Dear Professor Donald W Bowden,
Editor-in-chief of World Journal of Diabetes,
Center for Human Genomics,
Wake Forest University School of Medicine,
Winston-Salem, NC 27157, United States.

Thank you for promptly revising our review article submitted to World Journal of Diabetes (WJD) and providing us with insightful comments from the reviewer. We would like to resubmit our manuscript # 7980, entitled "Interrelationships between ghrelin, insulin and glucose homeostasis: physiological relevance" to WJD. Based on minor corrections suggested by the reviewer, we have revised the manuscript, with additional clarifications and corrections. More specifically, we have corrected minor typos, and we have included/discussed the different topics. Altogether, we feel that this addresses the comments raised by the reviewers. We have directly responded to their comments (and have **underlined them in green**), in a point by point form, in the **RESPONSES TO THE REVIEWER** section.

We appreciate to opportunity to submit this invited review to WJD, and we hope that the manuscript is now appropriate for publication.

Sincerely,

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RESPONSES TO THE REVIEWER

REVIEWER 1

COMMENT 1: This is a very interesting review on the interrelationship of ghrelin, insulin and glucose. The review is well structured and clearly written.

RESPONSE 1: We thank the reviewer for the positive appreciation of our review article.

COMMENT 2: I suggest adding and discussing two recent publications very relevant to the topic:

(a) Tong J et al. Physiologic concentrations of exogenously infused ghrelin reduces insulin secretion without affecting insulin sensitivity in healthy humans. J Clin Endocrinol Metab. 2013 Jun;98(6):2536-43.

RESPONSE 2 *(a)*: Although this reference was already cited in the text, we elaborated more on the topic and modified the sentence (P 11, paragraph 2, line 13): "At lower concentrations (0.3 to 1.5 ng/kg/h), AG infusions reduced insulin secretion without significantly altering glucose levels [101, 102]." to "At lower concentrations (0.3 to 1.5 ng/kg/h), AG infusions reduced insulin secretion and glucose levels [104]. The same authors have also observed a decrease in insulin secretion in response to the administration of physiological concentrations of AG (0.2 and 0.6 ng/kg/h) [26, 105]. Consequently, it is suggested that physiological levels of ghrelin directly impair β-cell functions but the mechanisms underlying these effects remain to be clarified [105]. One appealing hypothesis is that these inhibitory effects of AG on insulin release could be mediated through the stimulation of somatostatin (SRIF) production [106].

(b) Heppner KM et al. Both acyl and des-acyl ghrelin regulate adiposity and glucose metabolism via CNS ghrelin receptors. Diabetes. 2013 Sep 23. [Epub ahead of print].

RESPONSE 2 *(b)*: As suggested by REVIEWER 1, we on page 5 (paragraph 2, line 9), we have included the sentence: "It has recently been hypothesized that the adipogenic effects of both AG and UAG could be mediated in the CNS by the activation of GHS-R1a [50]."

COMMENT 3: I recommend to consider adding that there is also some evidence that the orexigenic effect of ghrelin may be also partly caused by a suppression of the anorexigenic hormones CART (de Lartigue G et al. MSH Cocaine- and amphetamine-regulated transcript: stimulation of expression in rat vagal afferent neurons by cholecystokinin and suppression by ghrelin. J Neurosci. 2007 Mar 14;27(11):2876-82.) and alpha-MSH (e.g. Kwon Jeong J, Ghrelin regulates hypothalamic prolyl carboxypeptidase expression in mice. Mol Metab. 2013 Jan 11;2(1):23-30. doi: 10.1016/j.molmet.2013.01.002.)

RESPONSE 3: As suggested by REVIEWER 1, we included both references to propose mechanisms through which ghrelin's orexigenic effects could be mediated. On page 5 (paragraph 2, line 13), we included the sentence: "In fact, in the hypothalamus, ghrelin promotes the expression of the enzyme prolylcarboxypeptidase (PRCR) and therefore the degradation of melanocortin receptor agonist α-melanocyte-stimulating hormone (α-MSH) [53]." Also, on page 6 (paragraph 1, line 2), the sentence is now presented as: "Since the central administration of ghrelin increases the mRNA expression of NPY and AgRP while inhibiting the transcription of POMC and CART, it has been suggested that the orexigenic actions of ghrelin are mediated through the activation of these neurons [29, 44-49, 58]."

COMMENT 4: There is not only evidence that ghrelin levels are altered in hypo- and hyperthyroidism but also vice versa that ghrelin affects the HPT axis. I suggest adding and discussing this information (Kluge M et al. Ghrelin affects the hypothalamus-pituitary-thyroid axis in humans by increasing free thyroxine and decreasing TSH in plasma. Eur J Endocrinol. 2010 Jun;162(6):1059-65.).

RESPONSE 4: As suggested by REVIEWER 1, on page 18 (paragraph 1, line 9), sentences: "The effect of ghrelin on the hypothalamo-pituitary-thyroid (HPT) axis was also investigated in healthy participants. In contrast to the results obtained in patients who underwent hyper- or hypothyroid normalization, the administration of AG (50 µg) directly increased free T4 while reducing thyroid stimulating hormone (TSH) concentrations in the circulation [146]. This suggests that the thyroid status does not influence the inhibitory effect of insulin on ghrelin secretion; however ghrelin treatment could directly regulate thyroid functions." were included.

REVIEWER 2

COMMENT 1: The manuscript is well-written and well composed covering most of the relevant literature in the field. It is, however, relevant also to take the clinical study by Vestergaard et al EJE 2005 153 545-549 into consideration when discussing the effect of insulin sensitivity on total ghrelin levels (manuscript page 16 last paragraph), because they showed that pharmacologically reversal of insulin resistance resulted in a reduction of total ghrelin levels in fasting individuals.

RESPONSE 1: As suggested by REVIEWER 2, we included the sentence (page 16, paragraph 3, line 6): "Also, under the euglycemic/hyperinsulinemic condition, total ghrelin levels were further reduced by the co-administration with GH and an inhibitor of hormone-sensitive lipase activity in GH-deficient patients [137]."