAIS	p
	Right adrenal	Left adrenal	Right Adrenal (intact)	Left Adrenal (intact)	Left Adrenal (remaining)	Right Adrenal (remaining)	
Weight (mg)	26.1±1.32^{d}	32.96±0.94^{c}	26.91±1.1^{d}	35.36±1.26^{c}	43.80±1.32^{b}	51.98±0.77^{a}	***
E (μg/g)	485.03±0.61^{a}	433.64±0.60^{c}	456.58±0.88^{b}	416.29±0.86^{d}	414.37±0.86^{d}	455.66±0.87^{b}	***
NE(μg/g)	174.51±0.60^{a}	144.43±0.59^{c}	165.30±0.87^{b}	134.45±0.87^{d}	135.29±0.86^{d}	165.63±0.86^{b}	***
DA (μg/g)	54.54±0.60^{b}	44.64±0.58^{c}	65.51±0.88^{a}	55.46±0.88^{b}	56.53±0.88^{b}	66.64±0.88^{a}	***
NO (nmol/g)	74.68±0.83^{b}	73.48±0.82^{b}	86.59±0.86^{a}	84.63±0.86^{a}	84.73±0.84^{a}	86.79±0.85^{a}	***

Data are expressed as mean ± SEM of 8 rats in each group. Means in the same horizontal row with different superscripts ($^{a, b, c, d}$) are significantly different. ***$p<0.001$
C – control; IS – immobilization stress; RAIS – right adrenalectomy immobilization stress; LAIS – left adrenalectomy immobilization stress; RT – right; LT – left; E – epinephrine; NE – norepinephrine; DA – dopamine; NO – nitric oxide

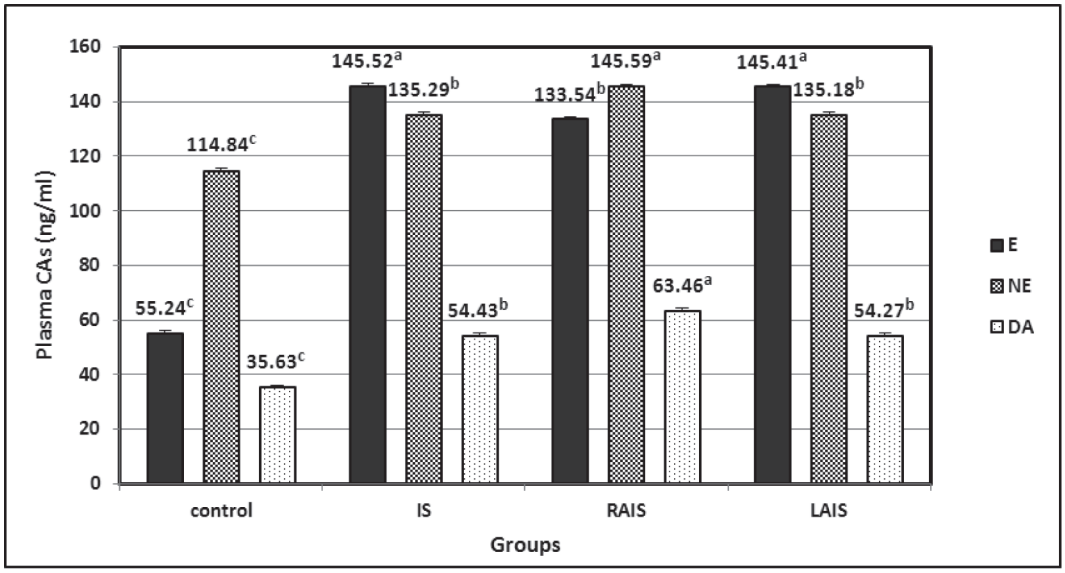

Fig. 4. Effect of immobilization stress (IS) with and without adrenalectomy on plasma catecholamines (CAs) levels. Data are represented as mean ± SEM of 8 rats in each group. Means of similar columns with different superscripts ([a, b, c]) are significantly different (p<0.05).
C – control; RAIS – right adrenalectomy immobilization stress; LAIS – left adrenalectomy immobilization stress; E – epinephrine; NE – norepinephrine; DA – dopamine

