EXCLI Journal 2017;16:742-747 – ISSN 1611-2156
Received: April 01, 2017, accepted: May 03, 2017, published: May 17, 2017

Letter to the editor:

RECENT UPDATE ON BIOLOGICAL ACTIVITIES AND PHARMACOLOGICAL ACTIONS OF LIRAGLUTIDE

Juhi Tiwari[1], Gaurav Gupta[1,2]*, Rajiv Dahiya[3], Kavita Pabreja[2], Rakesh Kumar Sharma[4], Anurag Mishra[4], Kamal Dua[5,6,7]

[1] School of Pharmacy, Jaipur National University, Jagatpura 302017, Jaipur, India
[2] School of Medicine and Public Health, University of Newcastle, Newcastle, NSW 2308, Australia
[3] Laboratory of Peptide Research and Development, School of Pharmacy, Faculty of Medical Sciences, The University of the West Indies, St. Augustine, Trinidad & Tobago, West Indies
[4] School of Pharmacy, Suresh Gyan Vihar University, Jagatpura 302017, Jaipur, India
[5] Discipline of Pharmacy, Graduate School of Health, University of Technology Sydney, Sydney, NSW 2007, Australia
[6] School of Biomedical Sciences and Pharmacy, University of Newcastle, Newcastle, NSW 2308, Australia
[7] School of Pharmaceutical Sciences, Shoolini University, Solan, Himachal Pradesh, 173229, India

* corresponding author: Dr. Gaurav Gupta, School of Pharmacy, Jaipur National University, Jagatpura 302017, Jaipur, India, E-mail: gauravpharma25@gmail.com; Contact number: +91 7014790412

http://dx.doi.org/10.17179/excli2017-323

Dear Editor,

Liraglutide (LG), an analog of human glucagon-like peptide 1 (GLP-1), has been permitted for type 2 diabetes therapy. LG triggers the GLP-1 receptor, leading to release of insulin in the presence of high glucose concentrations, it declines secretion of glucagon in a glucose-dependent manner and directly applying to the β cells of pancreas to help its proliferation and differentiation (Dharmalingam et al., 2011; Drucker et al., 2010). The mechanism of lowering blood glucose also includes a delay in gastric emptying. LG is approved by the European Medicines Agency (EMA) on July 3, 2009, and by the U.S. Food and Drug Administration (FDA) on January 25, 2010, for the treatment of type 2 diabetes mellitus (T2DM) (Ye et al., 2017). A number of studies suggest that LG, GLP-1 has additional benefits (Zhang et al., 2017). Here we have reviewed various pharmacological actions of LG (Table 1).

EXCLI Journal 2017;16:742-747 – ISSN 1611-2156
Received: April 01, 2017, accepted: May 03, 2017, published: May 17, 2017

Table 1: Recent update on biological activities and pharmacological actions of liraglutide

