Gastric Emptying and Intestinal Transit of Liquid and Solid Markers in Rats with Chronic Uremia

Shu-Chi Wang[1], Kuo-Yun Lu[1], Shu-Ming Chen[2] and Tze-Kong Young[1,2]

[1]*Institute of Physiology*
School of Life Science
National Yang-Ming University
and
[2]*Department of Medical Research and Education*
Taipei Veterans General Hospital
Taipei 112, Taiwan, ROC

Abstract

Gastrointestinal motor abnormalities may account for dyspeptic symptoms of chronic uremia patients. However, the data on gastric emptying are conflicting in human studies. We, therefore, assessed gastric emptying and gastrointestinal transit in a rat uremia model. Chronic uremia was induced by five-sixths nephrectomy in the rats. After 20-hour fasting, the rats were loaded with 70 glass beads as solid markers through a gastric catheter. Two hours later, the stomach was exposed and the small intestine was equally divided into 10 segments. The glass beads in the stomach and in each intestinal segment were counted. The gastric emptying was expressed as the ratio of the number of glass beads in the small intestine to that counted from the entire gastrointestinal tract. The intestinal transit was assessed by analyzing the geometric center of the distribution of glass beads in the intestinal segments. Two conventional nonabsorbable markers, radioactive chromate and charcoal, were also used to evaluate gastric emptying and intestinal transit in the fasted state. Additionally, similar experiments of glass beads were performed in the fed state. It was found that, in the fasted state, the gastric emptying and the intestinal transit of liquid or solid markers were little affected by uremia. In the fed state, however, chronic uremia significantly decreased the intestinal transit but hardly affected the gastric emptying. We conclude that the postprandial intestinal transit, but not the gastric emptying, of solid markers may be decreased in the fed state by chronic uremia in a severity-dependent manner of a rat model, which resembles the findings in uremic patients.

Key Words: gastric emptying, intestinal transit, liquid marker, solid marker, chronic uremia, rat model

Introduction

Abdominal distension, anorexia, nausea, vomiting and earlier satiety are symptoms which almost invariably accompany chronic uremia (23, 27), but little is known about the mechanisms responsible. Although the etiology of these symptoms is unclear, delayed gastric emptying has been proposed as a possible cause of these symptoms (27). However, gastric emptying studies have shown conflicting results in human studies. Some patients on maintenance dialysis treatment, whether or not symptomatic, have normal liquid and solid emptying times, as determined by radioisotope studies (31, 42, 49) or by radiopaque markers (2, 14), while some patients have delayed gastric emptying demonstrated by radioisotope studies (1, 24) or ultrasonography (12). In addition, uremic patients not on dialysis have normal (14, 17) or delayed gastric emptying (1, 31, 36). The physical presence of peritoneal dialysate retards solid emptying (2). Prolonged oral-cecal transit times have been shown in chronic uremic

Corresponding author: Dr. Tze-Kong Young, Ph.D., Institute of Physiology, National Yang-Ming University, Taipei 112, Taiwan, ROC, Tel: 886-2-2826-7083, Fax: 886-2-2826-4049, E-mail: tkyoung@ym.edu.tw
Received March 1, 2001; Revised May 1, 2001; Accepted May 2, 2001.

patients whether or not treated by maintenance hemodialysis (13). The uncertainty about the gastrointestinal motility changes in the human studies is likely to be attributed to a variety of underlying systemic or renal diseases, which can finally lead to uremia. We, therefore, assessed the gastric emptying and the gastrointestinal transit in a rat model of chronic uremia that was solely induced by five-sixths nephrectomy.

