Brain-derived neurotrophic factor after long term stress exposure of depressed mice: systematic literature review

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ABSTRACT
BDNF plays an important role in the management of chronic depression. Adequate levels of BDNF trigger the formation of new synapses in the brain, thereby improving symptoms of depression, which is a mechanism known as neuroplasticity. BDNF has a central role in brain cell development due to its ability to protect brain cells from a wide variety of pathological conditions. BDNF also affects the number of glial cells and indicates a good nerve synapse function. At some point, long-term exposure to stress, which causes chronic depression, actually stops BDNF from working itself, resulting in decreased neuroplasticity of the brain. This paper aims to analyze long-term stress exposure on BDNF levels in depressed mice. This systematic literature review uses the PubMed and Google Scholar databases for the period 2015-2020. A total of 322 articles at the beginning of identification, and those that met the inclusion criteria in this study were six articles. Data extraction results showed that the depression condition caused by various stressors resulted in BDNF levels in the hippocampus decreased significantly by p≤0.005. Based on the literature study, the BDFN levels in the brain in depressive conditions

Keywords:
Chronic depression, Stress, Brain-Derived Neurotrophic Factor, BDNF

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INTRODUCTION

Depression is a mental condition that causes individuals to experience cognitive deficits, both temporary and permanent (Jeon and Kim, 2016). Short exposure to stress can lead to acute depression where there is a reversible cognitive deficit, while long-term stress exposure can lead to chronic depression characterized by permanent cognitive deficits. Despite being declared remission from depression, some individuals still show sequelae in the form of anhedonia, and this anhedonia is closely related to permanent cognitive deficits to suicidal ideation (Winer et al., 2014; Hawes et al., 2018).

Several theories regarding the pathogenesis of depression are the monoamine hypothesis, neuroendocrine mechanisms, neuroimmunity, cytokines, and neuropsychiatric (Jeon and Kim, 2016; Yang et al., 2020). The monoamine hypothesis states that low serotonin (5-HT2) neurotransmitters cause depression in the postsynaptic cleft. This condition is reversible, but in chronic stress, there is the pruning of nerve cell dendrites so that the depression condition becomes irreversible. Recent findings in experimental animals show that serotonergic preparations are needed to increase serotonin levels in the synaptic cleft so that it triggers the formation of new dendrites to make depression conditions reversible (Massart, Mongeau, and Lanfumey, 2012). The results differ when these preparations cause resistance in cases of chronic depression (Diaz et al., 2016) and increase the risk of uncomfortable and even fatal side effects in long-term use.

Continuously low levels of serotonin (5-HT2) in the long run can activate the HPA (Hypothalamic Pituitary Adrenal) axis, which increases glucocorticoid (cortisol) then causes Ca2+ influx to increase. This activation of Ca2+ influx stimulates the N-methyl D-aspartate (NMDA) receptor from glutamate through the 5-HT2 receptor so that the Brain-Derived Neurotropic Factor (BDNF) levels will decrease (Tunisya, Maria Maramis, and Kusuma, 2010). Decreased BDNF will contribute to the pruning of nerve cell dendrites which makes depression irreversible even with extensive treatment.

BDNF is a linking variable between clinical depression and serotonin levels in the brain. BDNF has a central role in brain cell development due to its ability to protect brain cells from a wide variety of pathological conditions, including depression (Stadelmann et al., 2002). In addition to nerve cells, BDNF affects the number of glial cells (Sanyal et al., 2013), while the increase in the number of glial cells indicates a good nerve synapse function (Verkhratsky, 2010).

METHODS

This study used a review method with the PRISMA method. A literature search was using PubMed and Google Scholar in English. According to PICO, the search criteria are based on the inclusion criteria; namely, the population is experimental animals with intervention in the form of all methods that can make the animals become depressed, the comparison is control animals, and the desired result is BDNF.

The search results with keywords (Brain-Derived Neurotropic Factor OR BDNF) AND Stress AND Chronic Depression AND Experimental Study found 322 articles. After conducting a review that met the inclusion criteria, there were six articles.

