News Release

Title

NMDA receptor antagonist prevents cell death in the hippocampal dentate gyrus induced by hyponatremia accompanying adrenal insufficiency in rats

Key Points

- ○Reduced serum [Na+] was associated with apoptosis in the DG in ADX rats.
- ○Impaired synaptic transmission was also observed in the DG in hyponatremic ADX rats
- ○These effects were reversed by therapeutically relevant doses of memantine.

Summary

Associate Professor Yoshihisa Sugimura (Department of Endocrinology and Diabetes), graduate student Hisakazu Izumida (Department of Endocrinology and Diabetes) and their collaborators in Nagoya University Graduate School of Medicine (Dean: Masahide Takahashi, MD, PhD) showed that, using rat models to represent clinical hyponatremia accompanying adrenal insufficiency, reduced serum [Na+] was associated with selective apoptosis in the DG. Nine days after ADX, apoptotic cells were observed in the DG of rats whose serum [Na+] was <125 mEq/L (moderate hyponatremia), but rarely in those whose serum [Na+] was ≥ 125 mEq/L or in normonatremic rats. Although all hyponatremic ADX rats survived following treatment with corticosterone and saline started 7 days after ADX when apoptosis had not yet occurred, selective apoptosis on day 9 was not prevented in moderately hyponatremic rats. Interestingly, treatment with memantine, a noncompetitive NMDAR antagonist, prevented the selective apoptosis in the DG in moderately hyponatremic, ADX rats, and improved electrophysiological dysfunction, including impaired basal synaptic transmission and long-term potentiation at the entorhinal cortex-DG synapses. These results demonstrated that in adrenal insufficient rats, hyponatremia was associated with apoptosis in the DG, and that memantine prevented the apoptosis and improved cell function. Our data imply the importance of assessing the possibility of neurological impairments after treatment with CORT in patients with moderate or severe hyponatremia accompanying adrenal insufficiency and that memantine may represent a beneficial therapeutic strategy to prevent neurological impairments in such patients.

Research Background

Primary adrenal insufficiency is often accompanied by hyponatremia, especially in chronic or severe cases. For example, a case of untreated Addison's disease showed selective cell death of the dentate gyrus (DG) granule cells in the hippocampus. The central nervous system (CNS) pathophysiology of adrenal insufficiency, however, remains to be elucidated. The involvement of hyponatremia (a reduced extracellular [Na+]) in the CNS accompanying adrenal insufficiency is largely unknown. One of the reasons for the lack of such studies is the lack of

appropriate animal models of adrenal insufficiency accompanied by relatively chronic hyponatremia. Although many studies on cell degradation or apoptosis in the hippocampus following bilateral adrenalectomy (ADX) have been reported, animals in those studies were given saline after ADX to avoid decreases in serum [Na+] and death; in those previous studies; adrenalectomized rats without saline administration died several days after ADX. Sloviter et al. reported the selective loss of granule cells in the hippocampal DG of rats that were given free access to food and saline solution for three or four months after ADX.

Research Results

In the present study, the authors developed an animal model of relatively chronic hyponatremia by feeding low sodium or a sodium-free liquid diet that contained sufficient calories and water, instead of administering of saline, following ADX to investigate the pathophysiology of hyponatremia accompanying adrenal insufficiency.

The authors found that reduced serum [Na+] was associated with selective apoptosis in the DG. Nine days after ADX, apoptotic cells were observed in the DG of rats whose serum [Na+] was <125 mEq/L (moderate hyponatremia), but rarely in those whose serum [Na+] was ≥ 125 mEq/L or in normonatremic rats. Although all hyponatremic ADX rats survived following treatment with corticosterone and saline started 7 days after ADX when apoptosis had not yet occurred, selective apoptosis on day 9 was not prevented in moderately hyponatremic rats. Interestingly, treatment with memantine, a noncompetitive NMDAR antagonist, prevented the selective apoptosis in the DG in moderately hyponatremic, ADX rats, and improved electrophysiological dysfunction, including impaired basal synaptic transmission and long-term potentiation at the entorhinal cortex-DG synapses.

Research Summary and Future Perspective

In summary, in adrenal insufficient rats, hyponatremia was associated with apoptosis in the DG, and that memantine prevented the apoptosis and improved cell function. these data imply the importance of assessing the possibility of neurological impairments after treatment with CORT in patients with moderate or severe hyponatremia accompanying adrenal insufficiency and that memantine may represent a beneficial therapeutic strategy to prevent neurological impairments in such patients.