Key Findings	References
By targeting insulin receptor substrate 1 on the diabetic rat pancreas and insulin 1 cells, LG exhibits anti-apoptotic effect by decreased miR-139-5p expression.	Li et al., 2017
By declining the phosphorylation of tau, LG alleviates Alzheimer disease-like cognitive impairment.	Qi et al., 2017
In T2DM patients with non-alcoholic fatty liver disease, compare to metformin and gliclazide, LG showed a better recovery in hepatic function, decreases in integration host factor content and level of HbA1c, and reduction in weight.	Feng et al., 2017
LG in a one dose can acutely inhibit the ketogenesis.	Garg et al., 2017
Therapy with a combination of Insulin Degludec (IDeg) and LG (IDegLira) allows more patients with type 2 diabetes to sustain the level of blood glucose within target ranges all over the day compared to IDeg or LG alone.	King et al., 2017
LG can protect cardiomyocytes against reperfusion injury through modulation of intracellular calcium homeostasis.	Hu et al., 2017
LG and sitagliptin showed an auspicious approach to moderate the progression of Parkinson's disease by their anti-inflammatory, anti-apoptotic neurotrophic and neurogenic mechanistic activities.	Badawi et al., 2017
Treatment of LG 3.0 mg may deliver benefit for health in terms of reduced risk of diabetes in persons with obesity and prediabetes.	le Roux et al., 2017
LG 1.8 mg is likely to be cost-effective compared with lixisenatide 20 µg in T2D patients who have not attained glycemic control targets on metformin monotherapy.	Mezquita-Raya et al., 2017
LG therapy may help patients in primary care by postponing the need for further treatment strengthening.	Martinez et al., 2017
LG accompanying with metformin induces a significantly clinical enhancement in β-cell function in obese and patients with cardiovascular diseases with newly diagnosed well-controlled T2DM and coronary artery diseases.	Anholm et al., 2017
LG showed daytime variation in the effect on blood pressure without upsetting the blood pressure inconsistency or night-time blood pressure dropping.	Kumarathurai et al., 2017a
Treatment of T2DM patients with LG 1.8 mg is expected to be measured highly cost-effective compared with lixisenatide 20 µg in the UK setting.	Hunt et al., 2017
LG causes a considerable and quick EAT reduction. Liraglutide cardiometabolic effects may be EAT-mediated.	Iacobellis et al., 2017
LG treatment showed anti-inflammatory, reflected in decreases in TNF-α and MR-proADM, whereas a decrease in MR-proANP may signify a clinically relevant regarding cardiac failure.	von Scholten et al., 2017
LG 3.0 mg treatment showed safe and effective addition to the pharmacologic effect for chronic weight management in the overall population.	Manigault and Thurston, 2016
Through an effect on mTOR pathway, LG protected diabetes-dependent hippocampal neurodegeneration.	Palleria et al., 2017
In obese patients with T2D, LG expressively enhanced glycemic control and decreased the body weight without failing quality of life.	Ishii et al., 2017
LG has valuable effects in a mouse model of moderate uremia by decreasing atherosclerosis and inflammation of kidney.	Bisgaard et al., 2016
LG defends in contrast to IR injury of the hepatic tissue through anti-inflammatory and antioxidant activities along with inhibition of apoptosis.	Abdelsameea et al., 2017
IDegLira provided superior glycemic control versus unchanged GLP-1RA and represents an efficacious intensification approach in patients inadequately controlled on GLP-1Ras.	Jennings et al., 2016

Table 1 (cont.): Recent update on biological activities and pharmacological actions of liraglutide

Key Findings	References
LG treatment progresses myocardial recovery and infarct size after ST-segment-elevation myocardial infarction, possibly by reducing reperfusion injury, making it a promising treatment for evaluation in larger trials	Chen et al., 2016
LG treatment as add-on to insulin improved HR and did not progress other cardiovascular risk factors after 6 months of treatment in patients with chronic T1D.	Dejgaard et al., 2017
In insulin-treated patients with T2D, LG treatment may reduce visceral adiposity in parallel with the reduction of hepatic fat accumulation, albuminuria and micro-inflammation and progress quality of life associated with diabetes care.	Bouchi et al., 2017
LG treatment might improve the therapeutic efficacy of mesenchymal stem cells in the treatment of T1D.	Li et al., 2016a
LG treatment decreased ostomy wet weight production in end-jejunostomy patients with SBS-IF and improved their intestinal wet weight and energy absorption.	Hvistendahl et al., 2016
LG treatment delays onset of EAE in Lewis rats and is associated with improved protective capacity against oxidative stress.	Bouchi et al., 2017
In failing post-ischemic T2D patients, LG therapy improves heart function and functional capacity.	Arturi et al., 2016
LG improved heart rate and decreased heart rate variability despite weight loss and enhancement of metabolic parameters in overweight patients with CAD and newly diagnosed T2D. The rise in nocturnal heart rate in combination with a reduction in parasympathetic activity parameters proposes that LG may affect sympathovagal balance.	Kumarathurai et al., 2017b
Treatment of LG re-establishes angiogenesis in PA-impaired HUVECs via up-regulation of GTPCH1 and eNOS in a PI3K/Akt-Foxo1-dependent mechanism.	Ke et al., 2016
Pre-treatment with LG reduced lipopolysaccharide-induced acute lung injury by preventing the NLRP3 inflammasome pathway.	Zhou et al., 2016
LG has pleiotropic effects on renal risk factors.	Zobel et al., 2017
Due to its safety and hypoglycemic efficacy, liraglutide is an excellent choice for DM treatment in combination with other drugs. Its effects on the reduction of weight and other cardiovascular risk factors, make it an optimal treatment, especially in overweight or obese patients.	Calvo Gomez et al., 2016
Six months of treatment with liraglutide 1.2 mg/d significantly reduced LFC in patients with inadequately controlled type 2 diabetes and this effect was mainly driven by body weight reduction.	Petit et al., 2017
In Indian T2D patients, treatment of LG resulted in a significant and continued decrease in HbA1c and body weight over a year and it was associated with baseline HbA1c and weight, respectively.	Kaur et al., 2016
LG is safe and well tolerated for non-diabetic individuals with mood disorders as well as shows beneficial effects on objective measures of cognitive function.	Mansur et al., 2017
LG might be moderate in the conformation of the gut microbiota, leads to a more lean-related profile that was consistent with its weight-losing effect.	Wang et al., 2016a
Through modification of AMPK/mTOR signaling, LG weakens osteoblastic differentiation of MC3T3 E1 cells.	Hu et al., 2016
LG may have a beneficial role in pulmonary vascular remodeling, because of its defensive and therapeutic effects on monocrotaline-induced pulmonary arterial hypertension, through the eNOS/sGC/PKG and Rho kinase pathways.	Lee et al., 2016
LG may hinder in the metabolism of energy because analysis of different times of administrations, concentrations, and level of brain development leads to different outcomes.	Pra et al., 2016
The useful effects of LG on pancreatic islets seem to be linked to its anti-inflammatory and anti-oxidative properties. These conclusions showed that LG could be used to progress graft survival.	Langlois et al., 2016

