OPEN PEER REVIEW REPORT 2

Name of journal: Neural Regeneration Research
Manuscript NO: NRR-D-20-00554
Title: Toward three-dimensional in vitro models to study neurovascular unit functions in health and disease
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Reviewer's country: Russian Federation

COMMENTS TO AUTHORS

This area is of interest for studies of BBB function and organisation. The main weaknesses are lacks of figures and summarising table, section about coupling neuronal activity and BBB function.

The present manuscript covered the recent advantages in creating BBB models useful for in vitro studies. This area can provide perfect tools to pharmacological studies for potential drugs targeting BBB function itself as well as brain cell metabolism and survival. The paper has a nice organization, but there are no figures. I suggest to add figures for explanation of following sections: "Modelling the BBB and NVU using microfluidic platforms" and "Development of in vitro neurodegenerative models". Also, it will be useful to prepare table summarizing all models (advantages and disadvantages) mentioned in the text. Additionally, I suggest to describe in the separate section the detailed mechanism of metabolic coupling between neuronal activity and function of native BBB in rodent, human and model BBB (in vitro).

Abstract
Line 52: "changes in functions" instead of "change to the…"
Line 54: lack of space "couplingbut"
Introduction:
Please, briefly describe the differences between human and rodent NVU? And how specific features of rodent NVU make the rodent models useless.
line 44 - Suggest to correct the sentence: to be coupled with maintaining neuronal excitability and activity
Line 46: please clarify - can other neurotransmitters (like GABA, ACh, HE, Dopa, 5HT, ATP) cause an increase in astrocytic Ca2+ levels, resulting triggering the release of vasoactive substances? Which vasoactive molecules can be released by astrocytes?
Modelling the brain parenchyma using cerebral organoids
Lines 77-78: please specify which structural and physiological features are similar in cerebral organoids and developing human brain.
Line 96: What does it mean "support neuronal calcium signaling"? e.g. activity of Na-Ca exchange, Ca ATPase, Ca buffering, Ca2+ flux via VGCCs, RyR, IP3R…
Line 97: Please describe difference and similarity in myelinization of axons in organoids and in vivo?
Modelling the BBB and NVU using microfluidic platforms
Please could you compare hemodynamic parameters as well as permeability for various ions and compounds (Na, K, Ca, Cl, HCO3, glucose, fatty acids, sterols) of native and model BBB?