In contrast to human studies, the gastrointestinal motility studies in rats are usually performed in the fasted state (8, 21) rather than in the fed state for eliminating interference caused by the presence of food. Radiochromium and charcoal, in a calorie-free liquid test meal, are the two most frequently employed markers for these transit studies (4). Studies with these two nonabsorbable markers have revealed the stimulation effect of substance P (20, 41) and the inhibition effect of substance P antagonist on the gastrointestinal transit (21). Inhibition of gastric emptying caused by acute hyperglycemia in normal subjects (29, 35) and by diabetes mellitus (16, 22) has also been similarly observed in the normal rats (6) and the diabetic rats (5) by means of these markers. It demonstrates that both radiochromium and charcoal are adequate and useful markers for measuring the gastric emptying in rats. However, employment of solid markers for measurement of the gastrointestinal transit in rats is rare (28) and little information on the intestinal transit is available for uremic rats (37). We, therefore, examined the effect of chronic uremia on the gastric emptying and the intestinal transit using three different markers in a rat uremia model.

Materials and Methods

Animals

The experiments were conducted on 85 Sprague-Dawley male rats three months old and weighing between 250 to 300 g. The animals were maintained in individual metabolic cages with the room temperature controlled at 22°C on a 12-hour light-dark cycle. The rats received regular rat chow (Laboratory Rodent Diet 5001, Purina Feeds Inc., St. Louis, MO 63144, USA) and tap water ad libitum. The rats were matched for weight and divided into two groups. One group, the control rats, were not operated. The other group, the uremic rats, were induced by a two-stage, five-sixths nephrectomy. The upper and lower poles of the left kidney were first removed. One week later, the entire right kidney was then removed (43, 50). Three more weeks later, the experimental procedures were carried out on all the rats, when the plasma creatinine and the urea nitrogen levels of the uremic rats were constantly elevated.

Measurement of Gastric Emptying and Gastrointestinal Transit

Sixteen control rats and 14 uremic rats were used to study the gastric emptying and the gastrointestinal transit of both liquid marker and fine solid powder simultaneously. After fasting for 20 hours and at 9 AM on the experimental day, the rats were orally given physiological saline (3 ml/kg) containing $Na_2{}^{51}CrO_4$ (0.5 μCi/ml) and 10% charcoal powder via a catheter (PE-205, ID 1.67 mm, OD 2.42 mm, Clay Adams). The test meal solution was continuously stirred before instillation. Additional air (0.5 ml) was added to flush into the rats the residual charcoal suspension remaining in the catheter. They were decapitated exactly 15 min later. The stomach and the small intestine were exposed immediately by a laparotomy. After ligation of the esophagogastric, gastroduodenal and ileocecal junctions, the whole stomach and the small intestine were carefully mobilized and laid on a wooden board to observe the front, indicating the leading edge of the charcoal moving in the intestine. The small intestine was then equally divided into 10 segments. The radioactivity in the stomach and each segment of the small intestine were measured with an automatic gamma counter (1470 Wallac, Pharmacia, Turku, Finland). The gastric emptying was expressed as the ratio of the amount of labeled chromium in the small intestine to the total radioactivity detected from the stomach and the small intestine (7, 20). The intestinal transit was assessed by analyzing the geometric center of the distribution of radioactivity through these 10 equal-length segments (33). The gastrointestinal transit was also analyzed by expressing the charcoal transit ratio of the length of the small intestine where the charcoal had traversed to the total length of the small intestine.

Another 17 control rats and 16 uremic rats were used to study the gastric emptying and the intestinal transit of solid markers in the fasted state. Glass beads (Sigma), 1 mm in diameter, were used as nondigestible, nonabsorbable solid markers. After 20-hour fasting and at 9 AM on the day of experiment, the rats were orally loaded with 70 glass beads in physiological saline solution (3 ml/kg) through a gastric catheter. Two hours later, the rats were killed. The 2-hour test period was selected because the leading bead after this period had traveled 80% of the small intestine and no beads could be found in the cecum. The stomach was then exposed and the small intestine was equally divided into 10 segments. The glass beads in the stomach and in each intestinal segment were counted. The gastric emptying was expressed as the ratio of the number of glass beads in the small intestine to that counted from the entire gastrointestinal

Table 1. Laboratory Data in Control Rats and Chronic Uremic Rats

	Control rats	Uremic rats
Number of rats	44	41
Plasma urea nitrogen (mg/dl)	14.6 ± 0.4	47.9 ± 2.2*
Plasma creatinine (mg/dl)	0.49 ± 0.01	1.06 ± 0.04*
Plasma osmolality (mOsm/kg H_2O)	300 ± 1	315 ± 2*
Creatinine clearance (ml/min)	1.98 ± 0.07	0.83 ± 0.03*

Values represent means ± standard error of the mean. * $P < 0.001$ compared with control rats.

tract. The intestinal transit was assessed by analyzing the geometric center of the distribution of glass beads in these 10 intestinal segments.

