Original Research

Motor and behavioral changes in rats with adenine-induced chronic renal failure: influence of acacia gum treatment

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Abstract

Chronic renal failure (CRF) either occurring naturally in humans or induced surgically in rats causes alterations in behavior and motor functions. However, the effect of chemically induced CRF in rats on behavior is not known. We induced CRF in rats by feeding adenine (0.75% w/w, four weeks) and investigated the effect of the ensuing CRF on a depression model (forced swimming test, FST), analgesia (mechanical nociception), neuromuscular coordination (Rota-rod test) and motor activity (activity meter test). Further, we investigated the effect of giving acacia gum (AG, 10% w/v) in the drinking water concomitantly with adenine using the above models. AG has been previously shown to ameliorate the severity of CRF in humans and rats. Adenine-induced CRF significantly increased the plasma concentrations of urea and creatinine, and reduced creatinine clearance. Additionally, it significantly reduced motor activity and increased immobility time in the FST, suggesting a depressant-like effect. Both of these actions were significantly antagonized by AG treatment. Adenine insignificantly reduced the mechanical nociceptive threshold by 15%. The results of the tests for neuromuscular coordination were inconclusive. In conclusion, adenine-induced CRF caused motor and behavioral alterations, and these were significantly mitigated by administration of AG.

Keywords: acacia gum, adenine, behavior, chronic renal failure, rats

Experimental Biology and Medicine 2011; **236**: 107–112. DOI: 10.1258/ebm.2010.010163

Introduction

Chronic renal failure (CRF) in humans, and subtotal nephrectomy-induced CRF in rats have both been shown to cause several alterations in behavior.[1–3] In rats with CRF induced by renal mass reduction, these include marked diminution in locomotor, exploratory and emotional activities, and also decreased total number of electrical shocks received, and total numbers of avoidance and escape responses, when compared with those of healthy rats.[3] In human patients, depression is the commonest psychological disorder among CRF patients.[4,5] Other abnormalities include anxiety, which, together with depression, may lead to diminished sexual activities and quality of life.[6] In children, CRF may result in several neurocognitive deficits, such as impaired intelligence quotient, memory, language and academic achievements.[7]

There are two experimental animal models for CRF, namely the surgical model (7/8 remnant kidney model, or renal mass reduction model) and the chemical model (using adenine in the feed). The behavioral aspects associated with the latter experimental model, first introduced by Ormond and Miller[8] and recently used in our laboratory,[9] has not been reported.

This work is, as far as we are aware, the first investigation on the effects of adenine-induced CRF on certain behavioral parameters in rats. Furthermore, we attempted to see if treatment with acacia gum (AG), which we have previously shown to be effective in ameliorating several biochemical and histopathological indices of adenine-induced CRF,[9] would also mitigate some selected behavioral and locomotor parameters in rats. The mechanism for the nephroprotective action of AG is not known with certainty, but there are strong indications that AG may be acting through immunomodulatory, anti-inflammatory and antioxidant actions. These have been recently reviewed.[10]

Methods

Animals

This project was reviewed and approved by our Institutional Review Board and experiments were performed in accordance

*Deceased.

with protocols approved by the Institutional Animal Care and Research Advisory Committee.

Twenty-four male Wistar rats, initially weighing 150–155 g, were obtained from our University Animal House and were housed in groups of six under standard temperature ($22 \pm 2^{\circ}C$), humidity (50–60%) and light conditions (artificial light from 06:00 to 18:00 h). The rats had seven days to acclimatize to the new surroundings before being treated and tested. They had free access to water and a standard powder diet containing 0.85% phosphorus, 1.12% calcium, 0.35% magnesium, 25.3% crude protein and 2.5 IU/g vitamin D3 (Oman Flour Mills, Muscat, Oman). In the experiment, each rat was used only once. Body weight was taken at the beginning and the end of the experiment.

Experimental design

After an acclimatization period of seven days, rats were randomly divided into four equal groups of six rats each. The first group continued to receive the same diet without treatment until the end of the study (control group). The second group was switched to a powder diet containing adenine (0.75% w/w in feed, Sigma, St. Louis, MO, USA) for four weeks. The third group was given normal food and AG (Sigma) in drinking water at a concentration of 10% w/v for four weeks. The fourth group was given adenine in the feed together with AG, as above.

