Manipulation of BDNF causes the overshoot-and-decline effect in DG after the recovery from sleep deprivation

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ABSTRACT

This paper investigates the relationship between the neurogenesis of the dentate gyrus (DG) under sleep deprivation and brain-derived neurotrophic factors (BDNF). The study focuses on DG because it is a critical part of memory formation and is easily affected by neurodegeneration. The paper proposes that BDNF will affect controlling the overshoot and its decline in the period of sleep deprivation and recovery. This study contains two experiments to test this hypothesis. In experiment one, TrkB inhibitors are used to manipulate the amount of BDNF to test its function. In experiment two, Erk5/TrkB inhibitors are used during recovery to test what Bcl2 does to the overshoot. In the future, this finding could potentially be part of the method used to treat neurodegeneration diseases like Alzheimer's.

Keywords: Neurogenesis, BDNF/TrkB pathway, Erk5 inhibitors

1. INTRODUCTION

In recent days, most people have suffered from passive sleep deprivation due to massive workloads or some other reasons. It is known that sleep loss will induce a series of mental and physical dysfunctions, but how exactly will it impact our brain, especially the function of neurogenesis in the dentate gyrus?DG is part of the brain that helps form memories and is also where neurodegeneration happens and causes diseases.[1][9] First, we learned that all experiments and studies are performed in the dentate gyrus. Long-term sleep deprivations could inhibit adult neurogenesis in DG by elevating a stress hormone level, glucocorticoids.[2][11] Furthermore, through the Journal Club paper, we gain two requisite results to proceed with our hypothesis: there is a neurogenesis overshoot after a 1-week recovery from 72-hour sleep deprivation; Glucocorticoids do not affect suppressing the overshoot.[12] Therefore, our question arises – can we control the overshoot? Since the CORT level cannot slow down the overshoot, there must be something else that can influence the extent of the overshoot. Since BDNF is a main factor in adult hippocampal neurogenesis, it is possible that BDNF also manipulates the overshoot. [3][10] Thus, we have our hypothesis that BDNF can control the overshoot-and-decline effect in this specific sleep deprivation experiment. Nowadays, Alzheimer's is one of the leading diseases among older people and is even starting to affect younger populations. Most importantly, there is no cure for this, and the only thing doctors can do is slow down the degeneration process, which means the consequence will arrive only in a matter of time. If the hypothesis is proven, we can somehow facilitate this sleep deprivation technique to treat different neurological degeneration diseases, including Alzheimer's and Parkinson's, etc.[10][14][15]

2. LITERATURE REVIEW

To fully develop this question/hypothesis, we have constructed two experiments to verify it. First, we will inhibit BDNF through TrkB inhibitors to see if the overshoot changes/exists. [6] Second, we will manipulate the BDNF level during the recovery period through Erk5/TrkB inhibitors to see if Bcl2 sustains/further declines the overshoot. BDNF was found to be a senescence-associated secretory phenotype (SASP) factor that controls the viability of senescent cells, particularly by inhibiting apoptosis.[3][17] However, it does not control apoptosis directly; several pathways are included in this process. The first one is the BDNF-TrkB pathway. It contains three factors: BDNF, TrkB, and Erk5. In this scenario, TrkB stands for tropomyosin-related kinase receptor type B. BDNF binds to TrkB receptors to modulate neuron development, including survival, plasticity, and differentiation. Erk5 is downstream of the BDNF-TrkB pathway, and then it activates Bcl2, which is a protein that can mediate apoptosis.[3][10] The second one is the MAPK pathway. It is a signal pathway that consists of multiple proteins and regulates cell proliferation and death. Erk5 is the last protein that has been activated, enters the nucleus, and further activates the Bcl2 family proteins.[13][17][8][18] Figure 1 will introduce the mind map throughout the research and experiments.

