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Effect of gabapentin derivates on mechanical allodynia-like behaviour in a rat model of chronic sciatic constriction injury

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Abstract—A series of mutual prodrugs derivated from gabapentin, pregabalin, memantine, venlafaxine were synthesized and their pharmacological properties to treat neuropathic pain were investigated in a rat model of chronic sciatic nerve constriction injury (CCI). In vivo evaluation demonstrated that the mutual prodrugs 2002413A, 2002823A composed of two gabapentins, 2002414 composed of gabapentin and pregabalin were effective in reversal tactile allodynia in CCI rats. The prodrugs 2002413A, 2002414 had no significant influence on the rotarod activity. The result suggest that the prodrugs may be possible candidates for further development.

Neuropathic pain are defined as chronic, persistent pain mostly caused by peripheral or central neural injury. The characteristic symptoms of neuropathic pain are usually expressed as allodynia, hyperalgesia and spontaneous pain. Many classical analgesics such as opioids and NSAIDS (nonsteroid antiinflammation drugs) are not effective or have limit effect for the treatment of neuropathic pain, antidepressants, anticonvulsants antiarrhythmic drugs, local anaesthetic or NMDA receptor antagonists become an alternative way for the neuropathic pain treatment.

Different pain mechanisms may be involved in the neuropathic pain, for one mechanism could be responsible for many different symptoms, and the same symptom can be caused by different mechanisms.[1–3] Medicines focused on one specific target could only alleviate pain symptoms to some extent, complete symptom reduction or complete functional restoration is seldom achieved. Moreover, Some of the drugs exist severe adverse effects, for the most common adverse effects of anticonvulsants are sedation and cerebellar symptoms (nystagmus, tremor and incoordination).[4] Safer and more effective treatments for neuropathic pain have to be developed. The direction for new drug development is to use the combination of different kinds of drugs based on mechanism classification in order to block the pain symptom at different levels.[5] Combination is an effective way to increase efficiency of drugs and to reduce the adverse effect, for example, CNQX, a NMDA receptor antagonists, and gabapentin, when combined intrathecally, produce a potent synergistic antiallodynic effect on neuropathic pain in spinal nerve-ligated rats. Intrathecal gabapentin is effective against tactile allodynia and interacts synergistically with clonidine.[6–8]

Recently, the conjugation of two drugs having different pharmacological activities, which is termed a mutual prodrug has been synthesized to improve the therapeutic index and reduce adverse effect.[9,10]

In the present study, the antiallodynic effects of systemic administration of mutual prodrugs (the conjugates of gabapentin, pregabalin, memantine, venlafaxine) were investigated in chronic sciatic nerve constriction injury (CCI) rats.

The CCI surgery was conducted according to a procedure previously reported by Bennett and Xie.[11] Paw withdrawal threshold was measured by a series of von Frey filaments, the strength of a filament, which caused 4–6 responses in 10 times of stimulations was designated

Keywords: Neuropathic pain; CCI; Mutual prodrug.
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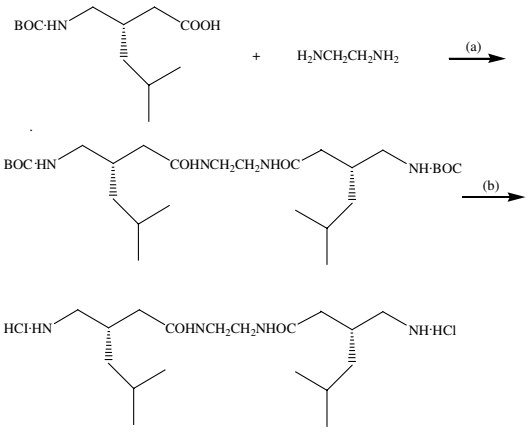
as 50% response threshold. The force of 26 g was designated as the cut-off point.