At the end of the treatment period, and after the end of the behavioral tests, rats were placed individually in metabolic cages to collect the urine voided in 24 h. Thereafter, the rats were anesthetized with an intraperitoneal injection of ketamine (75 mg/kg) and xylazine (5 mg/kg), and blood (3 mL) collected from the anterior vena cava was placed into heparinized tubes. The blood and urine were centrifuged at 900*g* at 4°C for 15 min. The plasma obtained, together with the urine specimens were stored frozen at –80°C pending analysis.

In all behavioral tests used, the sequence of animals to be tested was chosen in a blinded and randomized manner, and the tests conducted blind by the same investigator in a quiet room.

Biochemical measurements

The concentrations of creatinine in plasma and urine, and urea in plasma were measured using kits from Human GmbH (Mannheim, Germany).

Forced swimming test

The modified Porsolt forced swimming test (FST)[11] was used, as reported before.[12] Rats were placed singly and forced to swim in a Plexiglas cylinder with the following dimensions: 45 cm height, 27 cm internal diameter, filled with water, maintained at 28–29°C to a height of 24 cm. This ensured that the rat's feet did not touch the floor of the vessel and that it did not escape from the vessel.

Two sessions were conducted; an initial 15-min training session followed 24 h later by a 5-min test session. After that, the rats were removed from the cylinders, towel-dried and placed under a lamp for 5 min. They were then returned to the home cage for testing the next day. A rat was judged to be immobile whenever it remained floating in the water, without struggling, in an upright position making only very small movements necessary to keep its head above water. Scoring was made by an observer unaware of the drug treatment. The measure of immobility served as a quantitative measure of the animal's behavioral despair, where it is assumed that the animal has given up hope of escaping from the confines of the vessel.[13] Each animal was used only once. In accordance with the suggestion of Abel,[14] fresh water was used for each animal to minimize any effect of the soiled water from the previous rat (possibly containing 'alarm pheromones') inducing agitation and decreased motility.

The test was carried out in a room with no other non-treated animals in the same or adjacent room to avoid giving rise to signals or odors that may affect non-treated animals.[15] Rats were trained in the FST for 15 min (first session) as described above, and 24 h later they were subjected to a 5-min session in the FST.

Measurement of motor activity

In order to investigate whether changes in immobility in the FST above were owing to changes in motor activity, for example, hyperactivity, as described elsewhere,[13] the spontaneous activity of rats treated with adenine, with or without AG was studied. Locomotor (ambulatory) and behavioral (total) activity was measured using a computerized animal activity meter (Ugo Basil, Varese, Italy), as described before.[16] Total activity included the ambulatory (actual relocation) activity score and the activity confined to a small space, that is, repeated crossing of a single photocell. An array of 15 infrared emitter/detector pairs, spaced at 2.5-cm intervals, measured the animal activity along a single axis of motion. The counts of photo interruptions were displayed on the front panel meters as ambulatory activity and total activity. Immediately after acute treatment, each rat was placed in the transparent plastic cage (43 cm × 43 cm × 22 cm) of the activity meter. After a 5-min habituation period in the cage, the activity meter was zeroed and counts were then taken between 08:00 and 12:00 h each week. The activity of the animals was tested for 30 min weekly for four consecutive weeks.

Measurement of mechanical nociception (paw pressure test)

The animals were habituated to handling by the investigator during the week before the experiments. The nociceptive threshold in the hind paw of each rat was determined to measure the sensitivity of the animals to pain in an objective and reproducible way using an analgesimeter (Ugo Basil), according to the method described by Norcini *et al.*[17]

Measurement of neuromuscular coordination

Neuromuscular coordination was measured using a Rota-rod technique (Ugo Basil) and the time of fall from the rotating rod was monitored following the standard

procedure.[18] The apparatus consisted of a base platform and a rotating rod with a diameter of 6 cm and a non-slippery surface. The rod was placed at a height of 30 cm from the base. The rod, 40 cm in length, was divided into five equal sections by six disks. The speed of the apparatus was kept as 16 r.p.m.