DATA EXTRACTION

Several data were extracted from the six articles included in the inclusion criteria, including research title, researcher, year, research design, research sample, intervention, random, parameters studied, and research results.
There are no definite data on the incidence of diabetes insipidus in patients with traumatic severe brain injury. About 1.5 million people experience severe brain injury in the United States. There are more than 50,000 deaths and 500,000 incidents of permanent neurological sequelae. About 85% of mortality occurs in the first 2 weeks after the injury. One complication of brain injury requires complicated treatment. Therefore, adequate rehydration and administration of desmopressin, the patient's clinical and hemodynamic state was normal. In this case report, a male, 45 years old, was taken to the Emergency Installation (IRD) after experiencing a traffic accident 12 hours before being hospitalized. After surgery, the signs of diabetes insipidus were presented by polyuria of 300cc/hour urine production and 149mmol/hour hypernatremia, although the immediate administration of desmopressin, the patient's clinical and hemodynamic state was normal. The article is ready to be analyzed (n=6).

Figure 1. PRISMA Flowchart
Diabetes insipidus, brain injury, and 500,000 incidents of neurologically permanent disorders. About 85% of mortality occurs in the first 2 weeks after the injury. Traumatic severe brain injury is a fatal injury, with a mortality rate of up to 50%. About 1.5 million people experience severe brain injury in the United States. There are more than 50,000 deaths and 500,000 incidents of severe brain injury in Indonesia. Patients with traumatic severe brain injury require complicated treatment. Therefore, the authors are presenting a case report of diabetes insipidus in a patient with traumatic severe brain injury.

CASE REPORT

A year old patient, male, presented to the Emergency Installation (IRD) after experiencing a traffic accident 12 hours before being hospitalized. After the patient arrived in the resuscitation room of Dr. RSUD Tuban, the patient was intubated using ETT No. 7 and the lip border was in the supine position. The patient was prepared to be taken to the emergency installation. The patient has attached a collar brace at the neck and has oxygen saturation of 92% using an oxygen mask. The patient was alert and the level of consciousness was normal. The patient has the following findings:

- Increased heart rate
- Hypotension
- Polyuria
- Polydipsia
- Hypernatremia
- Desmopressin
- ICU

The patient's clinical and hemodynamic examination of anisocoria round pupils 4/3, hypertension, hypovolemia, and hypotension. The right parietooccipital wound with 2 cm length was stapled and closed with mattress and skin glue. The patient was transferred to the Emergency Installation. The patient was treated with adequate hypovolemic, polyuric, and hypernatremic corrections in the ICU. The patient's condition was stable and there was no improvement in symptoms. The patient was treated with desmopressin. The patient's clinical and hemodynamic examination was stable, but the patient's polyuria and polydipsia was not improved. The patient was treated with desmopressin. The patient's clinical and hemodynamic examination showed no improvement. The patient passed away in the fifth day.

ABSTRAK

Diabetes insipidus, cedera otak, dan 500,000 insiden gangguan neurologis permanen. Sekitar 85% kematian terjadi dalam 2 minggu. Cedera otak berat traumatis adalah cedera fatal, dengan tingkat kematian hingga 50%. Sekitar 1,5 juta orang mengalami cedera otak berat di Amerika Serikat. Terdapat lebih dari 50,000 kematian dan 500,000 insiden gangguan neurologis permanen. One of the complications of a severe brain injury is diabetes insipidus. Diabetes insipidus is a disease caused by the lower production, release, or action of antidiuretic hormone (ADH). Kidney abnormalities are marked by the unresponsiveness of renal tubules to ADH, causing an increase in urine production and a decrease in urine concentration. There is no definitive data on the incidence of diabetes insipidus.
### Case Report

Cedera otak berat traumatis adalah cedera fatal, dengan tingkat kematian hingga 50%. Sekitar 1,5 juta orang mengalami cedera otak berat di Amerika Serikat. Terdapat lebih dari 50,000 kematian dan 500,000 insiden gangguan neurologis permanen. Sekitar 85% kematian terjadi dalam 2 minggu setelah cedera. Salah satu komplikasi dari cedera otak yang parah adalah diabetes insipidus.

### ABSTRACT

Diabetes insipidus, brain injury, hypernatremia, desmopressin, ICU

### KEYWORDS

Tidak ada data pasti tentang kejadian diabetes insipidus pada pasien dengan cedera otak traumatis. Meningkatkan kesadaran dan edukasi pasien dan masyarakat tentang diabetes insipidus sangat penting. Perawatan diabetes insipidus dalam kasus ini melibatkan perbaikan hipernatremia, administrasi desmopressin, rehidrasi hipovolemi, dan polyuria.