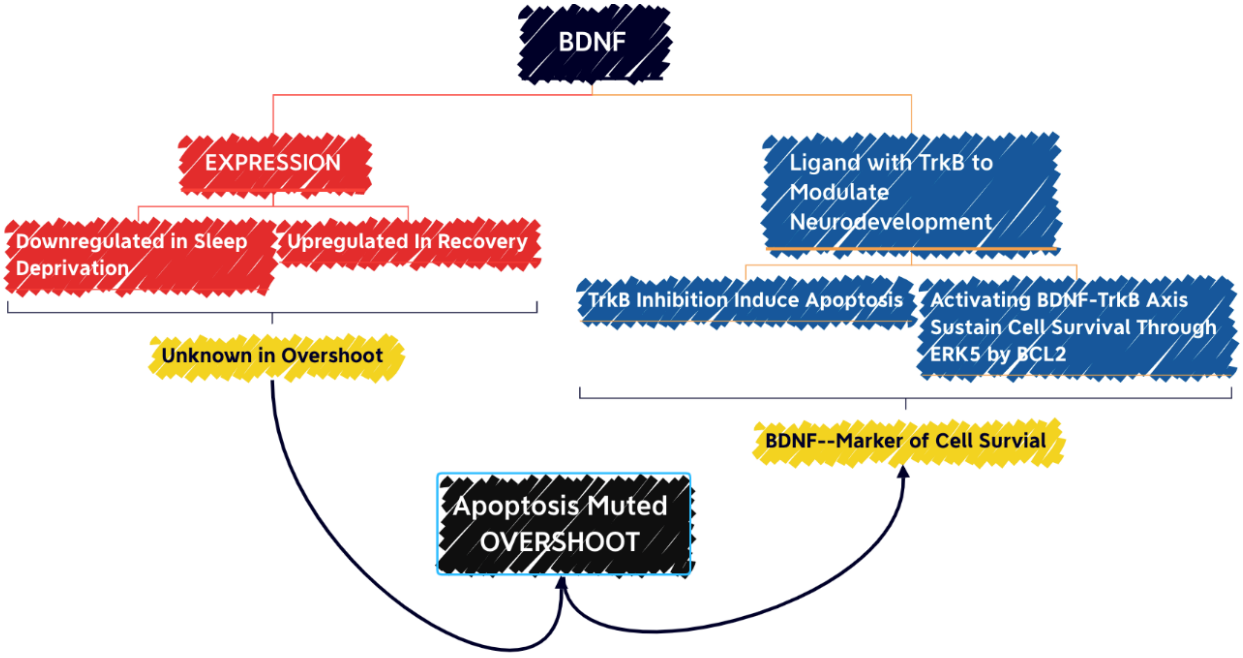

Fig. 1 Mind map of the thinking processes and experiment ideas

In the first experiment, we will introduce TrkB inhibitors before the recovery period to mediate the level of BDNF and further induce apoptosis. We used the same cage control and 72h sleep deprivation for the control group. If the experiment group has no overshoot or a significantly smaller amount of BrdU labeled cells observed, BDNF plays a role in the overshoot.[16] This result will lead us to the second experiment. Next, we will introduce Erk5 or TrKB inhibitors to see if we can upregulate or downregulate the overshoot by silence or activate apoptosis. Our focus is on experiment 2 because if verified, we can propose further research or even use it as a treatment.

3. EXPERIMENTS AND RESULTS

In both experiments, we will need Sprague-Dawley rats mainly because they are mostly calm and easy to handle. Also, some human disease models could be easily performed. We will use Larotrectinib as TrkB inhibitors and BrdU for labeling new cells.[5]

3.1 The experiment 1

Our general idea is to determine if BDNF is a factor in controlling adult neurogenesis. We will have four groups: cage control (CC), Small Platform sleep deprivation (SP), CC with TrkB inhibitor, and SP with TrkB inhibitor. The advantage is that the results could directly reflect the TrkB inhibitor's viability (Larotrectinib) viability and whether BDNF level influences neurogenesis/the overshoot. The disadvantage is that the dosage of Larotrectinib remains unknown, so we must handle it carefully. CC receives no sleep deprivation or treatment; SP keeps rats from falling asleep because they need to keep their balance over a disk, or they will fall into the water. We treat all SP groups with 72 hours of sleep deprivation, and CC receives nothing. After the platform exposure, we inject BrdU and examine the brain in 12-hour, 1-week, and 3-week time intervals. The level of the overshoot and the process of neurogenesis is determined by the number of BrdU-labeled cells since it only labels newly generated neurons. Fig. 2 is a graph that shows the potential outcomes.

