Intestinal motility in acute uremia and effects of erythropoietin

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ABSTRACT

The objectives of this study were to investigate intestinal motility changes due to acute uremia, and the effect of pretreatment with erythropoietin.

Methods: This randomized control study was conducted in the Department of Physiology, Faculty of Medicine, Ain Shams University, Cairo, Egypt from September 2010 to July 2011. Forty adult female Wistar albino rats were allocated into 3 groups: control group, gentamicin-treated group, receiving intraperitoneal gentamicin sulphate (100 mg/kg for 5 days), and erythropoietin-gentamicin-treated group, receiving subcutaneous erythropoietin (1000 IU/kg for 3 days) prior to gentamicin injection. Isolated segments of duodenum and descending colon were subjected to in vitro motility study. Plasma creatinine and urea were assayed.

Results: Induction of acute renal failure by gentamicin treatment resulted in a significant decrease in frequency of contraction of the duodenum and descending colon, an increase in the average duration of contraction of the duodenum, and a significant decrease in the average force of contraction in the descending colon. Moreover, the average force of contraction in response to acetylcholine was significantly decreased in the duodenum. The erythropoietin-gentamicin-treated group revealed a significant decrease in plasma creatinine and urea, and a significant increase in the duodenal average force of contraction and motility index, and colonic frequency. The duodenal absolute and average forces of contraction after acetylcholine increased significantly.

Conclusion: Acute uremia impairs small and large intestinal motility, probably due to uremic toxins and autonomic dysfunction. Erythropoietin pretreatment protected against intestinal dysmotility through the improvement of renal function and its neurotropic action.


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Gastrointestinal complications are known to commonly occur in patients with renal disease, however, results from studies addressing the effects of renal dysfunction on bowel motility are conflicting. Intestinal motility disorders in the form of both diarrhea and constipation have been reported in patients with end-stage renal disease. Disturbed small intestinal motility, as shown by fast small intestinal propagation velocity, was found to explain diarrhea in some patients with chronic renal failure. Conversely, prolongation of colonic transit was found in long-term hemodialysis patients. Although there is large number of available studies on gastrointestinal dysfunction in chronic renal failure, a limited number of studies are devoted to the disturbed intestinal function in acute uremia, and the underlying mechanisms are poorly understood. Erythropoietin is used in patients with chronic renal failure and anemia. It reduces the degree of diarrhea and colonic injury in mice with experimental colitis. The aim of the present study was to study the patterns of altered intestinal motility in acute renal failure induced by gentamicin, and also to investigate the possible protective effect of erythropoietin.

Methods. This study was conducted in the Department of Physiology, Faculty of Medicine, Ain Shams University, Cairo, Egypt from September 2010 to July 2011.

Animals. This work was performed on 40 adult female Wistar Albino rats, weighing 160–220 gm. Rats were from the Research Institute of Ophthalmology (Giza, Egypt) and maintained in the animal house of the Physiology Department under standard conditions of boarding and given regular diet consisting of bread, vegetables, and milk. Tap water was provided ad libitum. The experimental procedures were approved by the Research Ethics Committee at the Faculty of Medicine, Ain Shams University, Cairo, Egypt.

Experimental protocol. Wistar albino rats used in this study were allocated into 3 groups: Group I - control group (n=14). Group II - gentamicin-treated group (n=9): rats in this group were subjected to induction of acute renal failure by intraperitoneal (i.p.) injection of gentamicin sulphate (Memphis Company for Pharmacy and Chemical Ind., Cairo, Egypt) in a dose of 100 mg/kg daily for 5 days. Group III - erythropoietin-gentamicin-treated group (n=17): rats in this group received daily subcutaneous recombination human erythropoietin (Sigma Chemical Co., St. Louis, MO, USA) in a dose of 1000 IU/kg for 3 days. Then, rats were subjected to i.p. injection of gentamicin in a dose of 100 mg/kg for the following 5 days.