Statistical analysis

Values reported are means ± SEM (number of observations). Differences between groups were analyzed by a one-way analysis of variance (ANOVA) followed by Tukey's multiple comparison tests (Graphpad Prism version 4.03, San Diego, CA, USA). $P \leq 0.05$ was considered statistically significant.

Results

General effects

Figure 1 shows the body weight changes in the four groups studied. Adenine feeding (0.75% w/w for 4 weeks) caused a progressive decrease in body weight amounting to about 34% at the end of the treatment period, when compared with the initial body weight. Unlike our previous finding,[9] concomitant treatment with AG at concentrations of 10% w/w in water did not significantly influence this action. The reasons are unknown but may be related to the age/weight of rats or to other unknown factors.

The general appearance of the adenine-treated rats was improved by AG treatment. Kidneys of adenine-treated rats were pale, and a few adenine crystals were seen mainly in the cortex area. The morphological appearance of the kidneys of rats treated with adenine plus AG at the two doses used was improved compared with that of the kidneys of rats treated with adenine alone.

Figure 2 illustrates water consumption and urine volume in control rats, and rats treated with adenine in the feed, AG and with both adenine and AG given concomitantly for 28 d. Adenine treatment progressively and significantly increased water intake and urine output. This effect was reversed by AG treatment.

Biochemical measurements

Figure 3 shows the creatinine (A) and urea (B) plasma concentrations, and the creatinine clearance (C) in control rats, and rats treated with adenine in the feed, AG and with both adenine and AG. Adenine feeding (0.75% w/w for 4 weeks) caused significant increases ($P < 0.001$) in the concentrations of urea and creatinine in plasma, and a significant decrease in the creatinine clearance ($P < 0.001$). AG alone did not affect the plasma cratinine and urea, and creatinine clearance. The treatment with adenine and AG given concomitantly for 28 d significantly prevented the adenine-induced increase of plasma creatinine ($P < 0.001$) and urea ($P < 0.001$). Similarly, the decrease of creatinine clearance caused by adenine was significantly prevented by the AG treatment ($P < 0.001$).

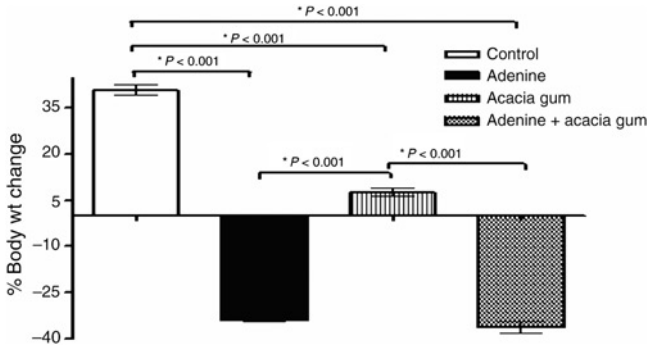

Figure 1 The change in body weight (wt) of control rats, and rats treated with adenine (0.75% w/w) in the feed, AG (10% w/v in the drinking water) and with both adenine and AG given concomitantly at the same dose for 28 d. Each column and vertical bar represent mean ± SEM ($n = 6$). Differences between the groups were assessed by one-way analysis of variance (ANOVA) followed by Tukey's multiple comparison tests. $P < 0.05$ was considered significant. AG, acacia gum