### RESULTS

- Weight of male, female mice and treatment
- BDNF control, CUMS, and SS
- <control (p <0.001)

### Table 1

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<td>Decreased BDNF in female but not male rats after exposure to stress: a sex-sensitive rat model of stress?</td>
<td>Experimental study</td>
<td>Eighty male and female rats aged 51-55 days</td>
<td>- Mice are placed in cages with hardwood plinths, - Rodent food is available (Harlan Teklad 4% Mouse / Rat Diet 7001), and water - Temperature is maintained at 23 °C with 40% relative humidity with a 12-hour reverse light cycle (05.00-17.00 dark) - Male and female rats separated divided into three groups (no stress, CUMS, and SS) CUMS, bright, fluorescent, and overhead lighting maintained for 20 minutes every day for 14 days. - On the first day, a stressor in the form of a cotton ball soaked in 10 mL of urine is placed in each rat cage in clear plastic (29x 18x12cm) for 20 minutes. - The next day the first 10 minutes of the cotton ball stressor, then the additional stressors vary (e.g.,</td>
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### REFERENCES

1. Weisbrod et al., 2019
2. Gage, 2000

### ACKNOWLEDGEMENTS

The authors would like to thank the staff of the Anesthesiology and Intensive Care Unit of RSUD Dr. Soetomo, Medical Faculty of Airlangga University for their support and assistance in conducting this research.
ABSTRACT

One of the complications of severe brain injury is diabetes insipidus. In cases of brain injury, diabetes insipidus requires complicated treatment. Diabetes insipidus in patients with traumatic severe brain injury of Indonesia so far has no definitive data on the incidence of diabetes insipidus. There are no definitive data on the incidence of diabetes insipidus in patients with traumatic severe brain injury in the United States. In the report of this case, a 45-year-old man was brought to the Emergency Room (IRD) after the accident occurred. First aid was given in the field. After the patient was immediately suctioned and oxygenated with a mask of 5 liters per minute, blood pressure was 110/75 mmHg (MAP 86), pulse 120 times per minute. Tip of the extremities were warm, dry, and red with an examination of capillary refill time <2 seconds. The right parietooccipital hematoma was found. The patient was prepared to be taken to the operating room. The patient was attached to a collar brace at the neck. On the second day of treatment in the Intensive Care Unit (ICU), the signs of diabetes insipidus were presented by polyuria of 300 cc/hour urine production and 149 mmol/l hypernatremia. After 2 days on days 18 to 20, OsmCIS was considered. On days 19 and 20, the patient was on 30% PCV mode with RR 16, PC 15, trigger 2, I:E 1:2, FiO2 50%.

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Tidak ada data pasti tentang kejadian diabetes insipidus pada pasien dengan cedera otak traumatis pertama setelah cedera. Salah satu komplikasi dari cedera otak yang parah adalah diabetes insipidus.

Cedera otak berat traumatis adalah cedera fatal, dengan tingkat kematian hingga 50%. Sekitar 1,5 juta orang mengalami cedera otak berat di Amerika Serikat. Terdapat lebih dari 50.000 kematian. About 85% of mortality are more than 50,000 deaths and 500,000 incidents of permanent neurological sequelae. About 85% of mortality occurred within 2 weeks.

ABSTRAK

Diabetes insipidus in patients with traumatic severe brain injury

ABSTRACT

Diabetes insipidus in traumatic severe brain injury requires complicated treatment. Therefore, diabetes insipidus treatment is an important management for traumatic severe brain injury cases. Diabetes insipidus in cases of traumatic severe brain injury is diabetes insipidus. There are no definitive data on the incidence of diabetes insipidus in patients with traumatic severe brain injury.

