

# Altered Glycemic Status Modulates Gastrointestinal Motility in Male Wistar Rats

Odukanmi Olugbenga Adeola

Laboratory for Gastrointestinal Secretions and Inflammation, Department of Physiology, University of Ibadan, Ibadan, Nigeria

## Email address:

odukanmi@yahoo.com

## To cite this article:

Odukanmi Olugbenga Adeola. Altered Glycemic Status Modulates Gastrointestinal Motility in Male Wistar Rats. *American Journal of Biomedical and Life Sciences*. Vol. 10, No. 2, 2022, pp. 49-54. doi: 10.11648/j.ajbls.20221002.18

Received: March 23, 2022; Accepted: April 7, 2022; Published: April 26, 2022

**Abstract:** Glucose derangement is a common endocrine disorder affecting over 463 million worldwide. Its attending complications on the gastrointestinal motility in altered glycemic states were investigated. Forty-five male Wistar rats were grouped into 3 (n=15/group): Group 1- Control, Group 2- Diabetes, Group 3- Postprandial hyperglycemia. The 15 rats per group were sub-grouped into 3 of 5 rats each. Each sub-group determined gastric emptying, intestinal propulsion, and colonic motility. Diabetes was induced with a single intraperitoneal 150 mg/kg alloxan and the postprandial received an oral D - glucose load of 2 g/kg. Before the commencement of each experimental procedure, rats in all groups fasted for 18 hours and blood glucose concentration was assessed by the glucose oxidase method after 45 min of onset of the experiment. The mean  $\pm$  SEM of data were subjected to one-way ANOVA analysis and values of  $p < 0.05$  were considered significant. There was a significant decrease in the fasting blood glucose level (mmol/L) in rats of control ( $3.64 \pm 0.10$ ) compared with the diabetic ( $31.94 \pm 2.38$ ). The percentage of gastric emptying in the control decreased significantly compared with the diabetics. The percentage of intestinal propulsion in the control ( $42.14 \pm 3.14$ ) increased significantly compared with the diabetic ( $7.43 \pm 1.05$ ) and significantly decrease when compared with the postprandial ( $72.91 \pm 5.47$ ). There colonic motility time in the control decreased significantly compared with the diabetic. Diabetes promotes delay in the different motility examined while the postprandial group supported intestinal propulsion. Further work should focus on identifying the mechanism involved.

**Keywords:** Diabetes, Gastrointestinal Motility, Gastric Emptying, Intestinal Propulsion, Colonic Motility, Postprandial Hyperglycemia

## 1. Introduction

Gastrointestinal motility is essential for digestion, absorption of the gut. It achieves these using the interaction of the mechanical, hormonal, and enzymatic processes of the gut and distant control from the nervous system. The delay in stomach motility is associated with up to 4 in 10 diabetics with just 1 of 10 presenting with serious symptoms [1]. Stringent glycemic control in diabetics is due to a decrease in micro-and macrovascular hitches. The role of acute postprandial blood glucose to total glycemic control is not well documented [2]. The rate of gastric emptying promotes a rise in postprandial glucose concentration [2]. Other factors that promote postprandial glycemia includes duodenal motility [3], the flow events [4], and the action of the core glucose transporters [5].

Delayed gastrointestinal emptying in diabetes is well

documented and this may have a huge effect on the absorption and utilization of nutrients [6]. It was often a belief that the dysmotility noticed in diabetes is a result of permanent neuropathy of the autonomic system [7], this position was since countered as it was clear that similar dysmotility could experienced in acute hyperglycemic states [8, 9]. So increase in postprandial blood glucose range may also affect gastrointestinal motor and sensory function [10]. Indeed, there are shreds of evidence from both human and animal studies indicating that blood glucose levels can act as a modulator of gastric motility [11].