The structures of the synthesized mutual prodrugs (provided by Beijing Institute of Pharmacology and Toxicology) were confirmed by IR and ^{1}H NMR spectroscopy and their purity was established by elemental analysis, all sample compounds screened were solved in 0.9% (W/V) saline. The synthesis methods of gabapentin and pregabalin mutual prodrug are shown in Scheme 1.

Two weeks after surgery, the mechanical paw withdrawal threshold was measured at 1 h after mutual prodrugs administration (60 mg/kg, ip). Broad screen found that compound 2002413A, 2002414, 2002823A, 2003414 (60 mm/kg, ip) exhibited antiallodynic effects in CCI rats by increasing the paw withdrawal threshold significantly when compared with that of the preinjection (see Table 1). The reason that most of the compounds composed of



Scheme 1. Reagents and conditions: (a) DCC, CH_2Cl_2, rt, 12 h; (b) HCl, Et_2O, rt, 1 h.

Table 1. Effect of mutual prodrugs on allodynia response in CCI rats

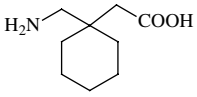
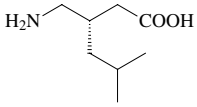
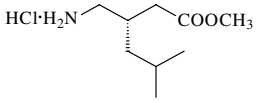
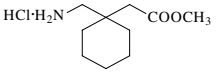
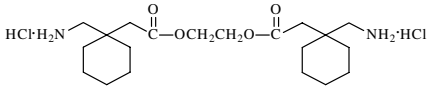
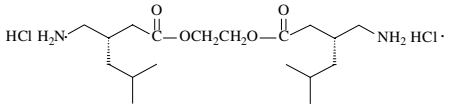
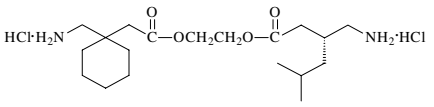
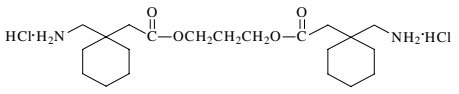
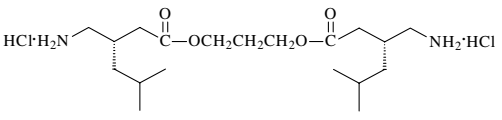
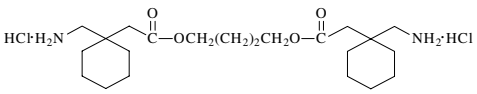
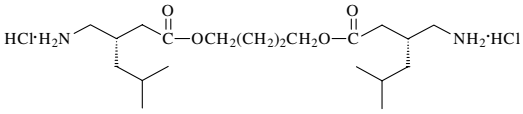
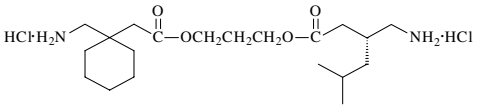
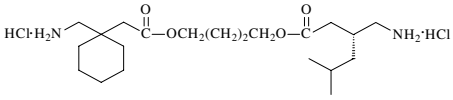
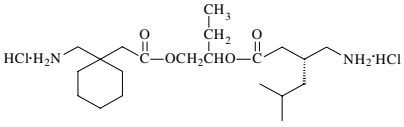
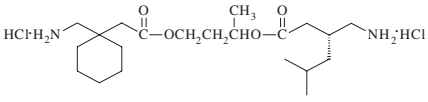
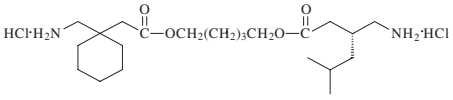
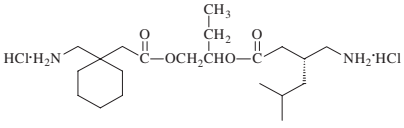
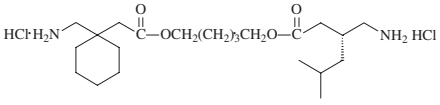
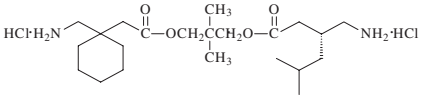
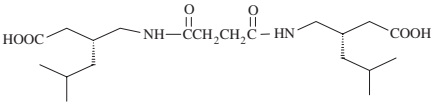
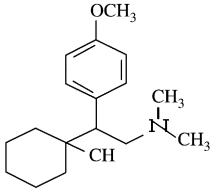
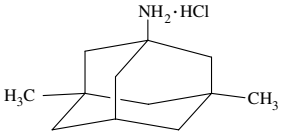
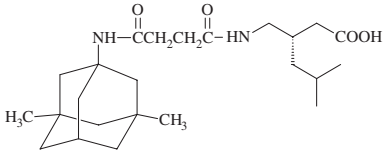
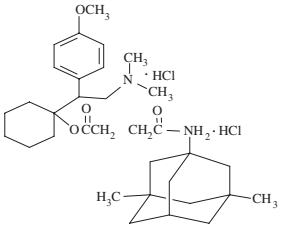
Treatment	Chemical structure	PWT (g) preinjection	PWT (g) postinjection
Gabapentin		2.23 ± 0.36	13.50 ± 4.35*
Pregabalin		3.43 ± 0.39	18.86 ± 3.64**
20030413		5.20 ± 0.44	6.80 ± 1.48
20030414		6.40 ± 0.36	22.80 ± 2.92**
20020413A		3.40 ± 0.77	18.67 ± 4.64*
20020413B		2.90 ± 0.49	7.90 ± 2.45
20020414		3.33 ± 0.42	19.00 ± 3.40**
2002823A		4.80 ± 0.44	19.40 ± 2.45**
2002823B		6.00 ± 0.00	10.33 ± 1.72