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Keywords:
Hypernatremia, Desmopressin, ICU

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| 3  | BDNF prevents central oxidative damage in a chronic unpredictable mild stress model: the possible role of PRDX-1 in anhedonic behavior | (Scotton et al., 2019) | Experimental study | Thirty-five male Wistar mice (45 days old, 220-250g). | Rats were housed alone in standard polycarbonate rat cages under standard environmental conditions, a 12 hour light / dark cycle (lights on between 7.00 am and 19.00 am), controlled temperature (22 ± 1°C), and food and water available. | No data | - Oxidative damage  
- Total antioxidant capacity  
- BDNF Level | BDNF Intervention in hippocampus> control (p = 0.001) |
Tidak ada data pasti tentang kejadian diabetes insipidus pada pasien dengan cedera otak traumatis pertama setelah cedera. Salah satu komplikasi dari cedera otak yang parah adalah diabetes insipidus. Traumatis severe brain injury is a fatal injury, with a mortality rate of up to 50%. About 85% of mortality occurs in the first 2 weeks after the injury, which exhibits sequelae (Agha and Thompson, 2006).

Cedera otak berat traumatis adalah cedera fatal, dengan tingkat kematian hingga 50%. Sekitar 85% kematian terjadi dalam 2 minggu, 1,5 juta orang mengalami cedera otak berat di Amerika Serikat. Terdapat lebih dari 50,000 kematian dan 500,000 insiden gangguan neurologis permanen. About 1,5 million people with severe brain injury in the United States have more than 50,000 deaths and 500,000 permanent neurological sequelae.

In the second day after injury, the second day was numbed where the patient improved and put in a sitting position. The patient was prepared to be brought to the trauma room with Jackson Reese 10 liters per minute, a two-lane chest to vacuum and oxygenate with immediate suction and oxygenation with hematoma was found. The patient was attached to collar brace at the neck and immediate examination was performed. The hypernatremia, even though the immediate administration of desmopressin was improper. Therefore, the authors are currently improving the treatment of diabetes insipidus.

The patient had attached a collar brace at the neck and immediate examination was performed. The hypernatremia, even though the immediate administration of desmopressin was improper. Therefore, the authors are currently improving the treatment of diabetes insipidus. Diabetes insipidus in cases of brain injury requires complicated treatment. Therefore, the authors are currently improving the treatment of diabetes insipidus.
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- SPT After two weeks of exposure to water and 1% sucrose solution in eight basic tests, which are carried out twice a week.  
- After 12 hours of lack of food and water, two bottles, one with a 1% sucrose solution and the other with water for animals for 1 hour. The bottles are weighed before and after the test to evaluate sucrose intake. All analyzes were performed half an hour after the start of the dark cycle. Based on the preference level of sucrose in the final baseline test, animals with an unstable and/or low basal sucrose preference (below 60%) were excluded. The remaining animals were divided into paired control (n = 7) and the CUMS group (n = 16). | No data | - Oxidative damage  
- Total antioxidant capacity  
- BDNF Level                        | BDNF Intervention in hippocampus> control (p = 0.001) |
Diabetes insipidus in patients with traumatic severe brain injury

Case Report

ABSTRACT

Correspondence:

Diabetes insipidus, brain injury, hypovolemia, hypernatremia, desmopressin, ICU

Tidak ada data pasti tentang kejadian diabetes insipidus pada pasien dengan cedera otak traumatis. Secara rata-rata, lebih dari 50.000 insiden gangguan neurologis permanen. Sekitar 85% kematian terjadi dalam 2 minggu pertama. Cedera otak berat traumatis adalah cedera fatal, dengan tingkat kematian hingga 50%. Sekitar 1,5 juta orang mengalami cedera otak berat di Amerika Serikat. Terdapat lebih dari 50.000 kematian dan 500,000 permanent neurological sequelae.

ABSTRACT

Traumatic severe brain injury is a fatal injury, with a mortality rate of more than 50%. In the United States so far, there are more than 50,000 deaths and 500,000 incidents of permanent neurological sequelae. About 85% of mortality occurs in the first 2 weeks after the injury. One complication of severe brain injury is diabetes insipidus. There are no definitive data on the incidence of diabetes insipidus in patients with traumatic severe brain injury so far. In this case report, a male, 45 years old, was taken to the hospital 12 hours after a traffic accident. After arrival in the resuscitation room of Dr. RSUD Soetomo, the patient responded to pain, with a blood pressure of 110/75 mmHg (MAP 86), pulse 120 times per minute, and respiratory rate of 28 breaths per minute. He was intubated using ETT No.7, and the lip border was 21cm. The ventilator used PCV mode with RR 16, PC 15, trigger 2, I:E 1:2, FiO2 50%.