Some studies have established the effect of different glycemic statuses on gastric motility on the upper gastrointestinal motor and sensory function [12]. However, no study has sufficiently described the motility from the upper gastrointestinal tract to the lower component in acute physiological hyperglycemia and diabetes conditions. More

so, research relating to intestinal dysfunction is less studied and/or sparsely reported in diabetes and acute hyperglycemic conditions. This study investigated the effect of postprandial hyperglycemia and experimental diabetes within an *in vivo* space on gastrointestinal motility in the rat.

## 2. Materials and Methods

### 2.1. Materials

Easymax<sup>®</sup> glucometer and glucose strips, weighing balance, cages, feeding troughs, rat feed, dissecting set and board, glass beads, syringes (1ml and 5ml), acacia gum, distilled water, filter paper, activated charcoal, sensitive scale, cotton wool, thread, stopwatch, oral cannula, glucose were sourced locally.

### 2.2. Animals Grouping, Husbandry, and Ethics

45 male rats (180-200g) of Wistar strain were obtained from the Animal House of the College of Medicine, University of Ibadan, Ibadan. The rats were acclimatized for 2 weeks under room temperature before they were used for the study. These animals were grouped into three (3), (n=15). Group 1: Normal control group, Group 2: Postprandial glucose rats (administered acute oral D – glucose load of 2g/kg through oral gavage after checking the initial fasting blood glucose concentration) and Group 3: Diabetic rats (induced with diabetes by administration of a single high dose of 150mg/kg alloxan intraperitoneally). Each group was sub-grouped into three of 5 animals each. Each subgroup was allocated for the gastric emptying, intestinal propulsion, and colonic motility experiments accordingly. The rats were housed in separate cages and were fed with standard rat chow and water. All animals fasted for 18 hours before the start of each study. This study was in line with the guidelines for animal experimentation in the Gastrointestinal Secretions and Inflammation Unit of the Department of Physiology, University of Ibadan which also adapted the Guidelines of the National Institute of Health—*Guide for the Care and Use of Laboratory Animals* [13].

### 2.3. Induction of Diabetes

After 18 hours of fasting, the before diabetes was induced with a single intraperitoneal injection of 150 mg/kg body weight of freshly prepared alloxan monohydrate dissolved in distilled water in a standard volumetric flask strapped with foil. The blood glucose levels of the rats were determined after 72 hours of alloxan administration by use of Easymax<sup>®</sup> glucometer based on the glucose oxidase method. Animals with blood glucose equal to or more than 11mmol/L were considered diabetic and were used for this study.

### 2.4. Glucose Load for Postprandial Test

Rats fasted for 18 hours and were administered 2g/kg of oral D – glucose (dissolved in distilled water) by oral gavage through oral cannula after the initial fasting blood glucose

(FBG) concentration test. Thereafter, blood samples were withdrawn from the tail vein of each animal (tail snipping) to determine the fasting blood sugar concentration. The blood glucose concentration was re-checked 45 minutes after the administration of oral D – glucose, before the commencement of the experiments.

### 2.5. Determination of Blood Glucose Level

The blood glucose level of each animal was checked before and during the experiment with Easymax<sup>®</sup> glucometer through the rat tail vein.

### 2.6. Preparation of Hydrated Meal and Charcoal Meal

The hydrated feed used for the gastric emptying experiment was prepared by dissolving 45g of grinded meal in 100mL of distilled water and stirred properly. The prepared meal was kept in the refrigerator at 4°C. The hydrated feeds were given daily to the animals for 72 hours before the start of the experiment to prepare the gut for the study.

The charcoal meal was freshly prepared by mixing 10g (10%) activated charcoal and 5g (5%) acacia gum and made up to 100 mL with distilled water.