Experimental procedure. On the day of work, overnight fasted rats, except for free access to water, were weighed and anesthetized by an i.p. injection of thiopental sodium (EPICO, 10th of Ramadan City, Egypt) in a dose of 40 mg/kg. A blood sample was collected from the abdominal aorta in 2 tubes; one tube containing EDTA for assessment of complete blood count. The other tube was the heparinized tube for plasma creatinine and urea levels. After blood collection, the different parts of the gastrointestinal tract were identified and segments of duodenum and descending colon were dissected and rapidly immersed in Tyrode's solution.

Intestinal motility studies. Preparation of intestinal segments and recording of in vitro intestinal motility was performed according to the technique described by Mohamed et al. Segments of either duodenum or descending colon approximately one cm long was suspended separately in an organ tissue bath containing 33 ml warmed (37°C) Tyrode's solution continuously bubbled with 95% O₂ and 5% CO₂. The examined intestinal segment was fixed from one end down in the bath, with the other end connected to isometric force displacement transducer (Biegestab K30, Hugo Sachs Elektronik, March-Hugstetten, Germany) for recording of isometric contractions. Intestinal motility was recorded on a 2-channel oscillograph (Washington MD2, Bioscience, Seattle, WA, USA) in which the downstroke represents contraction and the upstroke represents relaxation. The sensitivity of recording was 0.1. The speed of recording was 2.5 mm/sec for the duodenal recording, and was one mm/sec for the colonic recording. Baseline intestinal motility was recorded. Then, a record was obtained in the presence of acetylcholine (ACh) (Fluka, Buchs SG, Switzerland) (0.606 μg/ml bath). For evaluation of basal intestinal motility, the frequency of contraction, average duration of contraction, average force of contraction, and motility index was deduced from the record, and studied. For evaluation of intestinal motility after addition of ACh, the absolute force of contraction in response to ACh and the average force of contraction in response to ACh was studied.

Biochemical studies. Complete blood count (CBC). The measured parameters included the red blood cell (RBC) count, hemoglobin (Hb) content, packed cell volume, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, as well as the total leukocytic count, and platelet count. Moreover, the plasma creatinine level was estimated by Jaffé reaction and the plasma urea level was determined by Berthelot enzymatic colorimetric method.
using kits supplied by Diamond Diagnostics (Heliopolis, Egypt) for both. Measurements were performed according to the manufacturer’s instructions.

Statistical analysis. Data were expressed as mean ± SEM. Student’s t test for paired and unpaired data was used to assess the statistical significant intragroup and intergroupal differences respectively. A confidence level of 95% was considered statistically significant. Correlation coefficients were calculated by linear regression analysis using the Least Square Method. All statistical data, statistical significance, and correlation studies were performed using Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) version 16. A probability of p<0.05 was considered statistically significant.

Results. Responses of plasma creatinine and plasma urea. Plasma levels of creatinine (95% confidence interval [CI]: -4.37 to -1.81; p=0.000) and urea (95% CI: 154 to -86.4; p=0.000) were significantly increased in gentamicin-treated rats compared with control rats, which ensured the establishment of acute renal failure in the gentamicin-treated group. Erythropoietin pretreatment of the gentamicin-treated group resulted in a significant reduction in plasma creatinine (95% CI: 1.47 to 3.86; p=0.000) and urea (95% CI: 44.1 to 144.3; p=0.001) levels, although they remained significantly higher compared with the control group (95% CI: -0.71 to -0.13; p=0.006 and 95% CI: -51 to -9.8; p=0.042) (Table 1).

Changes in CBC parameters. Following gentamicin administration, a significant decrease in Hb content (95% CI: -0.10 to 1.76; p=0.03) was observed. The RBC count was decreased compared with the control, though insignificant (95% CI: -0.05 to 1.28; p=0.07). The other RBCs parameters together with total leukocytic count and platelet count were not significantly changed compared with the normal control group (Table 2).

Responses of duodenal motility parameters. In Table 3 and Figure 1, the gentamicin-treated group showed significant decrease in duodenal frequency of contraction (95% CI: 1.83 to 7.67; p=0.003), and significant increase in average duration of contraction (95% CI: -0.32 to -0.05; p=0.008) but insignificant decrease in the average force of contraction (95% CI: -0.02 to 0.19; p=0.101), and the motility index (95% CI: -1.01 to 11.5; p=0.096) as compared with the control group. Erythropoietin pretreatment significantly increased the duodenum average force of contraction (95% CI: -0.12 to -0.03; p=0.008) and motility index (95% CI: -0.74 to -0.25; p=0.009). The frequency of contraction increased (95% CI: -5.03 to 0.53; p=0.107) and the average duration of contraction decreased (95% CI: 0.04 to 0.24; p=0.159), but did not reach statistical significance, however, the frequency of contraction was significantly decreased (95% CI: -0.06 to -4.95; p=0.045) compared to its respective control value.

