**52**

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# ALTERATIONS OF BLADDER FUNCTIONS IN A RAT MODEL OF CEREBRAL INFARCTION: EFFECT OF THE B3-AGONISTS, MIRABEGRON AND BRL37344

Hypothesis / aims of study

Cerebral infarction (CI) impairs the suprapontine regulatory system for the micturition reflex and consequently causes neurogenic detrusor overactivity (DO). A β3-agonist is now a therapeutic option for overactive bladder syndrome. However, little is known about the effects of β3-agonists on neurogenic DO induced by CI *in vivo*: only one article reported that mirabegron improved DO in a rat model of DO [1]. We intended to confirm that the stimulation of β3-adrenoceptors improves neurogenic DO induced by CI. The aim of the present study ~~is~~ was to examine the effect of β3-agonists mirabegron and BRL37344 on the DO in a rat model of CI *in vivo*.

Study design, materials and methods

Female Sprague-Dawley rats (9 weeks old) were used for the experiment (n=14). A polyethylene catheter for cystometry was implanted through the bladder dome. One week later cystometry was performed with physiological saline in the awaken condition. The cystometric parameters for each rat were determined with repeated cystometry at least three times. Post-void residual was drained via the cystometry catheter and measured after three consecutive micturitions. After the bladder capacity (BC) was determined, the left middle cerebral artery was occluded using 4-0 monofilament nylon thread to create CI. After the creation of CI, the measurement of cystometric parameters, the determination of the BC were repeated before and after the intravenous administration of mirabegron (1mg/kg) (n=6) or BRL37344 ($10^{-3}$ mg/kg) (n=8). To confirm cerebral ischemic status, TCC (2% 2,3,5-triphenyl chloride) staining of sliced forebrain was performed in each rat. Data are expressed as mean ± SEM.

Results

TCC staining confirmed the presence of CI in all rats. The main results are shown in the Table1 and 2. The BC was significantly decreased by CI, and mirabegron and BRL37344 partially restored the decreased BC with a statistical significance. Post-void residual volume was small at baseline, after CI and after the administration of mirabegron or BRL37344 (mirabegron: 0.003 ± 0.002, 0.01 ± 0.004 and 0.002 ± 0.002 ml, respectively BRL37344: 0.07 ± 0.03, 0.250 ± 0.04 and 0.20 ± 0.07 ml, respectively). The micturition pressure was not changed by the mirabegron or BRL37344 administration. Mirabegron and BRL37344 improved DO without impairing the voiding function.

Table1. The changes in cystometric parameters by CI and the mirabegron administration (1 mg/kg)

| | After CI | mirabegron administration |
|---|---|---|
| Bladder capacity | 56.8 ± 5.8†† | 82.0 ± 7.1†,** |
| Threshold pressure | 69.9 ± 8.5 | 76.8 ± 13.5 |
| Micturition pressure | 71.0 ± 7.1 | 76.3 ± 11.3 |

The values are expressed as % of the baseline values (n=6). † p<0.05, †† p<0.01 compared to baseline: * p<0.05, ** p<0.01 compared to after CI

Table2. The changes in cystometric parameters by CI and the BRL37344 administration ($10^{-3}$ mg/kg)

| | After CI | BRL37344 administration |
|---|---|---|
| Bladder capacity | 51.3 ± 7.3†† | 72.5 ± 7.5†,** |
| Threshold pressure | 104.3 ± 8.6 | 97.5 ± 12.0 |
| Micturition pressure | 102.9 ± 7.5 | 94.2 ± 7.3 |

The values are expressed as % of the baseline values (n=8). † p<0.05, †† p<0.01 compared to baseline: * p<0.05, ** p<0.01 compared to after CI

Interpretation of results

Not only mirabegron but also BRL37344 increased the BC in a rat model of CI without impairing the voiding function *in vivo*. These results indicate that the stimulation of β3-adrenoceptors improves neurogenic DO induced by CI.

Concluding message

Mirabegron and BRL37344 increased the BC in a rat model of CI. We confirmed that neurogenic DO induced by CI is improved by the stimulation of β3-adrenoceptors.

References

1. Hatanaka T, Ukai M, Watanabe M, et al. Naunyn Schmiedebergs Arch Pharmacol. 2013;386:247-53.

Disclosures

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