3.2 The experiment 2

The basic setups and indications are the same as the experiment one. We focus on Bcl2 and its role in affecting the overshoot pattern. Eventually, we want to verify that Bcl2 (BDNF downstream) can manipulate the overshoot by controlling apoptosis. We have three groups: CC, SP, and SP with Erk5 (Bcl2 promotion). The advantage is that based on the results, we can directly tell if Bcl2 succeeds or fails to control the overshoot. The disadvantage is that it is hard to activate Bcl2 directly -- we have to control the upstream of the pathway to activate it. In this case, SP is present with excess Erk5, and the rest of the steps are the same as the previous experiment except for the examination time – we examine the brains 6hr, 1wk, and 2wk *after the recovery*. Fig. 3 is a graph I made that shows the potential outcomes. If the experimental results are similar to our predictions, we can say that BDNF can control the overshoot-and-decline effect in this specific sleep deprivation experiment. If so, we will modify this experiment's next step, making it more suitable

for treatment since 72-hour sleep deprivation is not reasonable. Since we did not find a viable Bcl2 activator, we manipulated its upstream (BDNF/Erk5) to get the same result. Finally, because BDNF eventually promotes and sustains the overshoot, we can use it to prevent or counter neurodegeneration diseases. Of course, many problems and aspects still have not been fully discussed yet, such as the dosage used and its performance on human models.

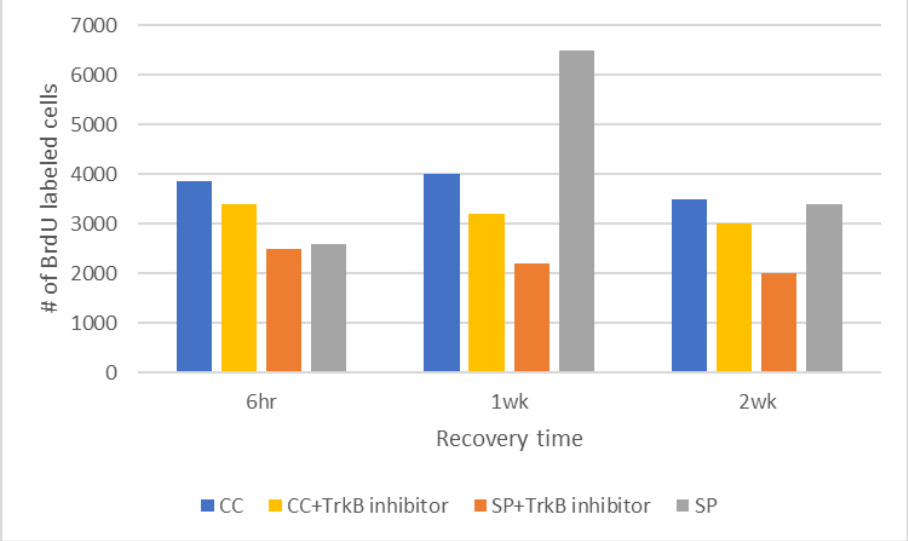

Fig. 2 Expected results from the experiment 1

The x-axis is the recovery time, and the y-axis is the # of BrdU cells labeled. Four groups are shown in the graph: CC, CC+TrkB inhibitor, SP+TrkB inhibitor, and SP. When SP and TrkB inhibitors are present, the number of cells does not increase or overshoot since BDNF is absent. It means that BDNF is effective in controlling neurogenesis or the overshoot process.

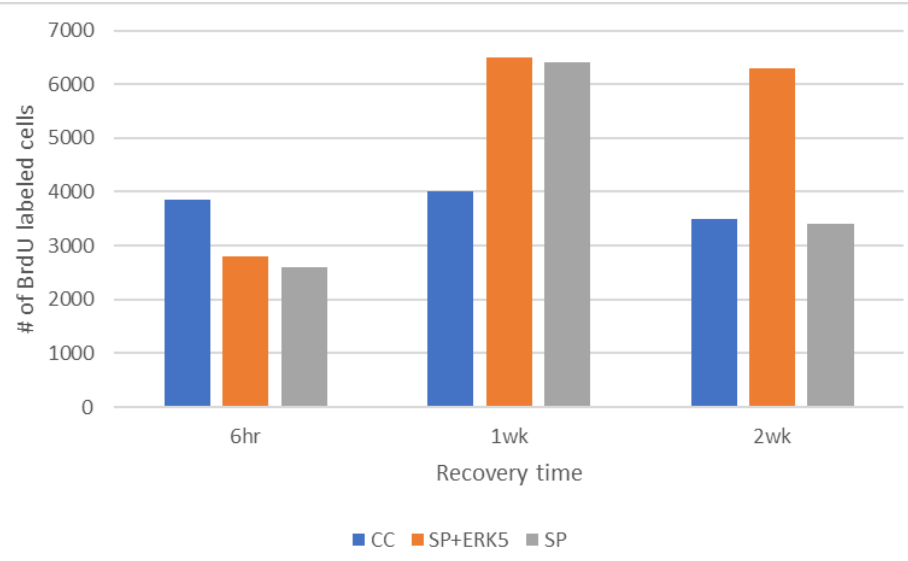

Fig. 3 Expected results from the experiment 2

The x-axis is the recovery time, and the y-axis is the # of BrdU-labeled cells. Three groups are shown in the graph: CC, SP+Erk5, and SP. When SP and Erk5 are both present, after 1wk of recovery, there is an overshoot, which is sustained 1wk after. It means that excess Erk5 will activate Bcl2 and further hinder apoptosis.

