Nitric oxide centrally induces frequent urination in rats

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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 sympatho-adrenomedullary (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 (Ad) levels were measured at just before and at 5 min after the icv administration. In some experiments, acute bilateral adrenalectomy (ADX) was performed before catheters insertion. In ADX rats, hydrocortisone (5 mg/kg, im) was administered after the surgery.

(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).

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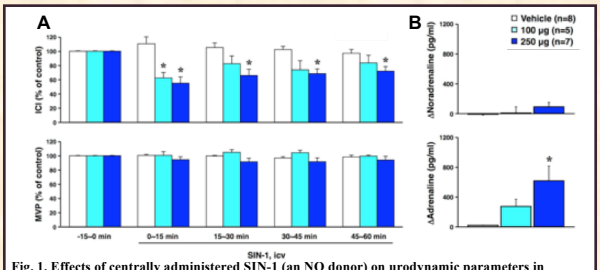

Fig. 1. Effects of centrally administered SIN-1 (an NO donor) on urodynamic parameters in continuous CMG and plasma levels of noradrenaline and adrenaline in rats. (A) Data of urodynamic parameters (ICI and MVP) were calculated as the ratio to the control values before icv administration (-15~0 min). (B) ΔNoradrenaline and ΔAdrenaline mean increments of plasma noradrenaline and adrenaline at 5 min after vehicle (saline, 10 μl/rat, icv) or SIN-1 (100 or 250 μg/rat, icv) administration in comparison with plasma noradrenaline and adrenaline measured just before the administration. *P<0.05, when compared with the Bonferroni method to the Vehicle group. Values are means ±SEM.

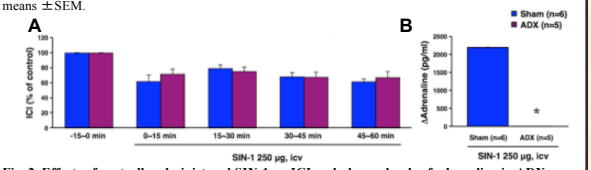

Fig. 2. Effects of centrally administered SIN-1 on ICI and plasma levels of adrenaline in ADX and sham-operated (Sham) rats. (A) Data of ICI were calculated as the ratio to the control values before icv administration (-15~0 min). (B) ΔAdrenaline means increments of plasma adrenaline at 5 min after SIN-1 (250 μg/rat, icv) administration in comparison with plasma adrenaline measured just before the administration. *P<0.05, when compared with an unpaired Student t-test to the Sham group. Values are means ±SEM.

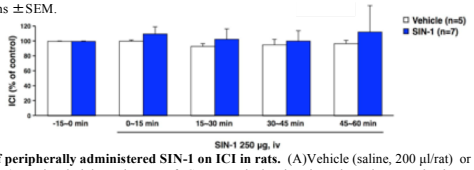

Fig. 3. Effect of peripherally administered SIN-1 on ICI in rats. (A)Vehicle (saline, 200 μl/rat) or SIN-1 (250 μg/rat) was iv administered. Data of ICI were calculated as the ratio to the control values before iv administration (-15~0 min). Values are means ±SEM.

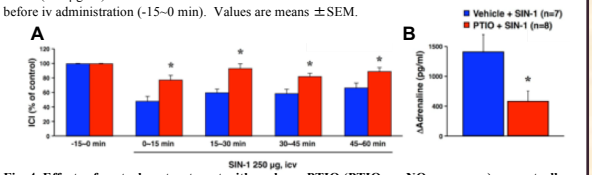

Fig. 4. Effects of central pretreatment with carboxy-PTIO (PTIO, an NO scavenger) on centrally administered SIN-1-induced responses in rats. Vehicle (saline, 5 μl/rat) or PTIO (750 μg/rat) was icv administered 30 min before SIN-1 administration (250 μg/rat, icv). (A) Data of ICI were calculated as the ratio to the control values before SIN-1 administration (-15~0 min). (B) ΔAdrenaline means increments of plasma adrenaline at 5 min after SIN-1 administration in comparison with plasma adrenaline measured just before the administration. *P<0.05, when compared with an unpaired Student t-test to the Vehicle + SIN-1 group. Values are means ±SEM.

Table 1. Effects of centrally administered SIN-1 on urodynamic parameters in single CMG in rats

Timing of evaluation	% of Control							
	Vv		Rv		BC		VE	
	Vehicle	SIN-1	Vehicle	SIN-1	Vehicle	SIN-1	Vehicle	SIN-1
Before icv	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0
After icv (0~15 min)	102.8 ± 9.3	62.5 ± 8.7*	123.7 ± 6.7	93.1 ± 26.4	118.4 ± 4.2	55.5 ± 9.2*	98.8 ± 1.2	110.0 ± 8.9
After icv (15~30 min)	104.5 ± 15.7	47.7 ± 7.0*	101.0 ± 28.9	87.7 ± 19.7	106.4 ± 12.1	42.0 ± 4.0*	103.2 ± 1.8	102.1 ± 11.0
After icv (30~45 min)	115.2 ± 25.4	46.2 ± 6.6*	95.7 ± 25.2	81.9 ± 46.4	117.1 ± 17.0	40.9 ± 3.6*	106.2 ± 3.4	105.8 ± 9.2
After icv (45~60 min)	94.6 ± 13.2	50.0 ± 3.7*	88.5 ± 11.8	75.1 ± 13.6	107.8 ± 24.7	54.3 ± 4.5	98.1 ± 2.1	100.8 ± 9.2

Vehicle (saline, 10 μl/rat) or SIN-1 (250 μg/rat) was icv administered (n=6 in each group). Data of urodynamic parameters were calculated as the ratio to the control values before icv administration (Before icv). *P<0.05, when compared with an unpaired Student t-test to the Vehicle group. Values are means ±SEM. BC: bladder capacity; Rv: post-voiding residual urine volume; VE: voiding efficiency; Vv: single-voided volume.

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.

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Disclosure

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