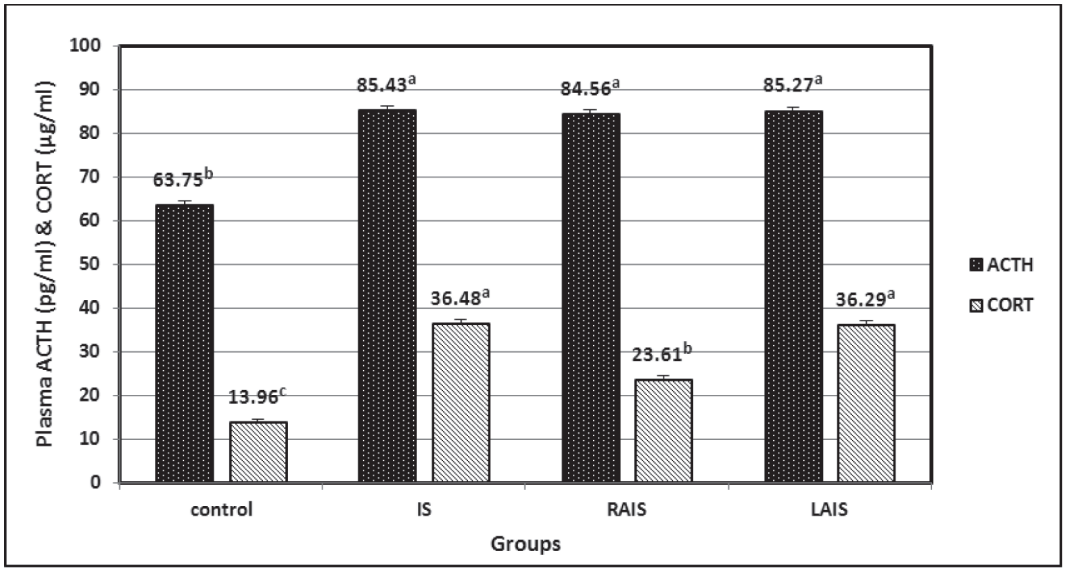

Fig. 5. Effect of immobilization stress (IS) with and without adrenalectomy on plasma adrenocorticotrophic hormone (ACTH) and corticosterone (CORT) levels. Data are represented as mean ± SEM of 8 rats in each group. Means of similar columns with different superscripts ([a, b, c]) are significantly different (p<0.05).
C – control; RAIS – right adrenalectomy immobilization stress; LAIS – left adrenalectomy immobilization stress

remaining right adrenal gland in LAIS group showed significantly higher compensatory adrenal weight and CAs contents than the remaining left adrenal in RAIS group (Table 3).

Effect of IS with or without adrenalectomy on plasma CAs, ACTH and CORT. Data presented in Fig. 4 and Fig. 5 show the effect of IS, RAIS and LAIS on plasma CAs, ACTH and CORT levels. Plasma levels of

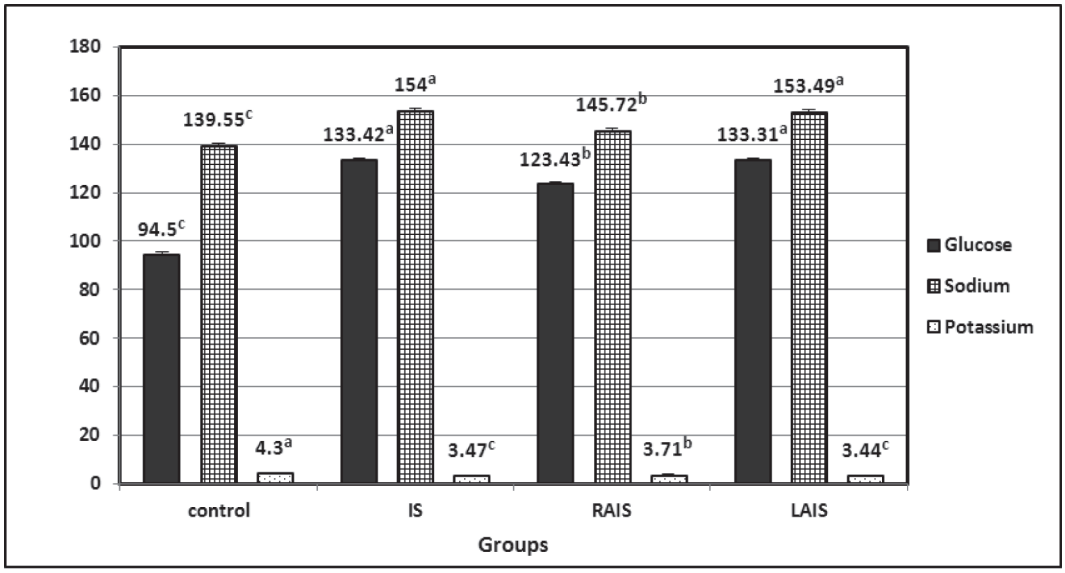

Fig. 6. Effect of immobilization stress (IS) with and without adrenalectomy on plasma glucose (mg/dl), sodium and potassium (mmol/l) levels. Data are represented as mean ± SEM of 8 rats in each group. Means of similar columns with different superscripts ([a, b, c]) are significantly different ($p < 0.05$).
C – control; RAIS – right adrenalectomy immobilization stress; LAIS – left adrenalectomy immobilization stress

E, NE, DA, ACTH, and CORT were significantly higher in IS, RAIS and LAIS groups than the C group. While E and CORT levels were significantly higher in LAIS group than RAIS group, the reverse was found for NE and DA levels. Plasma ACTH levels were not significantly different among the three groups (Fig. 4, 5).

