Nitrergic NO centrally induces frequent urination in rats

Takahiro Shimizu1, Hideaki Ono1, Shogo Shimizu2, Youichirou Higashi3, Suo Zou1, Masaki Yamamoto1, Takaaki Aratake1, Tomoya Hamada1, Yoshiaki Nagao1, Yusuke Ueba1, Masashi Honda2, Motoaki Saito1


Aim of Study

Psychological stress plays an important role in the induction of frequent urination and exacerbation of bladder dysfunction including overactive bladder (OAB) and bladder pain syndrome/interstitial cystitis (BPS/IC) [1-4]. Psychological stress-related information is conveyer to the brain, and then the brain recruits neuronal and neuroendocrine systems for adaptation to stressful conditions [5]. However, the brain pathophysiological mechanisms underlying psychological stress-induced effects on bladder function are still unclear.

Previously, we reported that the sympato-adrenergomulatory (SA) system, a representative response to stressful conditions, is activated by centrally administered SIN-1, a nitric oxide (NO) donor, in rats [6-7]. In the central nervous system, NO seems to have both inhibitory and facilitatory effects on micturition [8]. In this study, we investigated effects of centrally administered SIN-1 on micturition concerning with their dependence on the SA system in rats.

Methods

Urethane anesthetized (0.8 g/kg, ip) male Wistar rats (300-400 g) were used.

(I) Catheters were inserted into the bladder from the dome and the femoral artery to perform continuous cystometrograms (CMG, 12 ml/h saline instillation) and to collect blood samples, respectively. Three hours after the surgery, SIN-1 (100 or 250 µg/rat) or vehicle (saline, 10 µl/rat) was intracerebroventricularly (icv) administered. Saline infusion into the bladder and evaluation of intercontraction intervals (ICI) and maximal voiding pressure (MVP) were started 60 min before the icv administration. Plasma noradrenaline (NA) and adrenaline measured just before the administration. Plasma noradrenaline and adrenaline at 5 min after vehicle (saline, 10 µl/rat, icv) administration in comparison with plasma noradrenaline and adrenaline measured just before the administration. *P<0.05, when compared with the control group. Values are mean ± SEM.

(II) Catheters were inserted into the bladder from the dome and the femoral vein to perform continuous CMG (12 ml/h saline infusion) and to administer drugs (iv), respectively. Three hours after the surgery, SIN-1 (250 µg/rat) or vehicle (saline, 200 µl/rat) was iv administered. Continuous CMG was performed as described in (I).

(III) Effects of pretreatment with carboxy-PTIO (PTIO, an NO scavenger, 750 µg in 5 µl saline/rat, icv) on the SIN-1 (250 µg/rat, icv)-induced responses were evaluated.

(IV) Three hours after the surgery of a bladder catheter insertion, single CMG (12 ml/h saline infusion) was performed. After 4-5 times of single CMG, SIN-1 (250 µg/rat) or vehicle (saline, 10 µl/rat) was icv administered, then single CMG was continued for 60 min.

Results

(I) Centrally administered SIN-1 dose-dependently reduced ICI and elevated plasma Ad without altering MVP or plasma NA compared to the vehicle-treated group (Fig. 1). The SIN-1-induced ICI reduction was not affected by ADX, which abolished the SIN-1-induced elevation of plasma Ad (Fig. 2).

(II) Peripherally administered SIN-1 showed no significant effect on ICI or MVP compared to the vehicle-treated group (Fig. 3).

(III) Central pretreatment with PTIO significantly suppressed the SIN-1-induced reduction in ICI and elevation of plasma Ad (Fig. 4).

(IV) Centrally administered SIN-1 significantly reduced single-voided volume and bladder capacity without altering post VOIDing residual urine volume or voiding efficiency compared to the vehicle-treated group (Table 1).

Conclusions

Brain NO centrally induces frequent urination, which is independent of the SA outflow modulation. Thus, the central nitrergic mechanisms that can directly regulate micturition might be new targets for alleviation of psychological stress-induced exacerbation of bladder dysfunction such as OAB and BPS/IC.

References


Acknowledgements

This study was supported in part by JSPS KAKENHI (#17K09303), the Narishige Neuroscience Foundation in Japan, and the Smoking Research Foundation in Japan.

Disclosure

The first author has no conflict of interest to disclose with respect to this presentation.