Table 1 (cont.): Recent update on biological activities and pharmacological actions of liraglutide

Key Findings	References
LG in addition to insulin therapy declines HbA1c levels, total insulin dose, and body weight in a population that was usually demonstrative of subjects with T1D, together with increased rates of symptomatic hypoglycemia and hyperglycemia with ketosis, thereby limiting clinical use in this group.	Mathieu et al., 2016
LG and Linagliptin through the initiation of the ERK/NF-κB/pathway, prevent glucose- and Ang II-induced collagen formation in cardiac fibroblasts.	Wang et al., 2016b
In T2D patients, LG therapy for 180 days is associated with a perfection in diastolic function.	Saponaro et al., 2016
LG progresses endothelial function, weakens endothelial inflammatory signals, as well as converses leptin resistance.	Li et al., 2016b
In T2D patients, LG may be beneficial for treating insulin allergy and anti-insulin antibodies.	Htike et al., 2016
Without modifying the level of plasma insulin, LG effectively enhanced glycemic instability due to insulin antibodies.	Kato et al., 2016
Early use of LG may decrease metabolic insulin resistance and stop cardiovascular problems of diabetes. It exhibits their beneficial glycemic effect by improving microvascular insulin sensitivity and muscle capillary density during insulin resistance development.	Chai et al., 2016

REFERENCES

Abdelsameea AA, Abbas NA, Abdel Raouf SM. Liraglutide attenuates partial warm ischemia-reperfusion injury in rat livers. Naunyn Schmiedeberg's Arch Pharmacol. 2017;390:311-9.

Anholm C, Kumarathurai P, Pedersen LR, Nielsen OW, Kristiansen OP, Fenger M, et al. Liraglutide effects on beta-cell, insulin sensitivity and glucose effectiveness in patients with stable coronary artery disease and newly diagnosed type 2 diabetes. Diabetes Obes Metab. 2017;10.1111/dom.12891.

Arturi F, Succurro E, Miceli S, Cloro C, Ruffo M, Maio R, et al. Liraglutide improves cardiac function in patients with type 2 diabetes and chronic heart failure. Endocrine. 2016; epub ahead of print. 10.1007/s12020-016-1166-4.

Badawi GA, Abd El Fattah MA, Zaki HF, El Sayed MI. Sitagliptin and liraglutide reversed nigrostriatal degeneration of rodent brain in rotenone-induced Parkinson's disease. Inflammopharmacology. 2017; epub ahead of print. 10.1007/s10787-017-0331-6.

Bisgaard LS, Bosteen MH, Fink LN, Sorensen CM, Rosendahl A, Mogensen CK, et al. Liraglutide reduces both atherosclerosis and kidney inflammation in moderately uremic LDLr-/- mice. PLoS One. 2016;11(12): e0168396.