Under natural circumstances, the stomach and the intestine of a free-feeding rat always have some food present (45, 46). Thus, other 11 control rats and 11 uremic rats were used to study the gastric emptying and the intestinal transit of solid markers in the fed state. The rats were fasted for 20 hours but gained free access to water before experiment. On the day of experiment, the fasted rats were allowed to eat up 1.2 g powdered rat chow (equivalent to 4.8 Kcal) in 20 min. Then at 9 AM, 70 glass beads were orally loaded to the rats via a gastric catheter. Two hours later, the rats were killed and the gastric emptying and the intestinal transit of the glass beads were analyzed in the same manner as the above.

Analytical Methods

Twenty-four-hour urine sample of each rat was collected from the metabolic cage on the day of experiment. The shed blood samples during decapitation were also collected for determining plasma osmolality, urea nitrogen and creatinine. Osmolality was determined by freezing point depression with an osmometer (Model 3MO Plus, Advanced Instruments). Urea nitrogen and creatinine in plasma as well as in urine samples were analyzed with a Beckman BUN Analyzer 2 and a Beckman Creatinine Analyzer 2 (Beckman) respectively. Clearance of creatinine (C_{Cr}) was measured from timed 24-hour urine collection, according to the standard formula $C_{Cr} = U_{Cr}V/P_{Cr}$, where U_{Cr} and P_{Cr} represent the concentrations of creatinine in urine and in plasma respectively and V stands for the urine flow rate in ml/min (47).

Statistical Analyses

Analysis of variance and Student's *t*-test were used to analyze the data that were expressed as mean ± standard error of the mean. P values less than 0.05 were considered significant (10).

Results

Rat Uremia Model

Table 1 shows that three weeks after five-sixths nephrectomy, plasma urea nitrogen, plasma creatinine and plasma osmolality were significantly elevated in the uremic rats compared with those in the controls rats. All these findings resemble those in human uremia. The diminution of renal mass following nephrectomy was verified by the decrease in creatinine clearance in all uremic rats.

Gastrointestinal Transit of Radioactive Chromate and Charcoal

Table 2 shows that 15 min after markers were loaded, the uremic rats and the control rats had the similar gastric emptying of radioactive chromate, the similar gastrointestinal transit of charcoal, and the similar intestinal transit of radioactive chromate. These results indicate that gastrointestinal transit of liquid and fine powdered solids was not altered by chronic uremia when no food was present in the gastrointestinal tract.

Gastrointestinal Transit of Solid Markers

Table 3 shows that two hours after glass beads were loaded, there was no significant difference in the gastric emptying and the intestinal transit between the uremic rats and the control rats in the absence of food in the gastrointestinal tract. When the rats consumed 1.2 g rat chow, the postprandial intestinal transit of glass beads in the control rats was significantly ($P < 0.02$) increased in the fed state compared with that in the fasted state. After ingesting the same amount of food as the control rats, the uremic rats had a significant ($P < 0.01$) delay in the intestinal transit, while no significant change in the gastric emptying was noted. This intestinal transit of glass beads correlated well with the severity of chronic uremia. Fig. 1 depicts the negative correlation, with

Table 2. Gastrointestinal Transit of Radioactive Chromate and Charcoal in Control Rats and Chronic Uremic rats

	Control rats	Uremic rats
Number of rats	16	14
Gastric emptying of radioactive chromate (%)	50.1 ± 5.2	41.6 ± 4.2
Gastronintestinal transit of charcoal (%)	40.5 ± 1.9	42.8 ± 1.5
Intestinal transit of radioactive chromate, GC	3.24 ± 0.15	3.19 ± 0.10

Values represent means ± standard error of the mean. P values > 0.2 compared with controls. The gastrointestinal transit was determined l5 min after oral loading of radioactive chromate together with charcoal. GC indicates geometric center of marker distribution in the ten intestinal segments observed.