Effect of IS with or without adrenalectomy on plasma glucose, Na^+ and K^+ levels. As shown in Fig. 6, plasma glucose and Na^+ levels were significantly higher while, plasma K^+ level was significantly lower in IS, RAIS and LAIS groups in comparison with the C group. When the RAIS and LAIS groups were compared, plasma glucose and Na^+ levels were significantly higher and plasma K^+ level was significantly lower in LAIS group.

Discussion

The results of the present study proved that either gland could compensate for the other if unilaterally removed. However, the right adrenal gland seems to be the dominant one in terms of compensatory adrenal weight and CAs content.

In the control (C) non-adrenalectomized rats, although the weight of the left adrenal gland was significantly higher than that of the right adrenal, CAs including E and NE as well as DA content/gm tissue was significantly higher in the right adrenal without any significant change in NO content between both adrenals under basal conditions.

The higher CAs content in the right than the left adrenal could be attributed to the greater medullary mass of the right adrenal gland. It has been shown that the mass of adrenal medulla is larger in the right adrenal, while the mass of adrenal cortex is greater in the left adrenal gland (Adzic et al. 2009). Accordingly, the total CAs content would be expected to be higher in the right than the left adrenal gland, findings that were confirmed by the results of the present study. Similarly, Freel et al. (2010) have described significantly higher concentrations of E, NE and DA in the right than the left adrenal vein. Furthermore, Gerendai and Halsaz (2001) and Droste et al. (2007) have reported a predominant right-sided neuronal structure in the control of suprarenal gland, which could also explain the higher CAs and DA contents in the right adrenal than the left one. Thus, it could be stated that the increased right adrenal content of CAs substitutes for its lower weight than the left and equalizes the total content of both.

Following either, right (RA) or left adrenalectomy (LA), the remaining adrenal gland exhibited a significant compensatory higher weight than that of the corresponding C sham-operated group, which was highly

significant and more obvious in the remaining right than the left one.

In the current study, the weight of the remaining adrenal gland of rats following UA was significantly higher than that of the corresponding sham operated group. Therefore, the weight increase in the remaining adrenal gland after unilateral adrenalectomy (UA) could be considered to be a specific consequence of the removal of one adrenal rather than a nonspecific stress-related effect of the surgical procedure itself (Beuschlein et al. 2002; Simon and Hammer 2012).

UA removes half of the tissue capable of the secretion of adrenal steroids. In order to maintain hormonal homeostasis, rapid compensatory mechanisms must occur and the remaining adrenal gland undergoes hyperplasia and hypertrophy. This compensatory adrenal growth (CAG) response following UA is tightly controlled by both humoral and neuronal factors. Humoral factors may include the common precursor POMC derived peptides such as ACTH, ANGII, sex hormones, LH, TSH and growth hormone (GH) (Hoeflich and Bielohuby 2009). CAG may also be dependent upon a neural reflex arc via afferent nerve connections from one adrenal gland to the hypothalamus and an efferent limb back to the other adrenal (England et al. 2005; Gil-Lozano et al. 2013).

The greater compensatory adrenal growth (CAG) observed in the remaining right adrenal could be attributed to the relatively lower initial weight of the right adrenal than the left one, as it was shown that the extent of CAG following UA is inversely related to the initial adrenal weight (Bikas et al. 2002; Sfikakis et al. 2008). So, considering the lower initial weight of the right adrenal than the left one, the CAG would be greater in the remaining right than left gland; findings which are in agreement with the results of this study.

In the present study, no significant change was observed in any of the tested plasma parameters including, E, NE, DA, ACTH, CORT, glucose, Na^+ and K^+ levels between C, RA and LA groups after two weeks. In addition, the remaining left or right adrenal CAs contents/g tissue was nearly the same as that of the corresponding C group. These results could be explained by the efficiency of the CAG response of the remaining gland in preserving hormonal homeostasis and thus compensating for the removed gland. Similar results were reported by other authors (Nakayama et al. 1993; Sejian et al. 2008; Malendowicz et al. 2009; Huang et al. 2012), indicating the existence of a compensatory mechanism between the two adrenal glands. Therefore, when one gland loses its function the other gland takes up the function of the lost one to maintain the physiological functions at near normal level.

As regards adrenal NO content, both right and left adrenal NO content did not change significantly between C, RA and LA groups suggesting that NO may have no role in synthesis or secretion of adrenal hormones under basal conditions.