Bouchi R, Nakano Y, Fukuda T, Takeuchi T, Murakami M, Minami I, et al. Reduction of visceral fat by liraglutide is associated with ameliorations of hepatic steatosis, albuminuria, and micro-inflammation in type 2 diabetic patients with insulin treatment: a randomized control trial. Endocr J. 2017;64:269-81.

Calvo Gomez C, Gomez-Huelgas R, Lima Ruiz J, Masmiquel Comas L, Michan Dona A, Zapatero Gaviria A. Expert consensus on the use of liraglutide in the treatment of diabetes in internal medicine. Int J Clin Pharmacol Ther. 2016;54:880-90.

Chai W, Fu Z, Aylor KW, Barrett EJ, Liu Z. Liraglutide prevents microvascular insulin resistance and preserves muscle capillary density in high-fat diet-fed rats. Am J Physiol. 2016;311:E640-8.

Chen WR, Chen YD, Tian F, Yang N, Cheng LQ, Hu SY, et al. Effects of liraglutide on reperfusion injury in patients with ST-segment-elevation myocardial infarction. Circ Cardiovasc Imaging. 2016;9(12):e005146.

Dejgaard TF, Johansen NB, Frandsen CS, Asmar A, Tarnow L, Knop FK, et al. Effects of liraglutide on cardiovascular risk factors in patients with type 1 diabetes. Diabetes Obes Metab. 2017;19:734-8.

Dharmalingam M, Sriram U, Baruah MP. Liraglutide: A review of its therapeutic use as a once daily GLP-1 analog for the management of type 2 diabetes mellitus. Indian J Endocrinol Metab. 2011;15:9-17.

Drucker DJ, Dritselis A, Kirkpatrick P. Liraglutide. Nat Rev Drug Discov. 2010;9:267-8.

Feng W, Gao C, Bi Y, Wu M, Li P, Shen S, et al. A randomized trial comparing gliclazide, liraglutide, and metformin effects on diabetes with nonalcoholic fatty liver disease. J Diabetes. 2017; epub ahead of print. 10.1111/1753-0407.12555.

Garg M, Ghanim H, Kuhadiya ND, Green K, Hejna J, Abuaysheh S, et al. Liraglutide acutely suppresses glucagon, lipolysis and ketogenesis in type 1 diabetes. Diabetes Obes Metab. 2017; epub ahead of print. 10.1111/dom.12944.

Htike ZZ, Yates T, Brady EM, Webb D, Gray LJ, Swarbrick D, et al. Rationale and design of the randomised controlled trial to assess the impact of liraglutide on cardiac function and structure in young adults with type 2 diabetes (the LYDIA study). Cardiovasc Diabetol. 2016;15(1):102.

Hu SY, Zhang Y, Zhu PJ, Zhou H, Chen YD. Liraglutide directly protects cardiomyocytes against reperfusion injury possibly via modulation of intracellular calcium homeostasis. J Geriatr Cardiol. 2017;14:57-66.

Hu XK, Yin XH, Zhang HQ, Guo CF, Tang MX. Liraglutide attenuates the osteoblastic differentiation of MC3T3E1 cells by modulating AMPK/mTOR signaling. Mol Med Rep. 2016;14:3662-8.

Hunt B, Vega-Hernandez G, Valentine WJ, Kragh N. Evaluation of the long-term cost-effectiveness of liraglutide vs lixisenatide for treatment of type 2 diabetes mellitus in the UK setting. Diabetes Obes Metab. 2017; epub ahead of print. 10.1111/dom.12890.

Hvistendahl M, Brandt CF, Tribler S, Naimi RM, Hartmann B, Holst JJ, et al. Effect of liraglutide treatment on jejunostomy output in patients with short bowel syndrome: an open-label pilot study. JPEN J Parenter Enteral Nutr. 2016; epub ahead of print. 0.1177/0148607116672265.

Iacobellis G, Mohseni M, Bianco SD, Banga PK. Liraglutide causes large and rapid epicardial fat reduction. Obesity (Silver Spring). 2017;25:311-6.

Ishii H, Niiya T, Ono Y, Inaba N, Jinnouchi H, Watada H. Improvement of quality of life through glycemic control by liraglutide, a GLP-1 analog, in insulin-naive patients with type 2 diabetes mellitus: the PAGE1 study. Diabetol Metab Syndr. 2017;9:3.