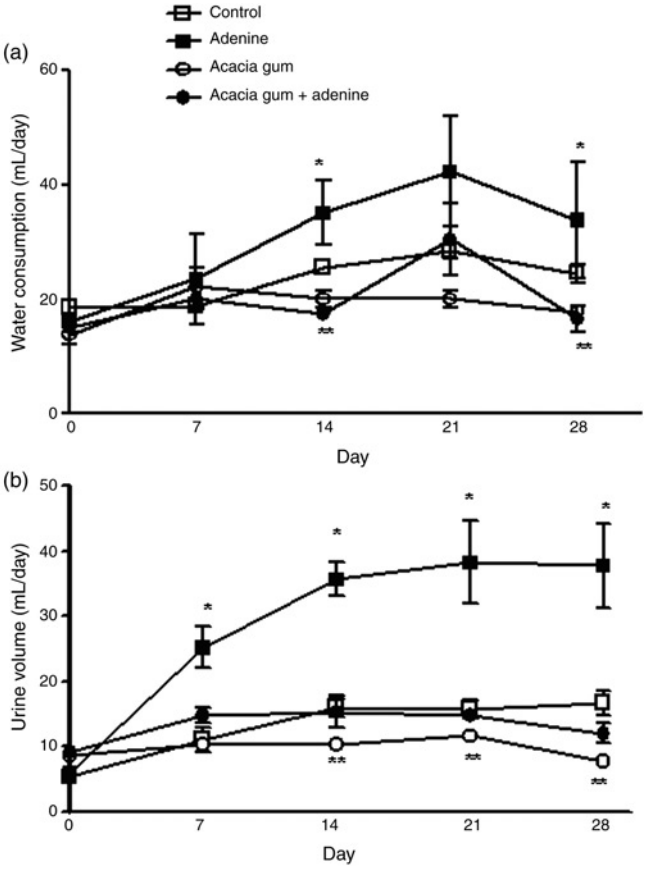

Figure 2 Water consumption (a) and urine (b) volume in control rats, and rats treated with adenine (0.75% w/w) in the feed, AG (10% w/v in the drinking water) and with both adenine and AG given concomitantly at the same dose for 28 d. Each point represents mean ± SEM ($n = 6$). Differences between the groups were assessed by one-way analysis of variance (ANOVA) followed by Tukey's multiple comparison tests. *Indicates the level of significant difference between the control and adenine-treated group, while **indicates the difference in level of significance between the AG-treated group and the group treated with AG and adenine (both $P < 0.05$ for all comparisons). AG, acacia gum

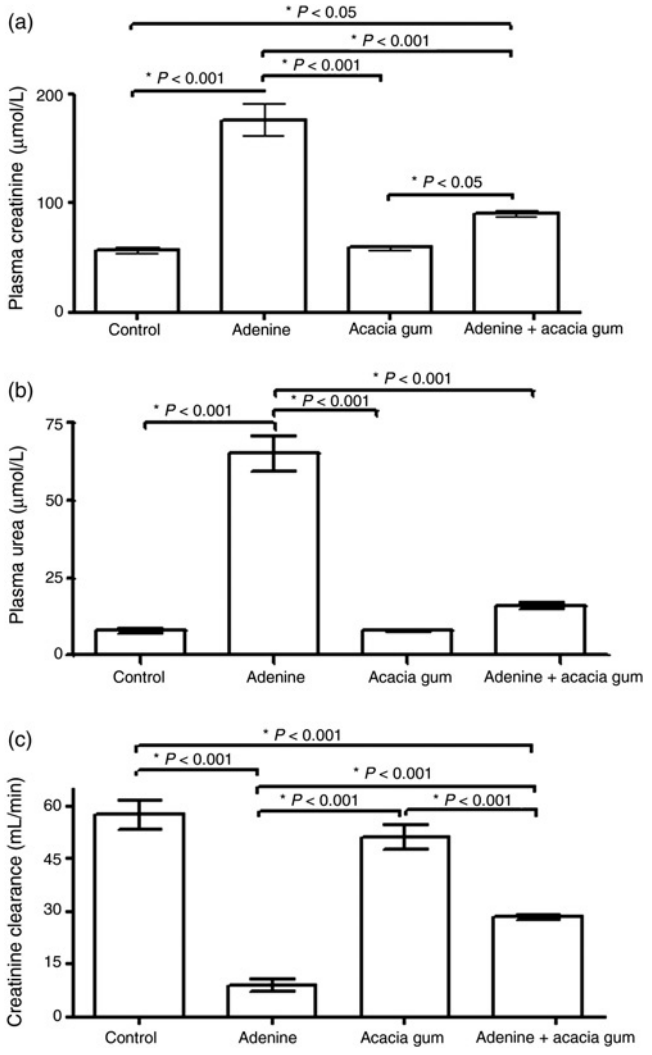

Figure 3 Creatinine (a) and urea (b) plasma concentrations, and the creatinine clearance (c) in control rats, and rats treated with adenine (0.75% w/w) in the feed, AG (10% w/v in the drinking water) and with both adenine and AG given concomitantly at the same dose for 28 d. Each column and vertical bar represent mean ± SEM ($n = 6$). Differences between the groups were assessed by one-way analysis of variance (ANOVA) followed by Tukey's multiple comparison tests. $P < 0.05$ was considered significant. AG, acacia gum