Table 1 (*continued*)

Treatment	Chemical structure	PWT (g) preinjection	PWT (g) postinjection
2002827A•		4.00 ± 0.57	5.60 ± 0.89
2002827B		4.50 ± 0.78	8.50 ± 0.78
200292A		3.60 ± 0.36	7.80 ± 2.01
2002293		4.17 ± 0.91	8.56 ± 3.75
2003415		4.40 ± 0.68	6.80 ± 0.73
2003416•		4.00 ± 0.82	11.40 ± 3.76
20030417		2.80 ± 0.73	13.80 ± 2.98**
2003325		4.00 ± 0.82	6.80 ± 1.09
2003327•		3.33 ± 0.47	20.67 ± 3.77***
2003328•		4.40 ± 0.36	7.20 ± 0.73
2002914B		4.00 ± 0.00	6.00 ± 1.15
Venlafaxine•		2.00 ± 0.00	22.00 ± 3.65***

(*continued on next page*)

Table 1 (*continued*)

Treatment	Chemical structure	PWT (g) preinjection	PWT (g) postinjection
Mementine•		2.80 ± 1.10	10.40 ± 2.99*
200295		3.32 ± 0.62	13.20 ± 4.78
20021024		3.36 ± 0.80	5.60 ± 1.06

All the compounds were administrated intraperitoneally at (60 mg/kg, ip) 1 h before testing. Data were expressed as mean ± S.E.M of 5–6 animals per group and analyzed by SASS data process soft. $^{**}P < 0.01$, $^{***}P < 0.001$ versus preinjection, Wilcoxon 2-Sample Test and Kruskal–Wallis Test. • represents compounds with severe adverse effects.

pregabalin did not exhibit antiallodynia effect may be due to the conformation of pregabalin. It has been reported that *trans* or *cis* conformation greatly influences the efficacy of pregabalin.

Compound 2002413A and 2002823A reversed allodynia effect when measured at 1 h after oral administered (p.o.). The ED50 for gabapentin, 2002413A, 2002823A, administered 1 h before testing in CCI rats, was: 85.80, 67.92 and 80.34 mg/kg (p.o.), respectively (see Fig. 1).

