Format for ANSWERING REVIEWERS

December 27, 2014

Dear Editor Of World Journal of Experimental Medicine

Please find enclosed the edited manuscript in Word format (ESPS Manuscript NO: 14249)

Title: *"Mood disorders: a potential link between ghrelin and leptin on human body?"*

Author: *Greta Wozniak, Stalo Zarouna and Anastasia I. Papachristou*

Name of Journal: *World Journal of Experimental Medicine*

ESPS Manuscript NO: 14249
We were pleased to know that our manuscript was rated as potentially acceptable for publication in your Journal. Based on the instructions provided in your letter, we made all the corrections you asked for.

The manuscript has been improved according to the suggestions of reviewers:
1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

1. First Reviewer
   Although leptin and ghrelin have hormones have a key role in energy balance, considering the multiple factors that are contributing in the development of mood disorders, why did the author emphasize the hormone? 2 .In this review, the author described Leptin's role in mood regulation and ghrelin role in mood regulation. They did not describe the interaction leptin and ghrelin in mood regulation. 3. The topic is interesting, however, the evidence from different studies on the association between mood disorders and the two hormones is controversial. It would be better discuss the point in greater detail. **Minor In the abstract, the author described leptin is an adipocyte-secreted hormone discovered in 1950. - 1994?**

Answer

Leptin receptors are expressed not only in the hypothalamus but also in other brain regions, particularly in the hippocampus. Thus some leptin receptors in the brain are classified as central (hypothalamic) and some as peripheral (non-hypothalamic).
Deficiency of leptin has been shown to alter brain proteins and neuronal functions of obese mice which can be restored by leptin injection.
In humans, low circulating plasma leptin has been associated with cognitive changes associated with mood disorders. **The existence of a hormone regulating hunger and energy expenditure was hypothesized based on studies of mutant obese mice that arose at random within a mouse colony at the Jackson Laboratory in 1950 (in abstract we filed this year).** Mice homozygous for the ob mutation (ob/ob) ate voraciously and were massively obese. In the 1960s, a second mutation causing obesity and a similar phenotype was identified by Douglas Coleman, also at the Jackson Laboratory, and was named diabetes (db), as both ob/ob and db/db were obese. **Rudolph Leibel and Jeffrey M. Friedman**

reported the mapping of the ob gene in 1994

2. Second Reviewer

The article by Greta Wozniak and colleagues reviews the link between leptin / ghrelin and mood disorders. Neuroendocrinology is an evolving field and our knowledge about CNS functions of "gut peptides" is rapidly increasing. The topic is relevant and might be of interest to the readership of the World Journal of Experimental Medicine. However, the selection of references is erratic and the authors cite a lot of secondary literature instead of original work. A revised version of the manuscript (structured, more primary literature) might be suitable for publication. **Minor comments:** - There was no cover page / abstract. - The authors should distinguish between acyl and desacyl ghrelin**. (We wrote already in the txt about AG)** - The authors might want to include obestatin (same precursor peptide) in their review. - Language needs to be checked by a native speaker. - Abbreviations in Table 1 need to be explained in the legend. - Table 2: "Schmid" instead of "Schimd" - Inclusion of cross references (to the reference list) in Table 1 and 2

Answer
Ghrelin is a 28-aa peptide hormone that is expressed at highest levels in the stomach and pancreas. Ghrelin is acylated [acyl ghrelin (AG)] by ghrelin O-acyl transferase (GOAT) in the stomach and 10–20% of circulating ghrelin exists in this form. Acylation is required for ghrelin to activate its receptor, the growth hormone secretagogue receptor (GHSR). AG activates GHSR-expressing neurons of the hypothalamus to stimulate food intake and secretion of growth hormone (GH).
Des-acyl ghrelin (DAG) is one of the three pre-proghrelin gene-encoded peptides. Compared with ghrelin and obestatin, it has not received the attention it deserves. DAG has long been considered an inert degradation product of acyl ghrelin (AG). Recent evidence, however, indicates that DAG behaves like a separate hormone. DAG can act together with AG, can antagonize AG, and seems to have AG-independent effects. Therefore, it is believed that DAG must activate its own receptor and that it may also interact with AG at this receptor. Of potential clinical importance is that an increasing number of studies suggest that DAG might be a functional inhibitor of ghrelin and that DAG can suppress ghrelin levels in humans. DAG works completely independently of ghrelin. ***(In our review article used only acyl ghrelin (AG)]***

Abbreviations, references and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Experimental Medicine*

Sincerely yours,

Wozniak Greta

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