In the case of being handled improperly, it can bring death. Therefore, the authors are interested in discussing the management of diabetes insipidus. Diabetes insipidus in cases of brain injury requires complicated treatment. Therefore, the main treatments for diabetes insipidus in traumatic severe brain injury patients are adequate rehydration and administration of desmopressin. The signs of diabetes insipidus were presented by polyuria of 300 cc/hour urine production and 149 mmol/l Na+. The initial impact of systemic hypotension and the first 2 weeks after the injury, which exhibits hypernatremia, although the immediate administration of desmopressin, the patient's clinical and hemodynamic was not shown any improvements. The patient passed away in the fifth day of treatment in the Intensive Care Unit (ICU). The hypernatremia corrections are the keys to the successful treatment of diabetes insipidus.

The results of the experimental study shows that: 0.7% of the group receiving 2 ml of desmopressin 3-month-old mice were found to have hypernatremia. In the group of 0.7 ml, 2 out of 9 died. In the control group, 7 out of 9 died.

Next Table I

| Parameters Studied | Results
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ABSTRACT

Traumatic severe brain injury is a fatal injury, with a mortality rate of up to 50%. About 1.5 million people experience severe brain injury in the United States. There are more than 50,000 deaths and 500,000 incidents of permanent neurological sequelae. About 85% of mortality occurs in the first 2 weeks after the injury. One complication of severe traumatic brain injury is diabetes insipidus. There is no definitive data on the incidence of diabetes insipidus in cases of severe traumatic brain injury.

The second day, all rats were given EX 50 minutes/day 5 days/week with an intensity of 60-75% maximum oxygen uptake. Each EX session begins with a warm-up for 10 minutes (gradual increase in speed) followed by 30 minutes of EX with 60-75% maximum oxygen intensity and 10 min speed reduced for cooling.

- EX at 09.00 - 12.00
- The physical stress group of mice received 0.5 mA, 1-second leg sting every 30 seconds for 10 minutes, five times a week for one minute.
- Emotional stress rats only looked at physical stress rats.
- A blood sample (2 ml) was taken from the ventral caudal artery of light etherized mice immediately after the first treatment and 12 hours after the last treatment (after two weeks). Blood samples were centrifuged for 10 minutes (3500 rounds) and stored at -20°C.
- BDNF levels were determined using ELISA.

- Calorie Intake
- Weight Loss
- SPT
- BDNF

Results

BDNF chronic stress intervention in hippocampus.
Diabetes insipidus in patients with traumatic severe brain injury

Tidak ada data pasti tentang kejadian diabetes insipidus pada pasien dengan cedera otak traumatis.

Cedera otak berat traumatis adalah cedera fatal, dengan tingkat kematian hingga 50%. Sekitar 1,5 hasta pengalaman tinggi, dengan 85% mortalitas terjadi dalam dua minggu setelah kejadian. One complication from severe brain injury is diabetes insipidus. The incidence of diabetes insipidus in cases of severe brain injury is not yet clear.

INTRODUCTION

Traumatic severe brain injury is a fatal injury, with a mortality rate of up to 50%. About 1.5 hasta pengalaman tinggi, dengan 85% mortalitas terjadi dalam dua minggu setelah kejadian. Approximately 85% of mortality occurs in the first 2 weeks after the injury. One complication from severe brain injury is diabetes insipidus. The incidence of diabetes insipidus in cases of severe brain injury is not yet clear.

Hormone (ADH).

Kidney abnormalities can lead to death when handled improperly. Diabetes insipidus is a disease caused by the lower production, and large amounts of urine (polyuria). There is hypernatremia, although the immediate administration of desmopressin, the patient's clinical and hemodynamic was not shown any improvements. The patient passed away in the fifth day of treatment in the Intensive Care Unit (ICU). The patient is unconscious since the accident occurred. First aid was given in the resuscitation room of Dr. RSUD Soetomo. Responding to pain, with the arrival to the doctor, the patient was taken intubated using ETT No. 7 and the lip border up position. The patient was prepared to be Jackson Reese 10 liters per minute, a two-lane traffic accident 12 hours before being hospitalized. After the operation, the patient showed signs of diabetes insipidus with polyuria production and hypovolemia, desmopressin, the patient's clinical and hemodynamic was not shown any improvements. The patient passed away in the fifth day of treatment in the Intensive Care Unit (ICU).
RESULTS AND DISCUSSION

Based on the six selected articles, all of them used experimental designs. The samples were mice whose ages were not the same; two articles showed the mice were three months old, while the others were eight weeks, 51-55 days, 45 days, and 60 days. In the division of the treatment and control groups in four articles using random and two articles, there is no information about how the groups are divided.