Jennings L, Nestor L, Molloy O, Hughes R, Moriarty B, Kirby B. The treatment of hidradenitis suppurativa with the glucagon-like peptide -1 agonist liraglutide. Br J Dermatol. 2016; epub ahead of print. 10.1111/bjd.15233.

Kato T, Iizuka K, Niwa H, Takeda J. Liraglutide improved glycaemic instability in a patient with diabetes with insulin antibodies. BMJ Case Rep. 2016;2016.

Kaur P, Mahendru S, Mithal A. Long-term efficacy of liraglutide in Indian patients with Type 2 diabetes in a real-world setting. Indian J Endocrinol Metab. 2016; 20:595-9.

Ke J, Wei R, Yu F, Zhang J, Hong T. Liraglutide restores angiogenesis in palmitate-impaired human endothelial cells through PI3K/Akt-Foxo1-GTPCH1 pathway. Peptides. 2016;86:95-101.

King AB, Philis-Tsimikas A, Kilpatrick ES, Langbakke IH, Begtrup K, Vilsboll T. A fixed ratio combination of insulin degludec and liraglutide (IDegLira) reduces glycemic fluctuation and brings more patients with Type 2 diabetes within blood glucose target ranges. Diabetes Technol Ther. 2017;19:255-64.

Kumarathurai P, Anholm C, Fabricius-Bjerre A, Nielsen OW, Kristiansen O, Madsbad S, et al. Effects of the glucagon-like peptide-1 receptor agonist liraglutide on 24-h ambulatory blood pressure in patients with type 2 diabetes and stable coronary artery disease: a randomized, double-blind, placebo-controlled, crossover study. J Hypertens. 2017a;35:1070-8.

Kumarathurai P, Anholm C, Larsen BS, Olsen RH, Madsbad S, Kristiansen O, et al. Effects of liraglutide on heart rate and heart rate variability: a randomized, double-blind, placebo-controlled crossover study. Diabetes Care. 2017b;40:117-24.

Langlois A, Dal S, Vivot K, Mura C, Seyfritz E, Bietiger W, et al. Improvement of islet graft function using liraglutide is correlated with its anti-inflammatory properties. Br J Pharmacol. 2016;173:3443-53.

le Roux CW, Astrup A, Fujioka K, Greenway F, Lau DC, Van Gaal L, et al. 3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial. Lancet. 2017;389(10077):1399-409.

Lee MY, Tsai KB, Hsu JH, Shin SJ, Wu JR, Yeh JL. Liraglutide prevents and reverses monocrotaline-induced pulmonary arterial hypertension by suppressing ET-1 and enhancing eNOS/sGC/PKG pathways. Sci Rep. 2016;6:31788.

Li LR, Jia XL, Hui H, Zhang J, Liu Y, Cui WJ, et al. Liraglutide enhances the efficacy of human mesenchymal stem cells in preserving islet beta-cell function in severe non-obese diabetic mice. Mol Med. 2016a; epub ahead of print. 10.2119/molmed.2016.00168.

Li N, Zhao Y, Yue Y, Chen L, Yao Z, Niu W. Liraglutide ameliorates palmitate-induced endothelial dysfunction through activating AMPK and reversing leptin resistance. Biochem Biophys Res Commun. 2016b; 478:46-52.

Li J, Su L, Gong YY, Ding ML, Hong SB, Yu S, et al. Downregulation of miR-139-5p contributes to the antiapoptotic effect of liraglutide on the diabetic rat pancreas and INS-1 cells by targeting IRS1. PLoS One. 2017;12(3):e0173576.

Manigault KR, Thurston MM. Liraglutide: a glucagon-like peptide-1 agonist for chronic weight management. Consult Pharm. 2016;31:685-97.

Mansur RB, Ahmed J, Cha DS, Woldeyohannes HO, Subramaniapillai M, Lovshin J, et al. Liraglutide promotes improvements in objective measures of cognitive dysfunction in individuals with mood disorders: A pilot, open-label study. J Affect Disord. 2017;207: 114-20.