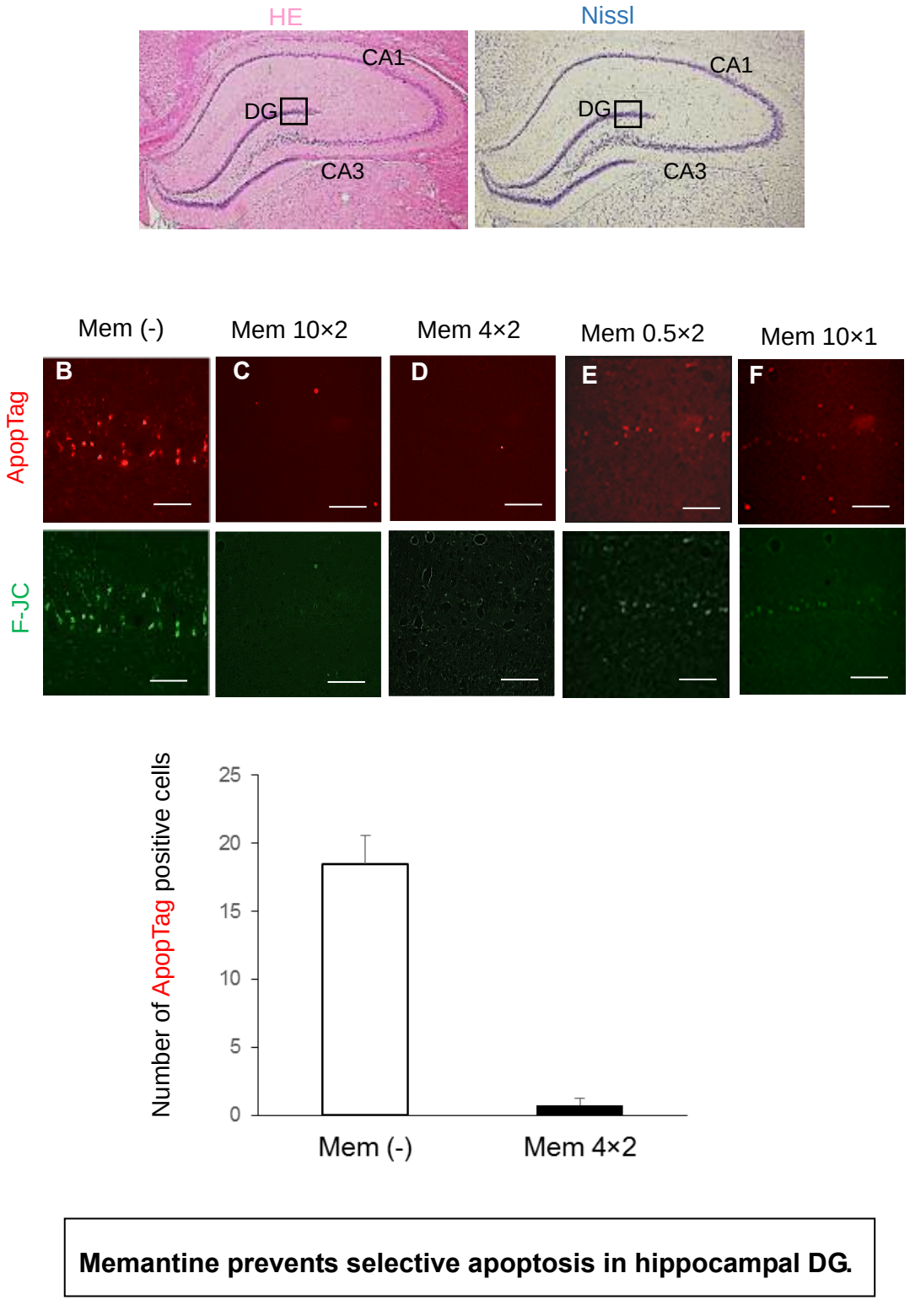
Publication

Izumida H, Takagi H, Fujisawa H, Iwata N, Nakashima K, Takeuchi S, Iwama S, Namba T, Komatu Y, Kaibuchi K, Oiso Y, Arima H, Sugimura Y. NMDA receptor antagonist prevents cell death in the hippocampal dentate gyrus induced by hyponatremia accompanying adrenal insufficiency in rats. *Experimental Neurology,* Aug. 18, 2016. pii: S0014-4886(16)30239-4. doi: 10.1016/j.expneurol.2016.08.007. [Epub ahead of print]