Responses of descending colon motility parameters. The gentamicin-treated group showed reduction in all descending colon motility parameters compared with the control group, being significant regarding frequency of contraction (95% CI: 2.55 to 5.95; p=0.000), average duration of contraction (95% CI: 0.45 to 4.39; p=0.000), average force of contraction (95% CI: 1.83 to 7.67; p=0.003), and motility index (95% CI: 0.04 to 0.24; p=0.159), but did not reach statistical significance, however, the frequency of contraction was significantly decreased (95% CI: -0.06 to -4.95; p=0.045) compared to its respective control value.

Table 1 • Plasma creatinine and plasma urea levels in the studied groups.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Creatinine (mg/dl)</th>
<th>Urea (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n)</td>
<td>0.63 ± 0.05</td>
<td>45.2 ± 4.26</td>
</tr>
<tr>
<td>Gentamicin-treated (n)</td>
<td>3.72 ± 0.77</td>
<td>165.3 ± 23.27</td>
</tr>
<tr>
<td>Erythropoietin-gentamicin-treated (n)</td>
<td>1.06 ± 0.12</td>
<td>71.1 ± 12.14</td>
</tr>
</tbody>
</table>

Data were expressed as means ± SEM. *Significance from control group calculated by student’s t test for paired data at p<0.05. †Significance from gentamicin-treated group calculated by student’s t test for unpaired data at p<0.05.

Table 2 • Complete blood count parameters in the studied groups.

<table>
<thead>
<tr>
<th>Groups</th>
<th>RBCs (10⁶/µl)</th>
<th>Hb (gm/dl)</th>
<th>PCV (%)</th>
<th>MCV (fl)</th>
<th>MCH (pg)</th>
<th>MCHC (gm/dl)</th>
<th>TLC (10³/µl)</th>
<th>Platelet count (10³/µl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n)</td>
<td>7.3 ± 0.18</td>
<td>13.2 ± 0.26</td>
<td>44.1 ± 1.20</td>
<td>60.2 ± 1.02</td>
<td>18.0 ± 0.20</td>
<td>30.0 ± 0.59</td>
<td>5.5 ± 0.40</td>
<td>961.3 ± 63.59</td>
</tr>
<tr>
<td>Gentamicin-treated (n)</td>
<td>6.7 ± 0.28</td>
<td>12.3 ± 0.30</td>
<td>41.6 ± 1.73</td>
<td>62.5 ± 1.47</td>
<td>18.8 ± 0.67</td>
<td>30.1 ± 0.85</td>
<td>6.9 ± 0.71</td>
<td>1076.9 ± 69.83</td>
</tr>
<tr>
<td>Erythropoietin-gentamicin-treated (n)</td>
<td>7.1 ± 0.16</td>
<td>13.2 ± 0.32</td>
<td>42.9 ± 1.24</td>
<td>60.1 ± 0.80</td>
<td>18.4 ± 0.23</td>
<td>30.3 ± 0.34</td>
<td>8.3 ± 0.90</td>
<td>1027.7 ± 64.77</td>
</tr>
</tbody>
</table>

Data were expressed as means ± SEM. *Significance from control group calculated by student’s t test for unpaired data at p<0.05. †Significance from gentamicin-treated group calculated by student’s t test for unpaired data at p<0.05.