### 2.7. Determination of Gastric Empty

The rats for the gastric emptying study fasted for 18 hours before the experiment. They were given a hydrated feed of about 2 mL through oral gavage with an oral cannula. The animals were sacrificed by cervical dislocation after 2 hours of administration of hydrated feed. Laparotomy was carried out after cervical dislocation, the stomach was ligated at the pyloric and cardia ends to prevent spilling of gastric contents. The stomach was isolated by cutting the ligated ends, and the full stomach was weighed. The stomach was then cut-open through the greater curvature to empty it. The emptied stomach was rinsed with distilled water and damped to dry on a filter paper. The damped stomach was then weighed and recorded. The percentage of gastric content emptied was expressed with this formula:

$$\% \text{ Gastric Emptied} = ((\text{Full stomach weight} - \text{empty stomach weight}) / \text{Bodyweight}) \times 100 \text{ (Source: [14])}$$

### 2.8. Determination of Intestinal Propulsion

Each rat received 1mL of a charcoal meal using an oral cannula. The animals were sacrificed by cervical dislocation after 30 minutes of being fed with charcoal. Laparotomy was carried out after cervical dislocation and the entire length of the intestine was isolated and clamped from the pyloric and ileocaecal junctions. The distance travelled by the charcoal meal and the total length of the intestine were determined according to the method described by Sandhiya *et al.*, [15]:

$$\% \text{ Propulsion} = (\text{Distance travelled by charcoal} / \text{Total length of the intestine}) \times 100$$

### 2.9. Determination of Colonic Motility

Colonic motility was determined by loading 3, 3mm glass beads through the anal opening. Firstly, a Teflon cannula (Rectal Cannula) was lubricated by Tween 80, after which the Teflon cannula was used to load the beads. The loaded beads were released into the colon, 2 cm from the anal opening. The time of insertion of the beads was noted and the beads were monitored until expelled. Colonic motility time was then determined by calculating the time (seconds) of the expulsion of the beads.

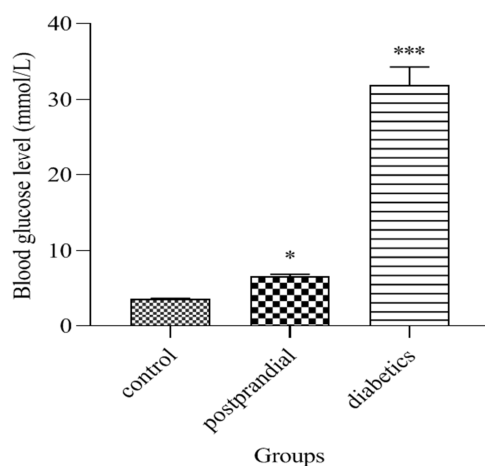
### 2.10. Statistical Analysis

The data collected from each experiment and group of rats were expressed as Mean  $\pm$  SEM. Comparisons between groups were done using one-way analysis of variance (ANOVA) and Newman-Keuls post hoc test using GraphPad prism 5.0 designed for Windows. Data were considered significant at  $p < 0.05$ .

## 3. Results

### 3.1. Effect of Altered Glycemic States on Blood Glucose Levels

There was a significant decrease in the blood glucose level in rats of control ( $3.64 \pm 0.10$ ) group when compared with the diabetic group ( $31.94 \pm 2.38$ ) and acute postprandial hyperglycemia ( $6.69 \pm 0.21$ ) group respectively (Figure 1).

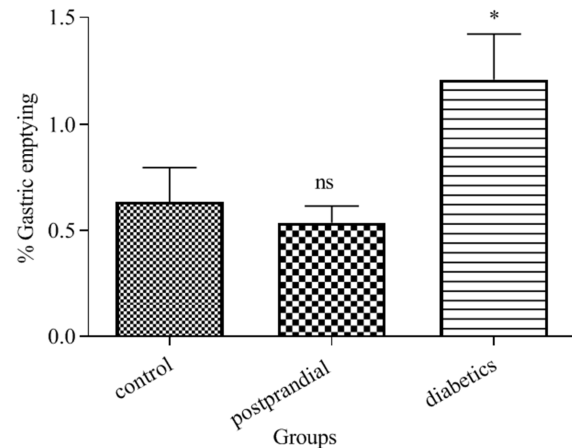


**Figure 1.** Effect of different hyperglycemic states on blood glucose level in Wistar rats.

\*\*\*Significant at  $p < 0.001$  compared with control and postprandial groups; \*significant at  $p < 0.05$  compared with control.