The role of NO on basal catecholamine secretion is a subject of controversy (Orlando et al. 2008). Some investigators have reported a long-term up regulation by NO of the genes encoding for the catecholamine biosynthetic enzymes (Kim et al. 2003). However, other studies have reported that plasma CORT, NE and E levels were similar in the nNOS KO and wild type (WT) genotypes under resting conditions. These contradictory results might be due to the use of dissociated chromaffin cells, which contain different proportions of adrenergic and noradrenergic cells according to the method of separation (Orlando et al. 2008). NOS has been shown to be unevenly distributed among chromaffin cells, with noradrenergic cells specialized in producing NO (Mcneill and Perry 2005), whereas adrenergic cells represent its main target (Kim et al. 2003; Rosmaninho-Salgado et al. 2009).

Based on these results, it could be stated that either adrenal gland can compensate for the other if removed under basal conditions. The right adrenal has more potent capacity to increase its weight. Although the CAs content per g tissue did not significantly change, yet increased weight X content means higher secretory capacity. In addition, the stable content in spite of increased weight indicates that the changes in the different cell types are proportionate.

As regards the effect of IS in right vs. left adrenalectomized rats, LAIS group was effective as the intact IS group and kept all plasma parameters unchanged. On the other hand, RAIS group showed significantly lower plasma E, CORT, glucose and Na^+ levels along with significantly higher plasma levels of NE, DA and K^+ levels than both IS and LAIS groups. Both RT and LT adrenal CAs and NO contents (in g tissue) did not change significantly between all stress groups.

The greater decline in plasma E observed in RAIS group could be explained by the current finding that both right adrenal CAs/g tissue and CAG in the remaining right adrenal after LA was significantly higher than the remaining left one after RA, thus the total right adrenal CAs content is higher than that of the left one, so it contributes more to plasma CAs during acute stress

exposure. That is why the remaining left adrenal in RAIS group was not enough to keep plasma CAs unchanged, especially E.

Khalil et al. (1987) have reported that removal of the right adrenal significantly reduced the increase in plasma E in response to stress, while plasma NE was significantly increased; findings that are in agreement with this study and may be explained by a compensatory increase in sympathetic NE secretion in response to stress.

During stress, the increment in plasma E is derived almost completely from the adrenal medulla, whereas most plasma NE (about 70%) is derived from sympathetic nerves (Kvetnansky et al. 2009). Previous studies have shown that IS significantly increased plasma free and conjugated NE and DA levels in adrenalectomized rats, while sympathectomy decreased plasma NE and DA levels in response to stress adding more evidence that the main source of plasma NE and DA during stress exposure is the SNS rather than the adrenal gland (Yoneda et al. 1985).

The corresponding decrease in plasma CORT along with CAs levels observed in RAIS group, also raises the possibility that the remaining right adrenal contributes more to plasma CORT during stress conditions. Uschold-Schmidt et al. (2012) have shown that the rise in adrenal CORT content in response to acute stress exposure was significantly higher only in the right adrenal gland of rats than that of control what indicates the dominant role of right adrenal gland in stress response.

Concerning the obtained finding of the differential responses in CORT plasma levels in the face of insignificant changes in ACTH plasma levels in response to GS with or without UA; this may indicate that the central effect of stress to stimulate ACTH release is stronger than any feedback mechanism. Bornstein et al. (2008) have reported that significant differential regulation of pituitary and adrenal gland activation exists leading to a dissociation of plasma ACTH and corticosteroid secretion. Mechanisms involved may include an altered adrenal sensitivity, aberrant receptor expression or modulation of adrenal function by cytokines, vasoactive factors or neuropeptides.

In RAIS group, plasma glucose and Na^+ levels were significantly lower while, K^+ level was higher in comparison with both IS and LAIS groups. Unlike the LAIS group that showed no significant difference in those parameters when compared to IS group. This could be explained by the corresponding reduction in both CORT and E plasma levels in RAIS compared to IS group.

These results confirm the greater power of the remaining right adrenal in LAIS group to restore the conditions almost completely during stress conditions.

In conclusion, either adrenal gland can compensate for the other if unilaterally removed. Therefore, any manifestations of adrenal insufficiency must include defects in both adrenals.

Biological lateralization do exists for the favor of the right adrenal in terms of compensatory adrenal weight and CAs production during both normal and stressful conditions. NO seems to have no role in adrenal hormone synthesis and release under basal conditions. However, the significant increase in adrenal NO content observed in the stressed groups raises the possibility of its potential involvement in cases of acute stress exposure.

Further research may be required to study the effects of unilateral adrenalectomy in relation to sex difference, the role of sympathetic nervous system regulation in adrenal gland function either via sympathectomy or receptor modulation. Finally, studying other factors, which may affect adrenal response to stress such as duration of stress exposure.

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