Motor and behavioral effects

The immobility time recorded in the FST in control rats, and rats treated with adenine, AG and with both adenine and AG given concomitantly for 28 d is illustrated in Figure 4. Adenine treatment significantly reduced motor (horizontal and vertical) activity ($P < 0.05$). The treatment AG alone did not affect the horizontal or vertical activities. However, AG treatment significantly prevented adenine-induced reduced vertical motor activity ($P < 0.05$).

Compared with the control group, adenine treatment caused a significant increase of the immobility time in the FST ($P < 0.05$, Figure 5). AG alone did not affect this parameter. However, the treatment with AG strongly and significantly prevented the increase of immobility time in the FST ($P < 0.01$).

As shown in Table 1, adenine treatment reduced the mechanical nociceptive threshold by 15%. However, this decrease

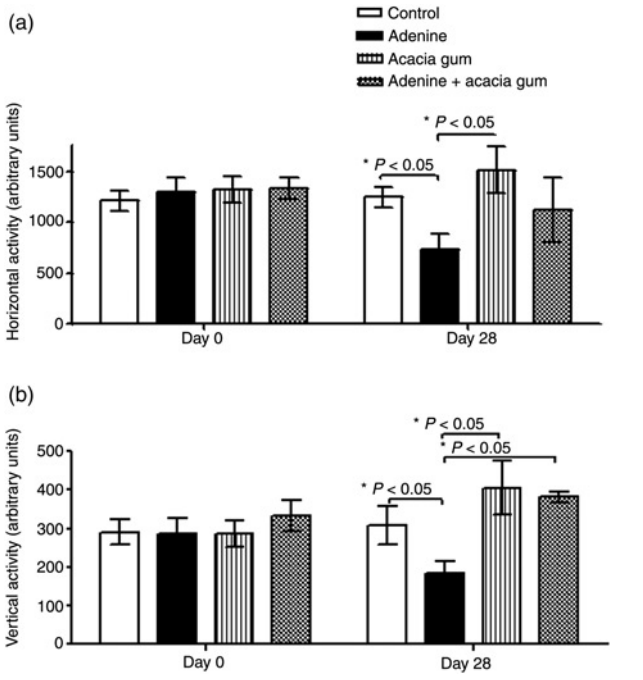

Figure 4 The change in horizontal (a) and vertical motor (b) activity in control rats and rats treated with adenine (0.75% w/w) in the feed, AG (10% w/v in the drinking water) and with both adenine and AG given concomitantly at the same dose for 28 d. Each column and vertical bar represent mean ± SEM ($n = 6$). Differences between the groups were assessed by one-way analysis of variance (ANOVA) followed by Tukey's multiple comparison tests. $P < 0.05$ was considered significant. AG, acacia gum

was statistically insignificant. Similarly, the results of the test for neuromuscular coordination were inconclusive.

Discussion

AG is used in some parts of Asia and Africa in the treatment of patients with CRF[10] and has been shown experimentally to be beneficial in rats with adenine-induced CRF,[9] but not in rats with surgically induced CRF.[19]

CRF is known to cause cardiovascular, behavioral, reproductive and other complications in both patients and the rat

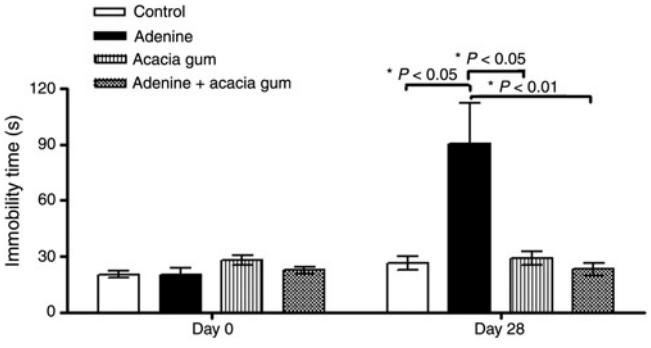

Figure 5 The immobility time (in seconds) recorded in the forced swimming test in control rats, and rats treated with adenine (0.75% w/w in the feed), AG (10% w/v in drinking water) and with both adenine and AG given concomitantly at the same dose for 28 d. Each column and vertical bar represent mean ± SEM ($n = 6$). Differences between the groups were assessed by one-way analysis of variance (ANOVA) followed by Tukey's multiple comparison tests. $P < 0.05$ was considered significant. AG, acacia gum