### 3.2. Effect of Altered Glycemic States on Gastric Emptying

There was a significant decrease in percentage gastric emptying in rats of the control ( $0.64 \pm 0.16$ ) group when compared with the diabetic ( $1.21 \pm 0.21$ ) group and no significant difference when compared with the postprandial ( $0.54 \pm 0.08$ ) group respectively (Figure 2).

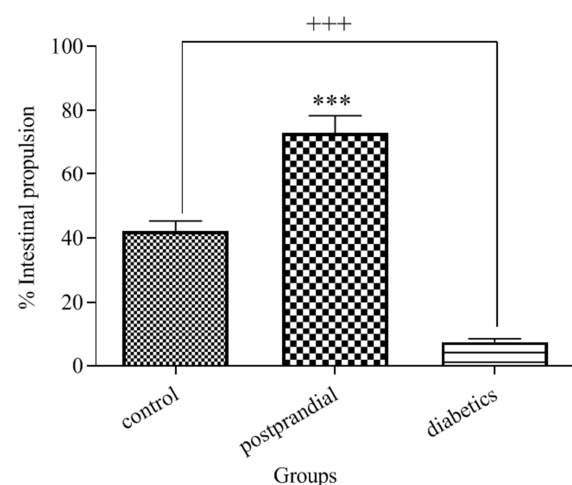


**Figure 2.** Effect of different hyperglycemic states on gastric emptying in Wistar rats.

\*Significant at  $p < 0.05$  compared to control and postprandial; ns- not significant compared with control.

### 3.3. Effect of Altered Glycemic States on Intestinal Propulsion

Figure 3 describes a significant increase in the percentage of intestinal propulsion in rats of control ( $42.14 \pm 3.14$ ) group when compared with the diabetic ( $7.43 \pm 1.05$ ) group and a significant decrease when compared with the postprandial ( $72.91 \pm 5.47$ ) group respectively.



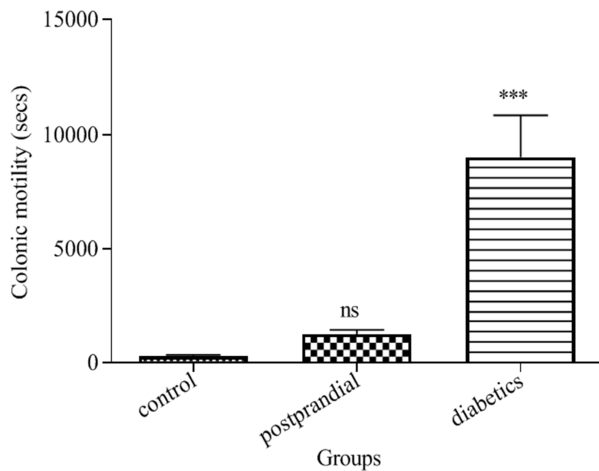
**Figure 3.** Effect of different hyperglycemic states on intestinal propulsion in Wistar rats.

+++Significant decrease at  $p < 0.001$  compared with control and postprandial groups

\*\*\*Significant increase at  $p < 0.001$  compared with Control.

### 3.4. Effect of Altered Glycemic States On Colonic Transit Time

There was a significant decrease in the colonic transit time in rats of the control ( $263.80 \pm 64.26$ ) group when compared with the diabetic group ( $9027.00 \pm 1813.00$ ) and no significant difference when compared with the postprandial ( $1235.00 \pm 178.40$ ) group respectively.



**Figure 4.** Effect of different hyperglycemic states on colonic motility time in Wistar rats.

\*\*\*Significant at  $p < 0.001$  compared with control and postprandial groups  
ns- not significant compared with control.