The rotarod results showed that 2002413A and 2002414 administered at 60 mg/kg (ip) had no significant influence on the rotarod activity for a total of 240 min, while gabapentin showed the tendency of inhibition of rotarod performance in rats. The antiallodynic effect, combined with its nontoxic effects on nerve function suggests that the prodrugs may be possible candidates for further development, kinetic profiles of these compounds need further to be investigated (Fig. 2).

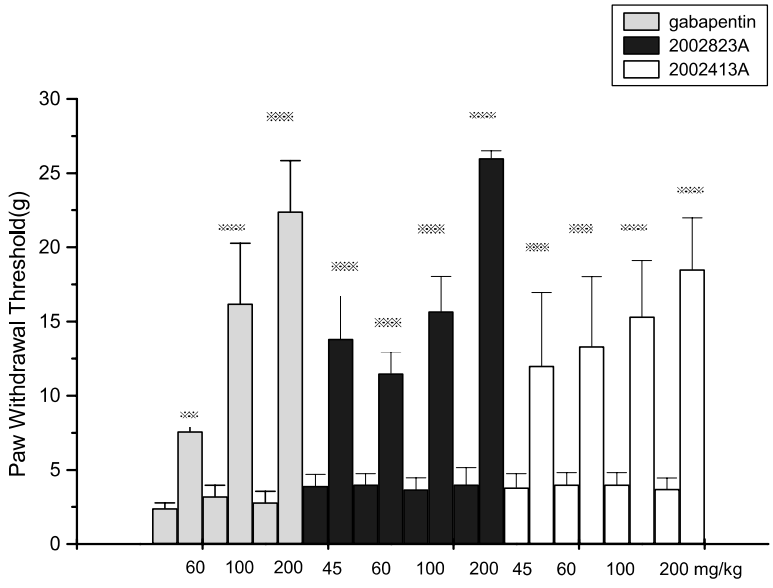


Figure 1. Effect of gabapentin, 2002823A, 2002413A on the tactile allodynia response in CCI rats. Results are expressed as mean ± SEM,$^{**}P < 0.01$, $^{***}P < 0.001$ versus preinjection. Each bar represents the mean threshold to paw withdrawal SEM of 5–6 animals per group.

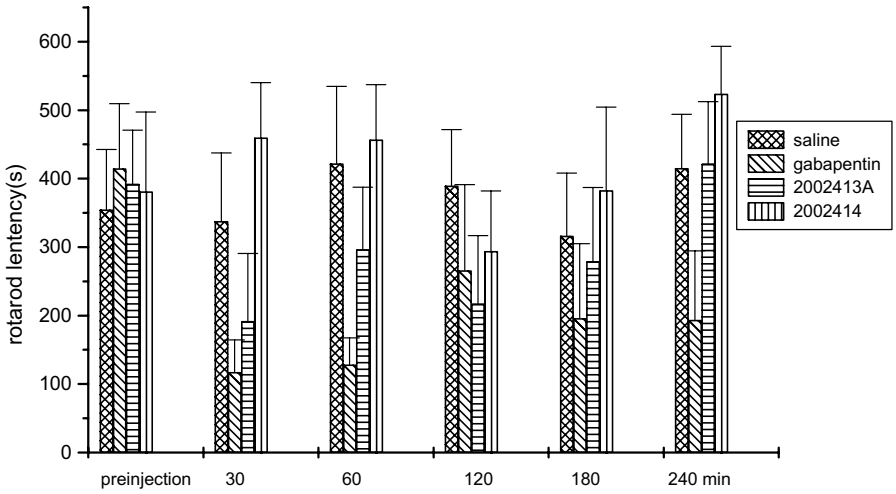


Figure 2. Rotarod performance time (s) before and after injection of gabapentin or mutual prodrugs compounds (60 mg/kg, ip) in rats ($n = 5$–6). Each bar represents the mean ± SEM of 5–6 animals per group.

Acknowledgements

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