Table 3. Gastrointestinal Transit of Glass Beads in Control Rats and Chronic Uremic Rats Both in Fasted and in Fed states

	State	Gastric emptying %	Intestinal transit GC
Control rats (n = 17)	Fasted	72.5 ± 6.3	5.72 ± 0.45
Uremic rats (n = 16)	Fasted	77.3 ± 6.2	6.35 ± 0.44
Control rats (n = 11)	Fed	77.8 ± 3.2	7.18 ± 0.29*
Uremic rats (n = 11)	Fed	74.7 ± 4.2	6.17 ± 0.16#

Values represent means ± standard error of the mean. * P < 0.02 compared with control rats in the fasted state. # P < 0.01 compared with control rats in the fed state. The gastrointestinal transit was measured 120 min after oral loading of 70 glass beads.

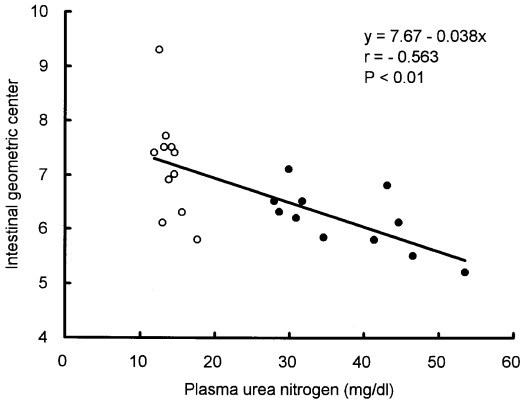


Fig. 1. Correlation between plasma urea nitrogen levels and the intestinal transit of glass beads in both control rats (open circles, n = 11) and uremic rats (solid circles, n = 11) in the fed state. The intestinal transit was evaluated by measuring the geometrical center of glass beads distribution in the ten intestinal segments 120 min after oral loading of 70 glass beads.

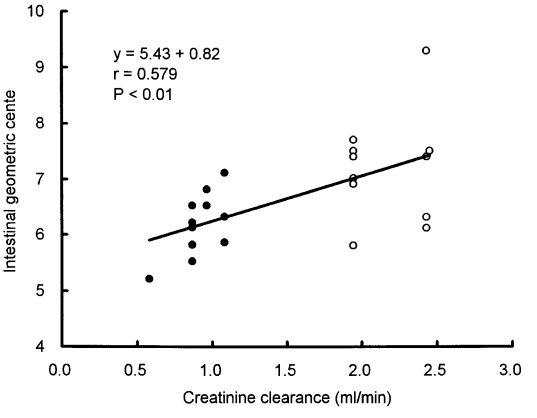


Fig. 2. Correlation between creatinine clearance and the intestinal transit of glass beads in both control rats (open circles, n = 11) and uremic rats (solid circles, n = 11) in the fed state. The intestinal transit was evaluated by measuring the geometrical center of glass beads distribution in the ten intestinal segments 120 min after oral loading of 70 glass beads.

a P value less than 0.01, between plasma urea nitrogen level and the intestinal transit expressed by the geometric center. In addition, Fig. 2 depicts a positive correlation, with a P value less than 0.01, between creatinine clearance and the intestinal transit of glass beads.

Discussion

Radiochromium in the form of $Na_2{}^{51}CrO_4$ and charcoal in the form of fine powder are two conventional markers employed to measure gastrointestinal transit in the rats (21). The

combination of the gastric emptying and the intestinal transit can be simply estimated by treating the gastrointestinal transit as a whole by gauging the leading edge of charcoal. With radiochromium as a liquid marker, however, both the gastric emptying and the intestinal transit can be simultaneously and individually measured because the intraluminal content of radiochromium can be accurately determined in the stomach and in the intestinal segments (4). It has been shown that the intestinal transit can be best estimated by the determining the geometric center (33). All motility studies should be performed at a certain fixed time to avoid the effect of circadian rhythm (44). Following the same procedures and precautions, the present findings with respect to the gastric emptying and the intestinal transit in the control rats are in accordance with those reported by many others (3-8, 20, 21, 38, 41). Table 2 shows that the uremic rats and the control rats have no significant differences in these three gastrointestinal motility parameters. It appears that chronic uremia induced by five-sixths nephrectomy may not influence the interdigestive gastrointestinal motility in a fasted rat model.