## 4. Discussion

Previous reports have it that diabetes, a systemic disease might affect more than one organ, including the gastrointestinal system. The length of the disease and condition of management constitutes an important factor in the development of gut complications in diabetes [16]. These complications were recognized to include both micro-and macro autonomic neuropathy. Beyond autonomic neuropathy constituting delayed gastric emptying, it is observed that acute postprandial hyperglycemia is also a factor, and it is assessed by the mode of nutrient delivery from the stomach into the small intestine [6].

In this study, contrary to the delay in gastric emptying that has been characteristically described in rats with diabetic gastropathy, a significant increase in the gastric emptying of the diabetic group was observed. In the report of Nowak *et al.*, [17], they found out that delayed and accelerated gastric emptying occurs highly differently in diabetic patients with or without symptoms of upper gastrointestinal dysfunction. The accelerated gastric emptying observed in this experiment shares similar findings with the outcome of accelerated gastric emptying reported previously in acute experimental diabetes [18, 19].

It is a good fact that autonomic neuropathy comes with a chronic diabetes condition and the neuropathy is often manifested after a long period of poorly controlled diabetes [20]. The accelerated gastric emptying observed in this study might be due to associated complications of the diabetic state occurring in the early stage. The postprandial gastric emptying rate did not differ from the control, which shares a similar view with the findings of Verhagen *et al.*, [21]. This is based on the observation that physiological acute hyperglycemia in the fasted state has little or no effect on proximal motility of the stomach and this depends on the value of blood glucose augmentation. The insignificant difference observed in this study might be due to the relative

euglycemic blood glucose level.

Furthermore, the decrease reported in the intestinal propulsion of the diabetic group when matched with the control in this study is in line with the findings of Björnsson *et al.*, [11] where it was observed that hyperglycemia in the range of 12–15 mmol/l (diabetic blood glucose level) reduces motility index and small intestinal waves of the jejunum and duodenum. Medical vagotomy was suggested to be the cause of the reduced cycle length of inner digestive motor activity in a hyperglycemic state [22]. Thus buttressing the possible role of autonomic neuropathy in chronic or massive hyperglycaemia as part of the cause of a reduced intestinal transit time since it is no longer considered a singular cause for reduced intestinal motility in diabetes [23, 24].

The increased intestinal propulsion of the postprandial group shares a similar opinion with the findings of Lingenfelser *et al.*, [25] where there was a report of antropyloroduodenal motor distension following acute physiologic hyperglycemia. The accelerated intestinal propulsion observed with the postprandial group could be due to a blood glucose level that is slightly above the euglycemic state and the acute nature of the hyperglycemia compared to the diabetic values.

The delayed colonic motility in the diabetic group is in line with the report of Imaeda *et al.* [26] which reported constipation in diabetic patients. A slow colonic transit time is associated with autonomic neuropathy, especially in diabetes, although different pathophysiology has been implicated as well. Reactive oxygen species have been associated with neuronal loss and depletion of antioxidants in hyperglycemia and diabetes [27–29] among other factors. It is however a limitation in this study that the redox and antioxidants status was not investigated. The acute hyperglycemia from the postprandial glucose was not sufficient to elicit change in colonic transit time and this shared view with the report of Maleki *et al.*, [30] where the indifference was associated with the different gas tension in both the colon and rectum of humans. Further, on the indifference in the acute hyperglycemic state to colonic motility, Sim *et al.*, [31] observed no change after mechanical stimulation of the stomach and reported the blunting effect on defaecation but the intracolonic pressure was not affected.

## 5. Conclusion

In conclusion, varying glycemic situations have a different effect on gastrointestinal motility. These effects are based on the chronicity and severity of hyperglycemia as supported by the findings from the two different hyperglycemic situations (acute and chronic) in this study. More research is required to further elucidate the possible mechanism(s) involved with the alteration of gastrointestinal motility in both the chronic and acute hyperglycemic conditions described in this study.