Table 1 Paw pressure (in g) of single mechanical nociceptive threshold in a mechanical hyperalgesia test in rats

Group	Day 0	Day 28
Control	5.25 ± 0.83	5.92 ± 0.85
Adenine	5.00 ± 0.38	4.25 ± 0.66
Acacia gum	5.58 ± 0.49	5.33 ± 0.80
Adenine + acacia gum	5.75 ± 0.42	5.83 ± 1.40

Control rats and rats treated with adenine (0.75% w/w) in the feed, AG (10% w/v in the drinking water) and with both adenine and AG given concomitantly at the same dose for 28 d. Data are expressed as mean ± SEM ($n = 6$). Differences between the groups were assessed by one-way analysis of variance (ANOVA) followed by Tukey's multiple comparison tests. AG, acacia gum

model of renal mass reduction.[20] However, such complications are not documented in rats with adenine-induced CRF. In this work we have recorded some signs and symptoms in rats with adenine-induced CRF, and investigated the effect of AG, given at a dose that has been successful in significantly ameliorating the effects of CRF on several indices of renal function. We have shown, probably for the first time, that in the CRF model used, there is evidence of a depression-like action, accompanied by a decrease in motor activity. AG was effective in ameliorating these actions. The action of AG might be ascribed to the general improvement that results from treatment with AG, which has been suggested to result in a urea-lowering effect by increasing urea nitrogen (N) excretion in stools, with a concomitant decrease in the total N excreted in urine (reviewed by Ali *et al.*[10]). In this study, we did not measure serum butyrates but others[21] have previously suggested that an increase in serum butyrate has potential beneficial effects in renal disease. It has been shown that treatment with AG increased serum butyrate, which at least *in vitro* has beneficial effects on renal pro-fibrotic cytokine generation. There is no direct evidence of an effect of AG on behavior in rats. In fact, AG used as vehicle at 1% or 5% has not been shown to interfere with behavioral tests.[22,23] In addition, Al Mosawi[24] has reported that treatment with AG given to one girl for six years was free from adverse effects. Moreover, during six years of therapy, the girl continued experiencing improved wellbeing and good participation in outdoor activities.

The mechanism(s) by which CRF induced the motor and behavioral alterations is not certain. However, it has been suggested to be multifactorial, and may involve alterations in cerebral neurotransmitters and their metabolism may be involved. Brain serotonin gamma-aminobutyric acid content, norepinephrine and acetylcholine release uptake and degradation are known to be affected by uremia.[25,26] It has also been reported that an increase in total calcium content of the cerebral cortex, accompanied by increased levels of cytosolic calcium in synaptosomes are common findings in rats with surgically induced CRF.[27] More recently, Smogorzewski and Massry[28] reported that in cerebral tissues isolated from rats with surgically induced CRF, the choline content and the activity of choline kinase of brain synaptosomes were decreased after three weeks of induction of the CRF, and were significantly lower than in normal controls.

Depression is a common problem in patients with chronic kidney disease, but has not been adequately diagnosed or studied,[4,5,29] and in experimental animals has not, as far as we are aware, been studied in the current model of CRF. In this work, adenine treatment caused a significant decrease in body weight. Several neurogenic factors may have been involved in the progressive decrease in body weight in rats treated with adenine. For example, inflammation is an important feature in adenine-induced CRF,[8] and inflammation and cachexia are known to be prevalent in CRF.[30] It has also been suggested that the stunted growth in CRF in nephrectomized rats may be related to impaired secretion of growth hormone.[31]

The motor and behavioral alterations reported here could also be related to alterations in the brain chemistry of animals treated with adenine. Recently, in patients with chronic renal disease, a sensorimotor disorder associated with depression and characterized by a strong urge to move the legs associated with paresthesias and motor restlessness has been described.[32,33] Mechanisms, both dependent and independent of insomnia, have been suggested as a basis for these effects.

