Reviewer's report

Title: Xylazine-induced Reduction of Tissue Sensitivity to Insulin Leads to Acute Hyperglycemia in Diabetic and Non-diabetic Monkeys

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Reviewer: Shiro Kurusu

Reviewer's report:

This study tested the impact of the exposure of monkeys to xylazine on blood glucose and its regulatory system. Authors confirmed a transient stimulating effect in this non-human primate as well as in many other species demonstrated before. On the comparative study, especially veterinary clinician and researchers, points of view, the findings may increase our understanding of anesthetics’ side effects and would cause the attention in the field of nutritional endocrinology and metabolism. However, the potential issue about how xyladine increases blood glucose is not resolved and well accounted for. The general (non-metabolic and endocrine) impacts of increased glucose seem limited in clinics and human drug-users though authors claimed some in the discussion.

Major revisions
1) The authors concluded that tissue sensitivity to insulin is the most probable cause. But the receptor and signaling caused by this hormone are not investigated at all. This is the core of the mechanistic of this paper and thus needs more investigation.
2) Xylazine-induced side effects including some mortal ones are well described, but the aims of studying blood glucose and using monkeys as experimental models are not sufficiently explained.
3) The comparison of diabetic and non-diabetic animals does not make significant xylazine-dependent difference and thus authors do not present meaningful insight from the data.

Minor revisions
1) There are some grammatical errors throughout the text.
2) Some descriptions in Result section should be moved to M and M section or be deleted.
3) Preparation of diabetic monkeys and evaluation of its pathological status are not described.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being
published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.