RBCs - red blood corpuscles, Hb - hemoglobin content, PCV - packed cell volume, MCV - mean corpuscular volume, MCH - mean corpuscular hemoglobin, MCHC - mean corpuscular hemoglobin concentration, TLCs - total leukocytic count
Table 3 - Duodenal motility parameters in the studied groups.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Frequency of contraction (no./min)</th>
<th>Average duration of contraction (sec)</th>
<th>Average force of contraction (gm)</th>
<th>Motility index (gm.min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n)</td>
<td>38.0 ± 0.87</td>
<td>1.6 ± 0.03</td>
<td>0.16 ± 0.04</td>
<td>9.5 ± 2.19</td>
</tr>
<tr>
<td>Gentamicin-treated (n)</td>
<td>33.3 ± 1.05</td>
<td>1.8 ± 0.06</td>
<td>0.07 ± 0.01</td>
<td>4.3 ± 0.82</td>
</tr>
<tr>
<td>Erythropoietin-gentamicin-treated (n)</td>
<td>35.5 ± 0.81</td>
<td>1.7 ± 0.03</td>
<td>0.15 ± 0.02</td>
<td>8.8 ± 1.09</td>
</tr>
</tbody>
</table>

Data were expressed as means ± SEM. *Significance from control group calculated by Student’s t test for unpaired data at p<0.05. **Significance from gentamicin-treated group calculated by student’s t test for unpaired data at p<0.05.

Table 4 - Descending colon motility parameters in the studied groups.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Frequency of contraction (no./min)</th>
<th>Average duration of contraction (sec)</th>
<th>Average force of contraction (gm)</th>
<th>Motility index (gm.min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n)</td>
<td>8.0 ± 0.36</td>
<td>7.6 ± 0.30</td>
<td>0.09 ± 0.01</td>
<td>5.6 ± 0.45</td>
</tr>
<tr>
<td>Gentamicin-treated (n)</td>
<td>3.8 ± 0.85</td>
<td>5.2 ± 1.15</td>
<td>0.04 ± 0.01</td>
<td>4.1 ± 0.66</td>
</tr>
<tr>
<td>Erythropoietin-gentamicin-treated (n)</td>
<td>6.2 ± 0.58</td>
<td>9.5 ± 0.86</td>
<td>0.11 ± 0.01</td>
<td>7.3 ± 1.06</td>
</tr>
</tbody>
</table>

Data were expressed as means ± SEM. *Significance from control group calculated by student’s t test for unpaired data at p<0.05. **Significance from gentamicin-treated group calculated by student’s t test for unpaired data at p<0.05.

Table 5 - Responses of duodenum and descending colon force of contraction to acetylcholine (ACh) administration in the studied groups.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Duodenum</th>
<th>Descending colon</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before ACh</td>
<td>After ACh</td>
</tr>
<tr>
<td></td>
<td>Average</td>
<td>Absolute</td>
</tr>
<tr>
<td></td>
<td>force</td>
<td>force</td>
</tr>
<tr>
<td>Control (n)</td>
<td>0.16 ± 0.04</td>
<td>0.65 ± 0.11</td>
</tr>
<tr>
<td>Gentamicin-treated (n)</td>
<td>0.07 ± 0.01</td>
<td>0.37 ± 0.10</td>
</tr>
<tr>
<td>Erythropoietin-gentamicin-treated (n)</td>
<td>0.15 ± 0.02e</td>
<td>0.74 ± 0.08e</td>
</tr>
</tbody>
</table>

Data were expressed as means ± SEM. *Significance from control group calculated by student’s t test for unpaired data at p<0.05. **Significance from gentamicin-treated group calculated by student’s t test for unpaired data at p<0.05. ***Significance from respective average force of contraction before ACh, calculated by student’s t test for paired data at p<0.05.

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Figure 1 - Tracing of duodenal motility before (basal) and after addition of acetylcholine (ACh) in the studied groups. Vertical arrow - represents intestinal motility after the addition of ACh. Speed of recording 2.5 mm/sec.

Figure 2 - Tracing of descending colon motility before (basal), and after addition of acetylcholine (ACh) in the studied groups. Vertical arrows - represents intestinal motility after the addition of ACh. Speed of recording 1 mm/sec.