Japanese ver.

http://www.med.nagoya-u.ac.jp/medical/dbps_data/_material_/nu_medical/_res/topix/2016/nmda_20160818jp.pdf

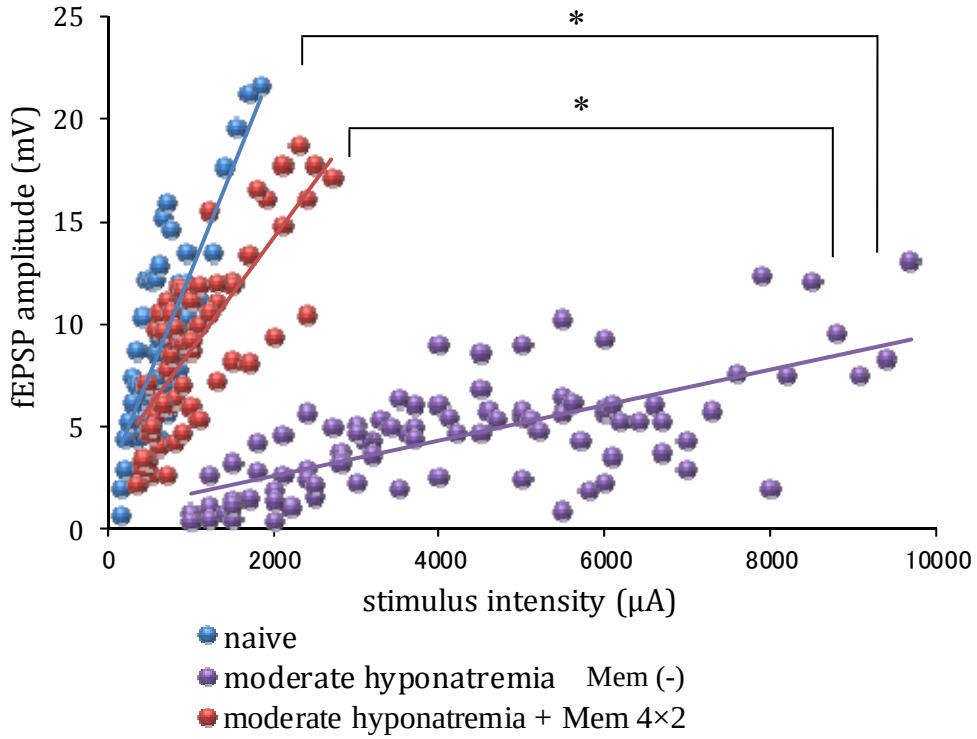
Figure 1



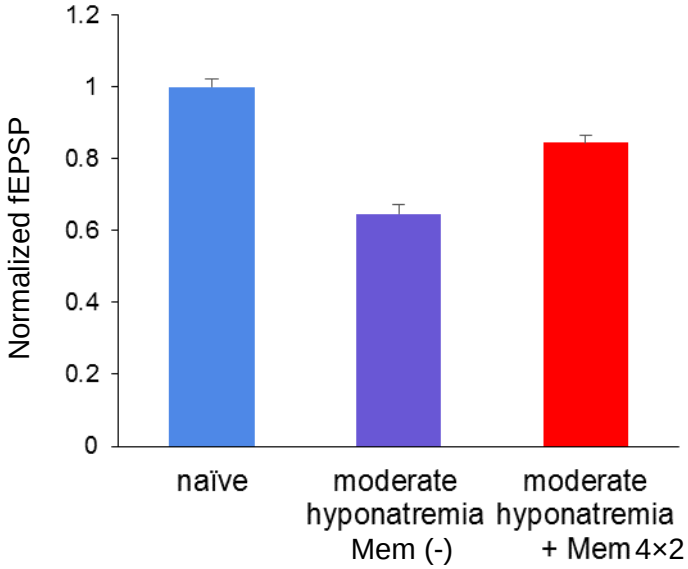
Memantine prevents selective apoptosis in hippocampal DG.

Figure 2

A



B



Memantine improved basal synaptic transmission (A) and LTP (B).