THE EFFECTS OF MELATONIN TREATMENT ON POSTOPERATIVE INDUCED COGNITIVE DYSFUNCTION IN AGED RATS: INVOLVMENT OF OXIDATIVE STRESS, PSD95, and CaMKII

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INTRODUCTION

Postoperative cognitive dysfunction (POCD) is a well-known complication following major surgery in elderly patients (1). Various mechanisms have been proposed for POCD pathophysiology including neuroinflammation, mitochondrial dysfunction, oxidative stress, the blood-brain barrier injury, reduced BDNF levels, and synaptic protein abnormalities (2,3,4,5).

Oxidative stress was considered to impair hippocampal long term potentiation; hence, leading to cognition decline (4). Previous studies have shown that decreased protein levels related to synaptic plasticity is an important mechanism underlying cognitive impairment in aged mice after laparotomy (6). The hippocampus plays a vital role in learning and memory processes(3).

Melatonin, a hormone mainly synthesized in the pineal gland, exerts regulatory roles on seasonal and circadian rhythms. In addition, melatonin contributes to the protection of nuclear and mitochondrial DNA damage (7) and is a highly effective direct free radical scavenger and indirect antioxidant. Melatonin influences hippocampal function, regulates the expression of synaptic proteins, and facilitates short-term memory in rats (8,9).

POCD is associated with prolonged hospitalization, delayed recovery, and increased risk of disability and mortality. There is a need to identify the mechanisms for POCD and develop strategies which can prevent this postoperative complications.

Considering the fact that melatonin acts as protective agent in various cognitive impairment, we aimed to investigate the neuroprotective effects of melatonin on rats with POCD and elucidate the underlying mechanism.

MATERIAL AND METHODS

A total of 40 male Sprague Dawley rats (age, 18 months; weight, 500–600 g) were provided by the Experimental Animal Care Center of Zonguldak Bülent Ecevit University. An abdominal surgery was used to establish a POCD model in aged rats. For this purpose, the intestinal tissue was exteriorized and strongly rubbed for 30 sec.

Rats were randomly divided into four groups:

1) **Control group;**
2) **Melatonin treated control group;**
3) **Surgery group,**
4) **Surgery+ melatonin treated group.**

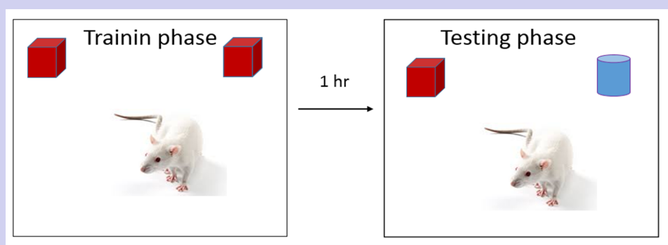
Melatonin (10 mg/kg) were administered intraperitoneally to rats for 7 days. Novel object recognition (NOR) test was performed to assess recognition memory in rats.

Behavioural Test

Novel Object Recognition (NOR) Test

This test included adaptation period, training period, and testing period. In the adaptation period, each rat was placed into an empty behavior box (50 cm long × 50 cm wide × 60 cm high) for 5 min. In the training period, two familiar objects were exhibited to each rat for 5 min. And the spending time in exploring objects was recorded by stopwatch. After one-hour interval, a familiar object (F) and a novel object (N) were placed in the test box, and then rats were allowed to explore the latter one. The testing period lasted 5 min for each rat. Moreover, the spending time in exploring two different objects was recorded. The discrimination index (DI) = [Time N – Time F] / [Time N + Time F], was used to assess learning and memory function of rats.

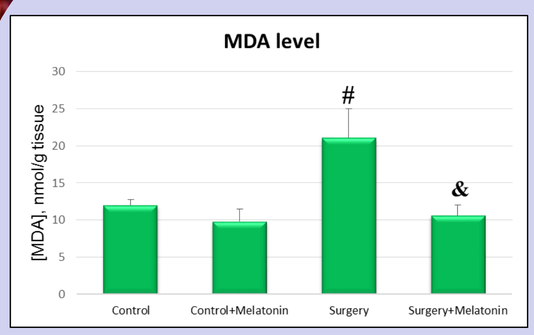
Statistical analyses of data were performed by Kruskal Wallis and Dunn Tests.