The basis of the ameliorative effect of AG on the motor and behavioral actions of adenine in this work is not certain. Earlier, we have shown that several histopathological, biochemical and physiological effects of adenine-induced CRF are mitigated by concomitant administration of AG, probably by its anti-inflammatory and antioxidant mechanisms.[9] Recently, AG has been shown to have significant immunomodulatory action in experimental animals,[10,34] and this salutary effect of AG on immunity may contribute to its ameliorative action in the signs and symptoms of CRF. Further work is warranted on the mechanisms of the induction of these motor and behavioral changes, and the protective effect of AG.

Author contributions: All authors have read and approved the final manuscript. BHA planned, supervised, performed the animal experimentations and wrote the article. AZ planned and supervised the experiments. IAH and SB performed the biochemical analysis and behavioral experiments. AN supervised the study and wrote the article.

ACKNOWLEDGEMENTS

The Research Council of Sultan Qaboos University provided financial support for the work (RC/MED/PHAR/10/01). We thank the staff of the SQU Small Animal House for looking after the rats, and Professor S Adawi for reading the manuscript.

REFERENCES

1 Chilcot J, Wellsted D, Vilar E, Farrington K. An association between residual renal function and depression symptoms in haemodialysis patients. *Nephron Clin Pract* 2009;**113**:C117–24

2 Costaesilva AD, Todorov JC, Darrochelalobo O. Effect of experimentally induced chronic renal-failure upon the behavior of rats. *Nephron* 1979;**24**:78–80