It has been reported that liquid and solid meals in humans are emptied from the stomach at different rates (49). The liquid emptying is rapid in an exponential manner, whereas the solid emptying is relatively slow in a linear fashion (1, 34). This difference between the liquid and solid gastric emptying is also seen in rats (38). The solid markers with the size of 1 mm in diameter were used in this study and others (28). Nevertheless, more markers, 70 glass beads in this study against 20 polystyrene beads, were adopted in each experiment for obtaining more accurate estimation. Two hours after the loading of glass beads, the gastric emptying of glass beads of the control rats was found to be $72.5 \pm 6.3\%$, identical to $72.7 \pm 8.6\%$ in the fasted control rats of polystyrene beads as solid markers (28). The results of glass beads and polystyrene beads on the intestinal transit in terms of geometric center are also compatible. Since no significant differences in both gastric emptying and intestinal transit were observed between the control rats and the uremic rats (Table 3), it seems that chronic uremia may not alter the gastrointestinal motility in the fasted state.

It has been reported that electrical spiking activity of the small intestine is quite different between the fed state and the fasted state as recorded in the same rat (39). Ingestion of a meal induces a distinct change in the myoelectrical activity in the small intestine. Regularly occurring myoelectrical complexes are replaced with an irregular spiking activity, which lasts for 2 to 3 hours in the rat (39). The intestinal transit is not necessarily the same in the postprandial period as in the interdigestive period (48). Thus the experimental results obtained in the fasted rats cannot be directly translated to the postprandial situation. After the fasted rats were fed with 1.2 g of rat chow in powder form, the gastrointestinal transit of glass beads was studied over a 2-hour postprandial period. In the control rats, the postprandial gastric emptying did not differ significantly from that in the fasted state. However, the postprandial intestinal transit of glass beads significantly ($P < 0.02$) increased compared with that in the fasted state (Table 3). Kotal *et al*. (25) reported that fasting decreases the intestinal motility evidenced by a significant increase in the intestinal transit time of the fasted Wistar rats. The present results in the control rats agree with their findings.

This study is the first to examine the effect of chronic uremia on the intestinal transit in a rat model. In contrast to the findings in the fasted state, we found that the intestinal transit of glass beads considerably decreased in the uremic rats in the fed state (Table 3). This decrease in the postprandial intestinal transit is consistent with the findings in human investigations such as El-Lakany *et al*. who reported that uremic patients had longer oral cecal transit times (13). In the present study, stagnation of the postprandial intestinal motility in the uremic rats was of such a statistical significance ($P < 0.01$) that it seems unlikely to be purely fortuitous. Since good correlations were found between the intestinal transit and plasma urea nitrogen (Fig. 1) and also between the intestinal transit and creatinine clearance (Fig. 2), the decrease in the intestinal transit of chronic uremia exists in a severity-dependent manner.

We have no explanation as to the underlying mechanism by which the intestinal transit of glass beads decreased in the uremic rats. It has been shown that acute hyperglycemia retards the duodenal-cecal transit in normal subjects (11, 18, 40) and decreases the gastrointestinal transit in rats (5). Glucose intolerance has been frequently observed in patients with chronic uremia (15, 30). Previous studies in our laboratory have revealed that the uremic rats show glucose intolerance. The area under the plasma glucose curves (AUC) in a period of 6 hours after oral glucose also increases compared with that of the control rats (9). Thus, postprandial hyperglycemia may be considered an influence on the intestinal transit in chronic uremia, in addition to the possible influence of hormonal or metabolic changes directly related to uremia or feeding. For instance, the plasma vasoactive intestinal peptide levels have been reported to be increased in uremic patients (19). Apart from postprandial hyperglycemia, however, thyroid hormones may also be involved. Clinical and experimental observations leave little doubt that the

motor activity of the gastrointestinal tract is increased in hyperthyroidism and decreased in hyperthyroidism (32). Low plasma triiodothyronine levels have been observed in a uremic rat model (26). The effect of thyroid hormone levels needs further studies to establish this involvement, if any.