## Conflict of Interest

The author does not have any possible conflicts of interest.

## References

- [1] Boland BS, Edelman S V., Wolosin JD. Gastrointestinal Complications of Diabetes. *Endocrinol Metab Clin North Am* 2013; 42: 809.
- [2] Kuo P, Wishart JM, Bellon M, et al. Effects of physiological hyperglycemia on duodenal motility and flow events, glucose absorption, and incretin secretion in healthy humans. *J Clin Endocrinol Metab* 2010; 95: 3893–3900.
- [3] Rayner CK, Schwartz MP, van Dam PS, et al. Small intestinal glucose absorption and duodenal motility in type 1 diabetes mellitus. *Am J Gastroenterol* 2002; 97: 3123–3130.
- [4] Chaikomin R, Keng LW, Doran S, et al. Concurrent duodenal manometric and impedance recording to evaluate the effects of hyoscine on motility and flow events, glucose absorption, and incretin release. *Am J Physiol Gastrointest Liver Physiol*; 292. Epub ahead of print April 2007. DOI: 10.1152/AJPGI.00519.2006.
- [5] Kellett GL, Brot-Laroche E. Apical GLUT2: a major pathway of intestinal sugar absorption. *Diabetes* 2005; 54: 3056–3062.
- [6] Rayner CK, Samsom M, Jones KL, et al. Relationships of upper gastrointestinal motor and sensory function with glycemic control. *Diabetes Care* 2001; 24: 371–381.
- [7] Horowitz M, Dent J. Disordered gastric emptying: mechanical basis, assessment and treatment. *Baillieres Clin Gastroenterol* 1991; 5: 371–407.
- [8] Andrews JM, Rayner CK, Doran S, et al. Physiological changes in blood glucose affect appetite and pyloric motility during intraduodenal lipid infusion. *Am J Physiol*; 275. Epub ahead of print 1998. DOI: 10.1152/AJPGI.1998.275.4.G797.
- [9] Schvarcz E, Palmer M, Aman J, et al. Physiological hyperglycemia slows gastric emptying in normal subjects and patients with insulin-dependent diabetes mellitus. *Gastroenterology* 1997; 113: 60–66.
- [10] Jones KL, Russo A, Stevens JE, et al. Predictors of delayed gastric emptying in diabetes. *Diabetes Care* 2001; 24: 1264–1269.
- [11] Björnsson ES, Urbanavicius V, Eliasson B, et al. Effects of Hyperglycemia on Interdigestive Gastrointestinal Motility in Humans. <http://dx.doi.org/10.103109/00365529409094894> 2009; 29: 1096–1104.
- [12] Horowitz M, Wu T, Rayner CK, et al. Spontaneous or Deliberate: Effects of Acute Variations in Glycemia on Gastric Emptying in Type 1 Diabetes. *Diabetes Care* 2021; 44: 316–318.
- [13] National Institute of Health. Guide for the Care and Use of Laboratory Animals Institute for Laboratory Animal Research Division on Earth and Life Studies. 2011; 8th Editio: 1–246.
- [14] Purdon RA, Bass P. Gastric and intestinal transit in rats measured by a radioactive test meal. *Gastroenterology* 1973; 64: 968–976.
- [15] Sandhiya S, Dkhar SA, Reddy P, et al. Role of ion channel modifiers in reversal of morphine-induced gastrointestinal inertia by prokinetic agents in mice. *Indian J Exp Biol* 2008; 46: 60–65.
- [16] Wolosin JD ES. Diabetes and the gastrointestinal tract. *Clin Diabets* 2000; 18: 1–7.
- [17] Nowak T V., Johnson CP, Kalbfleisch JH, et al. Highly variable gastric emptying in patients with insulin dependent diabetes mellitus. *Gut* 1995; 37: 23.
