

## News release

### Title

Chronic hyponatremia causes neurological and psychological impairments

### Key points

- Chronic hyponatremia induces gait disturbances and memory impairment.
- Chronic hyponatremia decreases the magnitude of long-term potentiation (LTP) at hippocampal CA3-CA1 synapses as an underlying mechanism of memory impairment.
- The extracellular glutamate concentration was elevated in the chronically hyponatremic rat brain through decreased astrocytic glutamate uptake, which seems to be the cause of decreased LTP.
- Chronic hyponatremia-induced behavioral abnormalities are suggested to be reversible.

### Summary

Professor Hiroshi Arima, Associate Professor Yoshihisa Sugimura, and graduate student Haruki Fujisawa (Department of Endocrinology and Diabetes) and their collaborators in Nagoya University Graduate School of Medicine (Dean: Masahide Takahashi, MD, PhD) investigated the effect of chronic hyponatremia on central nervous system. They showed that chronic hyponatremia induces gait disturbances, memory impairment and decreased LTP at hippocampal CA3-CA1 synapses as an underlying mechanism of memory impairment. Furthermore, the extracellular glutamate concentration was elevated in the chronically hyponatremic rat brain through decreased astrocytic glutamate uptake, which seems to be the cause of decreased LTP. In addition, chronic hyponatremia-induced behavioral abnormalities are suggested to be reversible. This work was published online in Journal of the American Society of Nephrology on Sep 16, 2015.

### Research Background

Hyponatremia is the most common clinical electrolyte disorder. Acute hyponatremia can cause neurological complications and death as a result of osmotically induced cerebral edema. On the other hand, chronic hyponatremia has been considered asymptomatic because the brain can successfully adapt to hyponatremia which is associated with hypoosmolality. However, recent evidence suggests that chronic hyponatremia may be linked to attention deficits, gait disturbances, a risk of fracture associated with falls and cognitive impairments. These neurologic impairments are associated with a reduction of

quality of life and may be a significant cause of mortality. However, because underlying diseases such as adrenal insufficiency, heart failure, liver cirrhosis, and cancer may affect brain function, the contribution of hyponatremia itself to neurologic manifestations remains unknown.

Brain cells can adapt to hyponatremia. After an acute decrease in external osmolality, cells will initially swell, as a result of water movement into the cells along an osmotic gradient. Very soon thereafter, intracellular solutes (electrolytes and organic osmolytes) are extruded together with osmotically obligated water to maintain brain cell volume. Glutamate, a known major excitatory neurotransmitter, is one such organic osmolyte that is extruded into the extracellular space during cellular adaptation to hyponatremia. In a chronically hyponatremic state, as a result of adaptation to hyponatremia, brain volume normalizes completely. However, the brain content of glutamate reportedly decreases by 38.6% after 14 days' sustained hyponatremia in rats, which suggests that synaptic excitatory neurotransmissions are affected by chronic hyponatremia.

### **Research Results**

The research team made a chronic hyponatremic rat model by injecting 1-deamino-8-D-arginine vasopressin (an agent which inhibits water diuresis) and liquid diet feeding. Using this rat model, they showed a reduction of serum sodium ion concentrations in chronic hyponatremia induced gait disturbances; facilitated the extinction of a contextual fear memory; caused cognitive impairment in a novel object recognition test and impaired long-term potentiation at hippocampal CA3-CA1 synapses. In vivo microdialysis revealed an elevated extracellular glutamate concentration in the hippocampus of chronically hyponatremic rats. A sustained low extracellular sodium ion concentrations also decreased glutamate uptake by primary astrocyte cultures, suggesting an underlying mechanism of impaired long-term potentiation. Furthermore, gait and memory performances of corrected hyponatremic rats were equivalent to that of control rats suggesting that chronic hyponatremia-induced behavioral abnormalities are reversible.

### **Research Summary and Future Perspective**

In summary, this study showed chronic hyponatremia, the importance of which has been constantly overlooked, induces gait disturbances and memory impairment in a rat model. These results suggest chronic hyponatremia in humans may cause gait disturbance and cognitive impairment; its careful correction may improve quality of life and reduce mortality.

**Article**

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**Japanese ver.**

[http://www.med.nagoya-u.ac.jp/medical/dbps\\_data/\\_material/\\_nu\\_medical/\\_res/topix/2015/Chronic\\_hyponatremia\\_20150917jp.pdf](http://www.med.nagoya-u.ac.jp/medical/dbps_data/_material/_nu_medical/_res/topix/2015/Chronic_hyponatremia_20150917jp.pdf)

Figure.1 Footprint images of rats

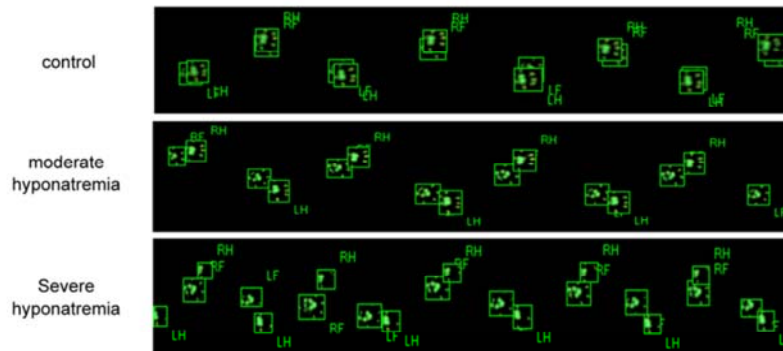


Figure.2 The hypothetical mechanism of chronic hyponatremia-induced memory impairment