From the present data, it is reasonable to conclude that chronic uremia decreases the intestinal motility evidenced by a decreased intestinal transit of solid markers during the fed state. However, no changes in either the gastric emptying or the intestinal transit of both liquid and solid makers can be demonstrated during the interdigestive period in a uremic rat model.

Acknowledgements

This study was partly supported by a grant NSC88-2314-B010-78 from the National Science Council of the Republic of China. The authors thank professor Ralph Kirby for reading the manuscript.

References

1. Bird, N.J., Streather, C.P., O'Doherty, M.J., Barton, I.K., Gaunt, J. I. and Nunan, T.O. Gastric emptying in patients with chronic renal failure on continuous ambulatory peritoneal dialysis. *Nephrol. Dial. Transpl.* 9: 287-290, 1993.
2. Brown-Cartwright, D., Smith, H.J. and Feldman, M. Gastric emptying of an indigestible solid in patients with end-stage renal disease on continuous ambulatory peritoneal dialysis. *Gastroenterology* 95: 49-51, 1988.
3. Chang, F.Y., Doong, M.L. Chen, T.S., Lee, S.D. and Wang, P.S. Altered intestinal transit is independent of gastroparesis in the early diabetic rats. *Chin. J. Physiol.* 40: 31-35, 1997.
4. Chang, F.Y., Lee, S.D., Yeh, G.H. and Wang, P.S. Comparison of two orogastric feeding markers for measuring gastrointestinal motor functions in rats. *Pharmacology* 49: 151-158, 1994.
5. Chang, F.Y., Lee, S.D., Yeh, G.H. and Wang, P.S. Hyperglycaemia is responsible for the inhibited gastrointestinal transit in the early diabetes rats. *Acta Physiol. Scand*. 155: 457-462, 1995.
6. Chang, F.Y., Lee, S.D., Yeh, G.H. and Wang, P.S. Influence of blood glucose levels on rat liquid gastric emptying. *Dig. Dis. Sci.* 41: 528-532, 1996.
7. Chen, T.S., Doong, M.L., Chang, F.Y., Lee, S.D. and Wang, P.S. Effects of sex steroid hormones on gastric emptying and gastrointestinal transit in rats. *Am. J. Physiol*. 268: G171-G176, 1995.
8. Chen, T.S., Doong, M.L., Wang, S.W., Tsai, S.C., Lu, C.C., Shih, H.C., Chen, Y.H., Chang, F.Y., Lee, S.D. and Wang, P.S. Gastric emptying and gastrointestinal transit during lactation in rats. *Am. J. Physiol.* 272: G626-G631, 1997.
9. Chen, S.M., Young, T.K. and Ho, L.T. Effects of parathyroid hormone infusion on glucose tolerance and glucose-stimulated insulin secretion in normal and uremic rats. *Diabetes Res. Clin. Pr*. 41: 85-94, 1998.
10. Christensen, R. Analysis of Variance, Design and Regression. London : Chapman & Hall, 1996.
11. De Boer, S.Y., Masclee, A.A.M., Lam, W.F., Schipper, J., Jansen I.B.M.J. and Lamers. C.B.H.W. Hyperglycemia modulates gallbladder motility and small intestine transit time in man. *Dig. Dis. Sci.* 38: 2228-2235, 1993.
12. Dumitrascu, D.L., Barnert, J., Kirschner, T. and Wienbeck, M. Antral emptying of semisolid meal measured by real-time ultrasonography in chronic renal failure. *Dig. Dis. Sci*. 40: 636-644, 1995.
13. El-Lakany, S., Eagon, P.K., Gavaler, J.S., Schade, R.R., Whiteside, T. and Van Thiel, D.H. Gastrointestinal function, morphology, and immune status in uremia. *Nutrition* 6: 461-468, 1990.
14. Folwaczny, C., Hundegger, K., Volger, C., Sorodoc, J., Kuhn, M., Tatsch K, Landgraf, R. and Karbach, U. Measurement of transit disorders in different gastrointestinal segments of patients with diabetes mellitus in relation to duration and severity of the disease by use of the metal-detector test. *Z. Gastroenterol.* 33: 517-526, 1995.