3.3 Timetable

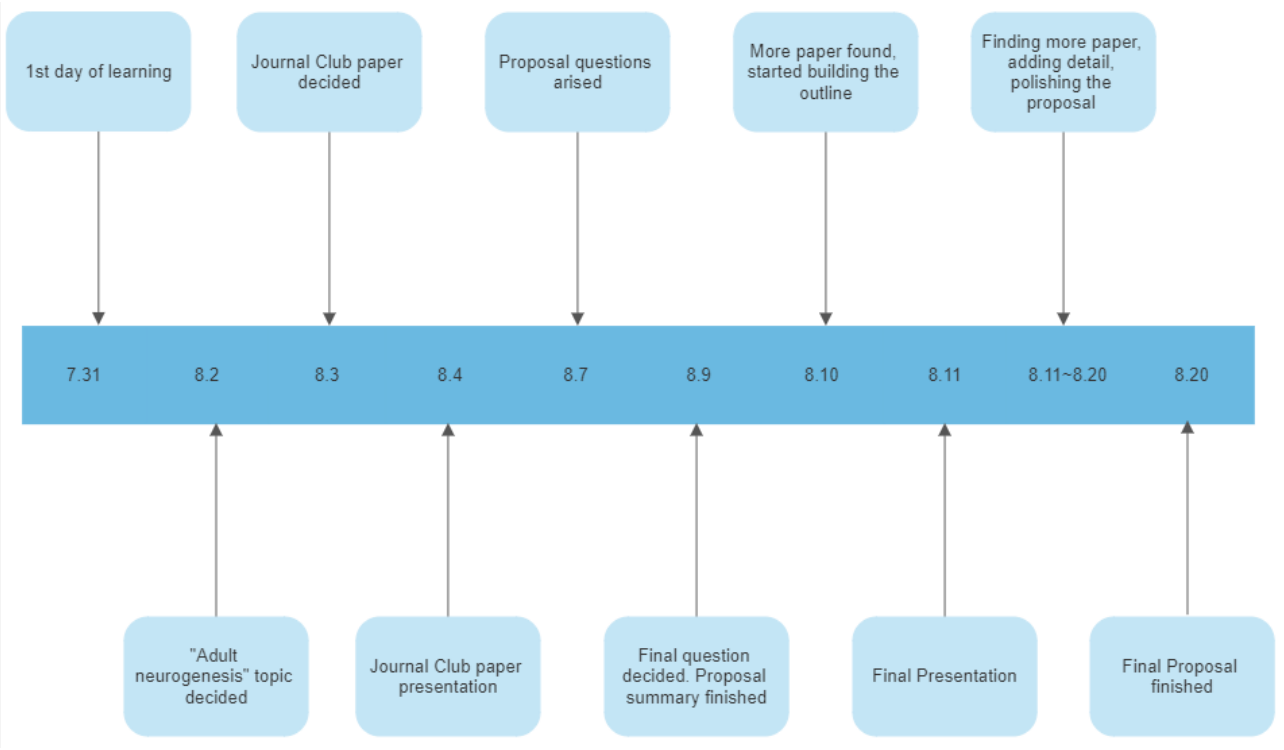

Fig.4 Timetable of the whole working period

(Amaral et al., 2007; Anacker et al., 2018; Anerillas et al., 2022; Boldrini et al., 2018; Brower et al., 2015; Federman & McDermott, 2019, 2019; Hairston et al., 2004; Hardwick & Soane, 2013; Hill et al., 2015; Hung et al., 2002; Jin, 2020; Ming & Song, 2011; Mirescu et al., 2006; Morrison, 2012; Poon et al., 2013; Sung et al., 2020; Wojtowicz & Kee, 2006; Yue & López, 2020; Zhang et al., 2020)

4. CONCLUSION

In conclusion, this paper provides a possible relationship between adult neurogenesis in the dentate gyrus under sleep deprivation and the function of BDNF. Several pathways were included in the procedure of these experiments, and by up or downregulating some of the factors, this series of experiments could find out how exactly BDNF does and affects the pathway that leads to neurogenesis. The results could be promising in understanding the impact of sleep loss on the brain and provide a plausible treatment for different neurodegeneration diseases.

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