Martinez L, Penfornis A, Gautier JF, Eschwege E, Charpentier G, Bouzidi A, et al. Effectiveness and persistence of liraglutide treatment among patients with Type 2 diabetes treated in primary care and specialist settings: a subgroup analysis from the evidence study, a prospective, 2-year follow-up, observational, post-marketing study. Adv Ther. 2017;34:674-85.

Mathieu C, Zinman B, Hemmingsson JU, Woo V, Colman P, Christiansen E, et al. Efficacy and safety of liraglutide added to insulin treatment in Type 1 diabetes: the adjunct one treat-to-target randomized trial. Diabetes Care. 2016;39:1702-10.

Mezquita-Raya P, Ramirez de Arellano A, Kragh N, Vega-Hernandez G, Pohlmann J, Valentine WJ, et al. Liraglutide versus lixisenatide: long-term cost-effectiveness of GLP-1 receptor agonist therapy for the treatment of Type 2 diabetes in Spain. Diabetes Ther. 2017;8:401-15.

Palleria C, Leo A, Andreozzi F, Citraro R, Iannone M, Spiga R, et al. Liraglutide prevents cognitive decline in a rat model of streptozotocin-induced diabetes independently from its peripheral metabolic effects. Behav Brain Res. 2017;321:157-69.

Petit JM, Cercueil JP, Loffroy R, Denimal D, Bouillet B, Fourmont C, et al. Effect of liraglutide therapy on liver fat content in patients with inadequately controlled type 2 diabetes. The Lira-NAFLD study. J Clin Endocrinol Metab. 2017;102:407-15.

Pra M, Ferreira GK, de Mello AH, Schraiber RB, Cardoso LC, Souza LD, et al. Single dose and repeated administrations of liraglutide alter energy metabolism in the brains of young and adult rats. Biochem Cell Biol. 2016;94:451-8.

Qi L, Chen Z, Wang Y, Liu X, Liu X, Ke L, et al. Subcutaneous liraglutide ameliorates methylglyoxal-induced Alzheimer-like tau pathology and cognitive impairment by modulating tau hyperphosphorylation and glycogen synthase kinase-3beta. Am J Transl Res. 2017;9:247-60.

Saponaro F, Sonaglioni A, Rossi A, Montefusco L, Lombardo M, Adda G, et al. Improved diastolic function in type 2 diabetes after a six month liraglutide treatment. Diabetes Res Clin Pract. 2016;118:21-8.

von Scholten BJ, Persson F, Rosenlund S, Eugen-Olsen J, Pielak T, Faber J, et al. Effects of liraglutide on cardiovascular risk biomarkers in patients with type 2 diabetes and albuminuria: A sub-analysis of a randomized, placebo-controlled, double-blind, crossover trial. Diabetes Obes Metab. 2017; epub ahead of print. 10.1111/dom.12884.

Wang L, Li P, Tang Z, Yan X, Feng B. Structural modulation of the gut microbiota and the relationship with body weight: compared evaluation of liraglutide and saxagliptin treatment. Sci Rep. 2016a;6:33251.

Wang XW, Zhang FX, Yang F, Ding ZF, Agarwal N, Guo ZK, et al. Effects of linagliptin and liraglutide on glucose- and angiotensin II-induced collagen formation and cytoskeleton degradation in cardiac fibroblasts in vitro. Acta Pharmacol Sin. 2016b;37:1349-58.

Ye X, Qi J, Yu D, Wu Y, Zhu S, Li S, et al. Pharmacological efficacy of FGF21 analogue, liraglutide and insulin glargine in treatment of type 2 diabetes. J Diabetes Complications. 2017;31:726-34.

Zhang Y, Ling Y, Yang L, Cheng Y, Yang P, Song X, et al. Liraglutide relieves myocardial damage by promoting autophagy via AMPK-mTOR signaling pathway in zucker diabetic fatty rat. Mol Cell Endocrinol. 2017;448:98-107.

Zhou F, Zhang Y, Chen J, Hu X, Xu Y. Liraglutide attenuates lipopolysaccharide-induced acute lung injury in mice. Eur J Pharmacol. 2016;791:735-40.

Zobel EH, von Scholten BJ, Lindhardt M, Persson F, Hansen TW, Rossing P. Pleiotropic effects of liraglutide treatment on renal risk factors in type 2 diabetes: Individual effects of treatment. J Diabetes Complications. 2017;31:162-8.