Figure 3 - Graphs showing correlations between a) plasma creatinine (mg/dl) and descending colon frequency of contraction (no./min), and b) average duration of contraction (sec) in the control (◊), gentamicin-treated (•) and erythropoietin-gentamicin-treated (º) groups.

showed significant reduction in duodenal force of contraction in response to ACh administration, being significant for average force (95% CI: 0.03 to 0.23; *p*=0.012) and insignificant for absolute force (95% CI: -0.62 to 0.6; *p*=0.104), as compared with the control group. Erythropoietin pretreatment resulted in a significant increase in both duodenal absolute (95% CI: -0.65 to -0.09; *p*=0.012) and average (95% CI: -0.25 to -0.03; *p*=0.014) forces of contraction in response to ACh. However, the descending colon showed insignificant changes in both absolute and average forces of contraction in response to ACh in the gentamicin-treated group (95% CI: -0.50 to 0.51; *p*=0.995) compared with the control group (95% CI: -0.05 to 0.16; *p*=0.07), as well as in the erythropoietin-treated group (95% CI: -0.68 to 0.36; *p*=0.53) compared with the gentamicin-treated group (95% CI: -0.17 to 0.01; *p*=0.09) as shown in Table 5.
Correlation studies. Significant negative relations were observed between plasma creatinine and descending colon frequency of contraction ($r = -0.610$, $p = 0.000$, $n=37$), average duration of contraction ($r = -0.441$, $p = 0.006$, $n=37$), average force of contraction before ACh ($r = -0.418$, $p = 0.01$, $n=37$) and average force of contraction in response to ACh ($r = -0.369$, $p = 0.035$, $n=33$) in the different studied groups. Also, a significant negative correlation was observed between plasma creatinine and duodenal absolute force of contraction in response to ACh administration ($r = -0.344$, $p = 0.04$, $n=36$) in the different studied groups (Figures 3-5).

Discussion. The aim of the study was to determine the effects of acute renal failure on intestinal motility using an experimental model of acute uremia induced by gentamicin, which is known for its toxic effects on the kidney, and to investigate the possible protective effects of erythropoietin on the intestinal dysfunction in acute uremia since this hormone is known to treat the anemia of renal failure, and might improve the metabolic disturbances of acute uremia. This was carried out in an attempt to satisfy the need for an effective treatment of acute uremia.

The results of the present study showed that gentamicin treatment produced acute uremia characterized by elevation of plasma creatinine and urea levels and a significant decrease in hemoglobin. These changes were associated with decreased motility in both the duodenum and the colon as evidenced by the significant decrease in frequency of contraction of both the duodenum and descending colon, increase in average duration of contraction of the duodenum and significant decrease in average force of contraction in the descending colon. The present motility results are in accordance with the study of Lefebvre et al showing that renal failure in dogs caused a decrease in propagation velocity in the myoelectrical migrating complex in the duodenojejunal segment and increase in duration of the meal response in duodenum. Also, a human study by Wu et al showed that both segmental and total colonic transit times were significantly longer in patients on hemodialysis or peritoneal dialysis. However, other investigators demonstrated contradictory data to the finding in this work. Fu et al observed a significantly reduced small intestinal transit time in rats with acute renal failure together with a rise in fecal water content. Also, Lefebvre et al showed decreased colonic transit time associated with watery quantity in feces indicating increased colonic motility. The discrepancy in these results from the present findings could be explained by
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the use of different animal species, dogs, in one study as well as the mode of induction or duration of acute renal failure in the other.

The current duodenal and colonic motility dysfunction in acute uremia could be explained by altered humoral environment by uremic toxins. This view is favored by the significant negative correlations between plasma creatinine levels and motility parameters suggesting a key role of metabolic toxic products of acute uremia on the intestinal function. It is noteworthy from the data of the present study that the anemia observed in gentamicin-induced acute uremia was restricted to reduced Hb content with a mild decrease in RBCs count, and other parameters of red cell function were unaffected. This may suggest that a hemolytic factor or factors might be involved in the anemia of acute renal failure, namely, an extra-corpuscular hemolytic component may be involved in the mechanism of anemia of acute uremia. The normochromic normocytic anemia of erythropoietin deficiency is recognized in advanced renal failure, but not in early renal disease.13