15. Foss, M.C., Gouveia, L.M.F.B., Neto, M.M., Paccola, G.M.G.F. and Piccinato, C.E. Effect of hemodialysis on peripheral glucose metabolism of patients with chronic renal failure. *Nephron* 73: 48-53, 1996.
16. Fraser, R.J., Horowitz, M., Maddox, A.F., Harding, P.E., Chatterton, B.E. and Dent, J. Hyperglycaemia slows gastric emptying in Type l (insulin-dependent) diabetes mellitus. *Diabetologia* 33: 675-680, 1990.
17. Freeman, J.G., Cobden, I., Heaton, A. and Keir, M. Gastric emptying in chronic renal failure. *Brit. Med. J.* 291: 1048, 1985.
18. Gielkens, H.A.J., Verkijk, M., Frolich, M., Lamers, C.B.H.W. and Masclee, A.A.M. Is the effect of acute hyperglycaemia on interdigestive antroduodenal motility and small-bowel transit mediated by insulin? *Eur. J. Clin. Invest*. 27: 703-710, 1997.
19. Hegbrant J, Thysell, H. and Ekman R. Plasma levels of gastrointestinal regulatory peptides in patients receiving maintenance hemodialysis. *Scand. J. Gastroenterol*. 26: 599-604, 1991.
20. Holzer, P. Stimulation and inhibition of gastrointestinal propulsion induced by substance P and substance K in the rat. *Brit. J. Pharmacol*. 86: 305-312, 1985.
21. Holzer, P., Holzer-Petsche, U. and Leander S. A tachykinin antagonist inhibits gastric emptying and gastrointestinal transit in the rat. *Brit. J. Pharmacol*. 89: 453-459, 1986.
22. Horowitz, M., Harding, P.E, Maddox, A.F., Wishart, J.M., Akkermans, L.M.A., Chatterton, B.E. and Shearman, D.J.C. Gastric and oesophageal emptying in patients with Type 2 (non-insulin-dependent) diabetes mellitus. *Diabetologia* 32: 151-159, 1989.
23. Kang, J.Y. The gastrointestinal tract in uremia. Dig. Dis. Sci. 38: 257-268, 1993.
24. Kao, C.H., Hsu, Y.H. and Wang, S.J. Delayed gastric emptying in patients with chronic renal failure. *Nucl. Med. Commun*. 17: 164-167, 1996.
25. Kotal, P., Viteck, L. and Fevery, J. Fasting-related hyperbilirubinemia in rats: The effect of decreased intestinal motility. *Gastroenterology* 111: 217-223, 1996.
26. Lim, V.S., Henriquez, C., Seo, H., Refetoff, S. and Marinto, E. Thyroid function in a uremic rat model. Evidence suggesting tissue hypothyroidism. *J. Clin. Invest*. 66: 946-954, 1980.
27. Lin, X., Mellow, M.H., Southmayd, L. Pan, J. and Chen, J.D.Z. Impaired gastric myoelectrical activity in patients with chronic renal failure. *Dig. Dis. Sci*. 42: 898-906, 1997.
28. Luck, M.S., White, J.C. and Bass, P. Gastrointestinal transit is not impaired by regional loss of myenteric neurons in rat jejunum. *Am. J. Physiol*. 265: G654-G659, 1993.
29. MacGregor, I.L., Gueller, R., Watts, H.D. and Meyer, J.H. The effect of acute hyperglycemia on gastric emptying in man. *Gastroenterology* 70: 190-199, 1976.
30. Mak, R.H.K. and DeFronzo, R.A. Glucose and insulin metabolism in uremia. *Nephron* 61: 377-382, 1992.
31. McNamee, P.T., Moore, G.W., McGeown, M.G., Doherty, C.C. and Collins, B.J. Gastric emptying in chronic renal failure. *Brit. Med. J.* 291: 310-311, 1985.
32. Middleton, W.R.J. and Morrow, A.W. Thyroid hormones and the gut. *Gut* 12: 172-177, 1971.
33. Miller, M.S., Galligan, J.J. and Burks, T.F. Accurate measurement of intestinal transit in the rat. *J. Pharmacol. Methods* 6: 211-217,