- [18] Green GM, Guan D, Schwartz JG, et al. Accelerated gastric emptying of glucose in Zucker type 2 diabetic rats: role in postprandial hyperglycaemia. *Diabetol* 1997 402 1997; 40: 136–142.
- [19] Granneman JG, Stricker EM. Food intake and gastric emptying in rats with streptozotocin-induced diabetes. <https://doi.org/10.1152/ajpregu19842476R1054>; 16. Epub ahead of print 1984. DOI: 10.1152/AJPREGU.1984.247.6.R1054.
- [20] Carmichael J, Fadavi H, Ishibashi F, et al. Advances in Screening, Early Diagnosis and Accurate Staging of Diabetic Neuropathy. *Front Endocrinol (Lausanne)*; 12. Epub ahead of print 26 May 2021. DOI: 10.3389/FENDO.2021.671257.
- [21] Verhagen MAMT, Rayner CK, Andrews JM, et al. Physiological changes in blood glucose do not affect gastric compliance and perception in normal subjects. *Am J Physiol - Gastrointest Liver Physiol*; 276. Epub ahead of print 1999. DOI: 10.1152/AJPGI.1999.276.3.G761/ASSET/IMAGES/LARGE/AGIJ30307002X.JPEG.
- [22] Øster-Jørgensen E, Qvist N, Pedersen SA, et al. The influence of induced hyperglycaemia on the characteristics of intestinal motility and bile kinetics in healthy men. *Scand J Gastroenterol* 1992; 27: 285–288.
- [23] Yarandi SS, Srinivasan S. Diabetic gastrointestinal motility disorders and the role of enteric nervous system: Current status and future directions. *Neurogastroenterol Motil* 2014; 26: 611.
- [24] Harder H, Hernando-Harder AC, Franke A, et al. Effect of acute hyperglycemia on intestinal gas transit and tolerance in nondiabetic humans. *Digestion* 2005; 71: 179–186.
- [25] Lingenfelser T, Sun WM, Hebbard GS, et al. Effects of duodenal distension on antropyloroduodenal pressures and perception are modified by hyperglycemia. *Am J Physiol - Gastrointest Liver Physiol*; 276. Epub ahead of print 1999. DOI: 10.1152/AJPGI.1999.276.3.G711/ASSET/IMAGES/LARGE/AGIJ30316008X.JPEG.
- [26] Imaeda K, Takano H, Koshita M, et al. Electrical properties of colonic smooth muscle in spontaneously non-insulin-dependent diabetic rats. *J Smooth Muscle Res* 1998; 34: 1–11.
- [27] Voss U, Sand E, Olde B, et al. Enteric neuropathy can be induced by high fat diet in vivo and palmitic acid exposure in vitro. *PLoS One*; 8. Epub ahead of print 3 December 2013. DOI: 10.1371/JOURNAL.PONE.0081413.
- [28] Nezami BG, Mwangi SM, Lee JE, et al. MicroRNA 375 mediates palmitate-induced enteric neuronal damage and high-fat diet-induced delayed intestinal transit in mice. *Gastroenterology*; 146. Epub ahead of print 2014. DOI: 10.1053/J.GASTRO.2013.10.053.

- [29] Chandrasekharan B, Anitha M, Blatt R, et al. Colonic motor dysfunction in human diabetes is associated with enteric neuronal loss and increased oxidative stress. *Neurogastroenterol Motil*; 23. Epub ahead of print February 2011. DOI: 10.1111/J.1365-2982.2010.01611.X.
- [30] Maleki D, Camilleri M, Zinsmeister AR, et al. Effect of acute hyperglycemia on colorectal motor and sensory function in humans. *Am J Physiol - Gastrointest Liver Physiol*; 273. Epub ahead of print 1997. DOI: 10.1152/AJPGI.1997.273.4.G859.
- [31] Sims MA, Hasler WL, Chey WD, et al. Hyperglycemia inhibits mechanoreceptor-mediated gastrocolonic responses and colonic peristaltic reflexes in healthy humans. *Gastroenterology* 1995; 108: 350–359.