OPEN PEER REVIEW REPORT 1

Name of journal: Neural Regeneration Research
Manuscript NO: NRR-D-18-00739
Title: Rapid transport of insulin to the brain following intranasal administration in rats
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Date sent for review: 2018-11-05
Date reviewed: 2018-11-10
Review time: 5 days

COMMENTS TO AUTHORS

This is a manuscript reported the intranasal administration of florescence-tagged human recombinant insulin (rh-Ins) interacts with substantial nigra dopaminergic (and other) neurons in rats. They clearly described the pharmacokinetics of rh-Ins in the brain. In addition, the results of the fluorescent section also showed rh-Ins can also activates Akt/PI3K pathway in DA neurons. This is a well-conducted and well-written article containing interesting results which merit publication. Their results showed that intranasal administration of insulin may be a convincing pathway in stimulation of brain insulin signaling. I have only some minor concerns list below:

1. Table 1: Because it is administered via the nasal cavity, the time and concentration of insulin reaching OB should be the earliest and highest. However, the concentration of striatum and cerebellum is relatively high, and even the concentration of dorsal cortex is very low. Is there a possible explanation for this?
2. Fig. 1: The concentration of the insulator of the brain stem is not high, which seems to be inconsistent with the results of Table 1. This result will be easier to read if the concentrations of rh-Ins can be quantified.
3. Fig. 3: authors stated "most TH+ neurons co-localized with Alex546-Ins"; however, only a few TH+ cells are co-localized with rh-Ins. Actually, most of the TH+ cells are not associated with rh-Ins.
4. Fig. 4: pAkt is indeed a downstream effector of insulin signaling. However, Akt may also be regulated by many other pathways besides insulin. I suggest the tyr-p-IRS may be more specific foe this figure.