1981.
34. Minami, H. and McCallum, R.W. The physiology and pathophysiology of gastric emptying in humans. *Gastroenterology* 86: 1592-1610, 1984.
35. Oster-Jorgensen, E., Pedersen, S.A. and Larsen, M.L. The influence of induced hyperglycaemia on gastric emptying rate in healthy humans. *Scand. J. Clin. Lab. Invest.* 50: 831-836, 1990.
36. Ravelli, A.M., Ledermann, S.E., Bisset, W.M., Trompeter, R.S., Barratt, T.M. and Milla, P.J. Foregut motor function in chronic renal failure. *Arch. Dis. Child*. 67: 1343-1347, 1992.
37. Raybould, H.E., Plourde, V., Zittel T., Bover J. and Quintero, E. Gastric emptying of solids but not liquids is decreased in rats with chronic renal failure. *Dig. Dis. Sci*. 39: 2301-2305, 1994.
38. Reilly, J.A., Forst, C.F., Quigley, E.M.M. and Rikkers, L.F. Gastric emptying of liquids and solids in the portal hypertensive rat. *Dig. Dis. Sci*. 35: 781-786, 1990.
39. Ruckebusch, M. and Fioramonti, J. Electrical spiking activity and propulsion in small intestine in fed and fasted rats. *Gastroenterology* 68: 1500-1508, 1975.
40. Russo, A., Fraser, R. and Horowitz, M. The effect of acute hyperglycaemia on small intestinal motility in normal subjects. *Diabetologia* 39: 984-989, 1996.
41. Silkoff, P., Karmeli, F., Goldin, E., Ewenson, A., Gilon, C., Chorev, M., Laufer, R., Selinger, Z. and Rachmilewitz, D. Effect of substance P on rat gastrointestinal transit. *Dig. Dis. Sci*. 33: 74-77, 1988.
42. Soffer, E.E., Geva, B., Helman, C., Avni, Y. and Bar-Meir, S. Gastric emptying in chronic renal failure patients on hemodialysis. *J. Clin. Gastroenterol*. 9: 651-653, 1987.
43. Sterner, G. Experimental chronic renal failure in rats. *Nephron* 24: 207-208, 1979.
44. Triantaphyllidis, H. and Bader, J.P. Circadian rhythmicity of the intestinal transit in rats and its disturbance through experimental hyperthyroidism. *Scand. J. Gastroenterol.* 9: 487-494, 1974.
45. Vachon, C. and Savoie, L. Circadian variation of food intake and digestive tract contents in the rat. *Physiol. Behav*. 39: 629-632, 1987.
46. Van der Velde, P., Koslowsky I. And Koopman, H.S. Measurement of gastric emptying during and between meal intake in free-feeding Lewis rats. *Am. J. Physiol*. 276: R597-R605, 1999.
47. Wetzels, J.F.M., Huysmans, F.T.M. and Koene, R.A.P. Creatinine as a marker of glomerular filtrate rate. *Neth. J. Med*. 33: 144-153, 1988.
48. Wilen, T., Gustavsson, S. and Jung, B. Effect of feeding on the pattern of small bowel transit in the rat. *Acta Chir. Scand.* 149: 617-621, 1983.
49. Wright, R.A., Clemente R. and Wathen, R. Gastric emptying in patients with chronic renal failure receiving hemodialysis. *Arch. Intern. Med*. 144: 495-496, 1984.
50. Young, T.K, Tsai, S.M., Chen, S.M. and Lin, C.W. Diminution of antidiuretic and natriuretic response to arginine vasopressin in rats with five-sixths nephrectomy. *Chin. J. Physiol*. 36: 205-209, 1993.