The administration of erythropoietin 3 days before induction of renal failure in rats of this work resulted in significant decrease in plasma creatinine and urea. These results extend previous observations of Vesey et al,14 who found attenuation of creatinine rise and early initiation of tubular regeneration by using erythropoietin 30 minutes before initiation of ischemic acute renal injury. Also, Sharples and Yaqoob15 studied the effect of administration of erythropoietin both before and after the acute renal injury, and found that erythropoietin significantly reduced renal dysfunction better with the pretreatment regimen. However, at variance with the present data, Nemoto et al16 found that erythropoietin administration did not significantly affect serum creatinine in shorter courses of acute renal failure induction, such as ischemic acute renal failure. The decrease in plasma creatinine and urea following erythropoietin in the present study suggests that erythropoietin could play a role in the improvement of renal condition and reversal of acute renal failure. This is in agreement with the data of Bagnis et al16 showing that erythropoietin significantly enhanced the rate of recovery from acute renal failure induced by cisplatin.

The observed beneficial effects of erythropoietin on renal function could be ascribed to the presence of erythropoietin receptors in the glomerulus, mesangial, and tubular epithelial cells, which was found to attenuate the dysfunction and histological changes associated with ischemia-reperfusion injury with a reduction in apoptotic cell death.15 Erythropoietin receptors expressed by capillary endothelial cells facilitate the ability of erythropoietin to antagonize apoptosis of endothelial cells subjected to hypoxic stress.17 In addition, erythropoietin has been shown to be a potent stimulator of endothelial progenitor cell mobilization from bone marrow, increasing their circulation, and thus, contribute to the generation of damaged endothelium and to stimulate mitogenesis and angiogenesis,18 promotion of neovascularization, and tissue regeneration.19

Accompanying the aforementioned effects of erythropoietin pretreatment, intestinal dysfunction was also corrected as shown by a significant increase in duodenal average force of contraction and motility index together with significant increase in colonic frequency of contraction and average force of contraction. Similar beneficial effects of erythropoietin on the intestine were reported in necrotizing enterocolitis,20 inflammatory bowel disease,21 and ischemia/intestinal reperfusion injury.22 The protective effects of erythropoietin on intestinal dysfunction in acute uremia could be the consequence of improved renal function, abolishment of uremic toxins, and restoration of the normal humoral environment that affects the function of intestinal smooth muscles. Also, this protective effect on intestinal motility could be through enhancing cholinergic activity via muscarinic receptor mechanism, or cholinergic neurons. This is evidenced by markedly increased duodenal force of contraction in response to ACh in the erythropoietin-pretreated rats. Erythropoietin was found to exert a neuroprotective effect by reducing the nitric oxide-mediated formation of free radicals or antagonizing their toxicity and decreasing apoptotic death of neuronal cells.23,24 Moreover, erythropoietin action as trophic and angiogenic growth factor, as well as its prokinetic effects in the intestine provide an additional explanation for improved intestinal hypofunction. Erythropoietin was found to act as a trophic factor in the developing rat small intestine,25 and to act as an angiogenic growth factor stimulating intestinal mesentery microvascular endothelial cell proliferation and increasing intestinal blood flow,26 and to have prokinetic effects on hypoperistalsis, thus restoring bowel damage.27

Additional mechanisms for the protective effect of erythropoietin against intestinal injury could be through its antioxidant activities as it improves enzymatic antioxidant parameters like superoxide dismutase, catalase, and glutathione peroxidase,28 as well as through its inhibitory effect on nitric oxide overproduction.29 The observation in the current study that pretreatment with erythropoietin protected against anemia of acute uremia is in agreement with similar observation
of Nemoto et al, who showed that erythropoietin treatment could rapidly improve HB levels and could be a useful therapeutic approach during acute renal failure. The high mortality of rats exposed to acute renal failure induced by gentamicin resulted in low number of rats in this group, thereby limiting our study.

In conclusion, acute renal failure induces small and large intestine hypomotility, most probably due to uremic toxins and autonomic dysfunction. Pretreatment with erythropoietin protected against intestinal dysmotility through improvement of renal function and its neurotropic action. These beneficial effects of erythropoietin, if extrapolated to human studies, may serve as a novel therapeutic target for intestinal motility disorders in patients suffering from acute renal failure. Further studies are required to clarify the neurotropic action of erythropoietin on intestinal ACh receptors in normal and uremic rats.

References