3 Topczewska-Bruns J, Tankiewicz A, Pawlak D, Buczko W. Behavioral changes in the course of chronic renal insufficiency in rats. *Polish J Pharmacol* 2001;**53**:263–9
4 Tavallaii SA, Ebrahimnia M, Shamspour N, Assari S. Effect of depression on health care utilization in patients with end-stage renal disease treated with hemodialysis. *Eur J Internal Med* 2009;**20**:411–4
5 Kimmel PL, Peterson RA. Depression in end-stage renal disease patients treated with hemodialysis: tools, correlates, outcomes, and needs. *Sem Dialysis* 2005;**18**:91–7
6 Lew-Starowicz M, Gellert R. The sexuality and quality of life of hemodialyzed patients-ASED multicenter study. *J Sexual Med* 2009;**6**:1062–71
7 Gipson DS, Duquette PJ, Icard PF, Hooper SR. The central nervous system in childhood chronic kidney disease. *Pediatr Nephrol* 2007;**22**:1703–10
8 Ormrod D, Miller T. Description of a model producing varying degrees of stable uremia. *Nephron* 1980;**26**:249–54
9 Ali BH, Al-Salam S, Al Husseni I, Kayed RR, Al-Masroori N, Al-Harthi T, Al Zaabi M, Nemmar A. Effects of gum arabic in rats with adenine-induced chronic renal failure. *Exp Biol Med* 2010;**235**:373–82
10 Ali BH, Ziada A, Blunden G. Biological effects of gum arabic: a review of some recent research. *Food Chem Toxicol* 2009;**47**:1–8
11 Benvenga MJ, Leander JD. Antidepressant-like effect of ly228729 as measured in the rodent forced swim paradigm. *Eur J Pharmacol* 1993;**239**:249–52
12 Ali BH, Bashir AK, Tanira MO. The effect of rhazya stricta decne, a traditional medicinal plant, on the forced swimming test in rats. *Pharmacol Biochem Behav* 1998;**59**:547–50
13 Porsolt RD, Anton G, Blavet N, Jalfre M. Behavioural despair in rats: a new model sensitive to antidepressant treatments. *Eur J Pharmacol* 1978;**47**:379–91
14 Abel EL. Behavioral-effects of isatin on open-field activity and immobility in the forced swim test in rats. *Physiol Behav* 1995;**57**:611–3
15 de Laat JM, van Tintelen G, Beynen AC. Transportation of rats affects behaviour of non-transported rats in the absence of physical contact (preliminary communication). *Z Versuchstierkd* 1989;**32**:235–7
16 Ali BH, Bashir AK, Tanira MO. The effect of rhazya stricta decne, a traditional medicinal plant, on spontaneous and drug-induced alterations in activity of rats. *Pharmacol Biochem Behav* 1999;**64**:455–60
17 Norcini M, Vivoli E, Galeotti N, Bianchi E, Bartolini A, Ghelardini C. Supraspinal role of protein kinase C in oxaliplatin-induced neuropathy in rat. *Pain* 2009;**146**:141–7
18 Ali BH, Bashir AK, Tanira MO. Some effects of Cassia italica on the central nervous system in mice. *J Pharm Pharmacol* 1979;**49**:500–4
19 Ali BH, Alqarawi AA, Ahmed IH. Does treatment with gum arabic affect experimental chronic renal failure in rats? *Fundam Clin Pharmacol* 2004;**18**:327–9
20 Baig SZ, Coats WC, Aggarwl KB, Alpert MA. Assessing cardiovascular disease in the dialysis patient. *Adv Perit Dial* 2009;**25**:147–54
21 Matsumoto N, Riley S, Fraser D, Al Assaf S, Ishimura E, Wolever T, Phillips GO, Phillips AO. Butyrate modulates TGF-beta 1 generation and function: potential renal benefit for acacia(sen) SUPERGUM (TM) (gum arabic)? *Kidney Int* 2006;**69**:257–65
22 Gamoh S, Hashimoto M, Hossain S, Masumura S. Chronic administration of docosahexaenoic acid improves the performance of radial arm maze task in aged rats. *Clin Exp Pharmacol Physiol* 2001;**28**:266–70
23 Romaniuk A, Strzelczuk M, Wieczorek M. Further evidence against using sorbitans in the brain mechanisms investigation. *Acta Neurobiol Exp (Wars)* 1990;**50**:619–27
24 Al Mosawi AJ. Six-year dialysis freedom in end-stage renal disease. *Clin Exp Nephrol* 2009;**13**:494–500
25 Klein K, Daschner M, Vogel M, Oh J, Feuerstein TF, Schaefer F. Impaired autofeedback regulation of hypothalamic norepinephrine release in experimental uremia. *J Am Soc Nephrol* 2005;**16**:2081–7
26 Schaefer F, Vogel M, Kerkhoff G, Woitzik J, Daschner M, Mehls O. Experimental uremia affects hypothalamic amino acid neurotransmitter milieu. *J Am Soc Nephrol* 2001;**12**:1218–27
27 Smogorzewski MJ. Central nervous dysfunction in uremia. *Am J Kidney Diseases* 2001;**38**:S122–8
28 Smogorzewski MJ, Massry SG. Altered acetylcholine in uremia: role metabolism of brain of secondary hyperparathyroidism. *J Renal Nutr* 2008;**18**:122–6
29 Fabrazzo M, De Santo RM. Depression in chronic kidney disease. *Sem Nephrol* 2006;**26**:56–60
30 Cheung WW, Paik KH, Mak RH. Inflammation and cachexia in chronic kidney disease. *Pediatr Nephrol* 2010;**25**:711–24
31 Garcia E, Santos F, Rodriguez J, Martinez V, Rey C, Veldhuis J, Krieg RJ. Impaired secretion of growth hormone in experimental uremia: relevance of caloric deficiency. *Kidney Int* 1997;**52**:648–53
32 Szentkiralyi A, Molnar MZ, Czira ME, Deak G, Lindner AV, Szeifert L, Torzsa P, Vamos EP, Zoller R, Mucsi I, Nova KM. Association between restless legs syndrome and depression in patients with chronic kidney disease. *J Psychosom Res* 2009;**67**:173–80
33 Cavallini L, Impedovo A, Abaterusso C, Loschiavo C, Lupo AG. [Restless legs syndrome in kidney patients]. *Ital Nefrol* 2010;**27**:37–46
34 Xuan NT, Shumilina E, Nasir O, Bobbala D, Gotz F, Lang F. Stimulation of mouse dendritic cells by gum arabic. *Cell Physiol Biochem* 2010;**25**:641–8

(Received May 19, 2010, Accepted October 2, 2010)