Almost all of the lighting obtained in the study used artificial light. Only the study of Shishkina et al. (2018) uses natural lighting. Lighting is made from 07.00 to 19.00, but in the research of Weisbrod et al. (2019), lighting applies 12 hours backward, which is dark at 05.00-17.00. The lighting in this study is almost all the same, namely bright conditions in the morning. The intervention was given in the morning, where the time in the morning is the time to rest the mice because they are nocturnal animals. This condition creates stressors for mice in addition to the stressors given. In the study of Weisbrod et al. (2019), the lighting is given a different time, namely, at night; this is to show the disruption of circadian rhythms as well as being a stressor.

Various kinds of intervention methods were used to get stressed mice. Some studies have the same form of treatment and are added to other forms of treatment. The intervention method is that rats are placed in a tube, given stress stimuli in the form of heat stress, cold stress, shaken back and forth, tilted cage and humid environment, lack of food and water, hypercaloric diet, day and night reversal, giving cotton balls soaked in urine are placed in the cage, the whistle blew, the lights blinked, the rats restrain their heads and bodies immobilized in the tube, electric shocks, pinching the tails, giving sucrose solutions, swimming, treadmill, and only seeing the group of mice that were treated. The intervention method used in each study was different; there was a single intervention or a combination of other interventions. This can represent a picture of stressors that occur both mild, moderate, and severe (Weisbrod et al., 2019). Mental stress can lead to depression (Qiao et al., 2020).

The duration of treatment in each study was almost the same, namely for two weeks except in Scotton et al. (2019) in mice with CUMS for six weeks, and in the Ghooshchi and Jahromi (2018) study, there was an EX (exercise) group who received 1-2 sessions of recording to show acute conditions and two weeks for chronic. The duration of the intervention showed the duration of the stressor given to the mice, and almost all studies lasted two weeks which could indicate chronic conditions. A meta-analysis showed that the sensitivity of mice varied between species, with the Wistar mouse species showing a more optimal distress response at exposure at the third week, while at exposure beyond that time, these mice tended to be non-responsive, which would have been expected there is an adaptation or even fatigue (Antoniuk et al., 2019).

In this study, besides measuring the ratio of BDNF levels in stressed mice to control mice, it also measured stress by weight, stress with receptor levels glucocorticoids (GR), and stress with monoamine neurotransmitters, neuroendocrine in HPA, stress with oxidative stress, stress with gut microbiotic, antioxidant capacity, tryptophan hydroxylase levels, and calorie intake.

From the study results, five studies were showing a significant reduction in BDNF levels in stressed mice compared to controls, and one study showed an increase in BDNF in stressed mice, namely Scotton et al. (2019) (p = 0.001). Research by Weisbrod et al. (2019) showed that the BDNF results in male and female rats with CUMS stressors were higher than controls, but with SS stress, BDNF levels in female rats decreased significantly (p <0.001).
The study examined in this article demonstrated decreased BDNF levels in stressed mice, although not all studies have shown decreased BDNF results. In chronically stressed mice, there was a decrease in BDNF levels because chronic stress would affect the HPA axis, so that high glucocorticoid levels caused Ca2+ influx to increase. This activation Ca2+ influx stimulates the NMDA receptor from glutamate through the 5-HT2 receptor to decrease the BDNF levels (Tunisya, Maria Maramis, and Kusuma, 2010). The research of Scotton et al. (2019) obtained hypertrophy of the adrenal glands due to stress which should have increased glucocorticoid levels and decreased BDNF, but in fact, there was an increase in BDNF, which was probably a compensatory response to maintaining hippocampal homeostasis.

**CONCLUSION**

Chronic stressors persistently affect the HPA axis which can lead to decreased BDNF levels in the hippocampus.

**ACKNOWLEDGEMENT**

We would like to thank LPPM UNUSA and RISTEKBRIN for providing the opportunity to carry out research.

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