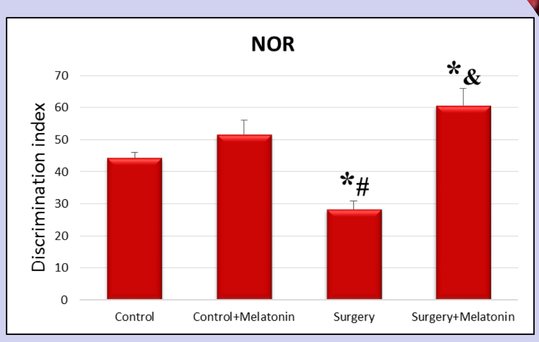
After performing behavioral test on day 7th following the operation, the hippocampal tissues were isolated for the measurement of the levels of Ca2+/calmodulin-dependent protein kinase II (CaMKII) and postsynaptic density 95 (PSD-95) protein by using the ELISA technique according to the manufacturer's protocol.

The content of Malondialdehyde (MDA), an oxidative stress marker, was estimated by spectrophotometric method in the hippocampal tissue as well (10).

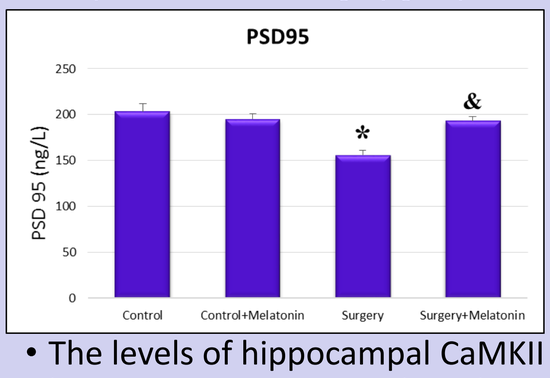
RESULTS

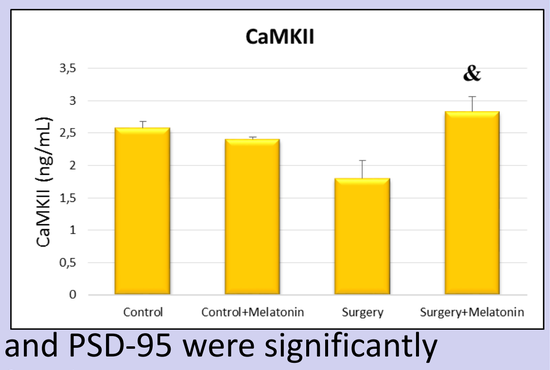


- The level of MDA increased significantly in the surgery group compared to those of melatonin treated control and melatonin treated surgery groups (***P*** < 0.05).
- However, administration of melatonin caused a significant decrease in MDA , compared to that of surgery group.



- DI was significantly diminished in surgery group in comparison with those of control and melatonin treated groups (***P*** < 0.05).
- Melatonin ameliorated learning and memory impairments in the Morris water maze test.





- The levels of hippocampal CaMKII and PSD-95 were significantly lower in surgery group than that of melatonin treated surgery group.
- Melatonin enhanced CaMKII and PSD-95 contents in the hippocampus
- * shows a significant difference between control and surgery;
- # indicates a significant difference between surgery and melatonin treated control group;
- & shows difference between surgery and melatonin treated surgery groups (*, **#, & p<0,05)**

DISCUSSION

In the present study, we have demonstrated that abdominal surgery triggers a neurocognitive decline in aged rats that is associated with brain oxidative stress response and synaptic protein dysregulation.

Melatonin may significantly improve postoperative cognition of aged rats by ameliorating oxidative stress and increasing levels of CaMKII and PSD95 in the hippocampus. These results seem to be consistent with previous studies showing the beneficial effect of melatonin on PSD95 and CaMKII levels in the hippocampus (8,11).

CaMKII is involved in many signaling cascades and thought to be an important mediator of learning and memory.

The decrease in PSD-95 indicates that the strength of the synapse may be aggravated by distorted clustering of N-methyl-D-aspartate receptor (NMDAR). The NMDAR signaling in the hippocampus plays a considerable role in synaptogenesis and synaptic plasticity (11).

CONCLUSION

The results postulate that the treatment with melatonin upregulates both CaMKII and PSD95 in the hippocampus, which may, in turn, improve working memory in rats. Thus, melatonin might be a therapeutic option for the treatment in aged patient suffering from learning and memory impairments following major surgery.

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