Communications to the Editor

[Chem. Pharm. Bull. 25(7)1837—1839(1977)]

UDC 615.212.015.4.076.9 : 612.73.08

Effects of Central Muscle Relaxants on the Morphine-induced Straub Tail Reaction

An investigation of the pharmacological mechanism of the Straub tail reaction (STR) was made of the intracerebral (*i.c.*) injection of morphine. In addition, the effects of central muscle relaxants on the STR were examined. The STR was elicited by *i.c.* injection of morphine. Meprobamate, haloperidol, 1,3-diphenyl-5-(2-dimethylaminopropionamide)-pyrazole [difenamizole] and β-(*p*-chlorophenyl)-γ-aminobutyric acid [baclofen] apparently decreased the STR by systemic administration. In mice injected *i.c.* with difenamizole or baclofen, moreover, the STR was noticeably inhibited. Especially, baclofen decreased the STR in the approximate one-thousandth of the dose by systemic administration. Thus it appears that the central nervous system may have a profound significance for the manifestation of the STR due to morphine in mice.

Keywords——morphine; Straub tail reaction; central muscle relaxants; intracerebral injection; Baclofen; Difenamizole

Elucidation of the pharmacological mechanism of the Straub tail reaction (STR)[1] has been complicated by many reports. For example, it has been shown that the STR is inhibited by peripheral muscle relaxants but not by central muscle relaxants,[2] thus suggesting that the STR may be inhibited without affecting the central nervous system (CNS). On the contrary, several investigators have indicated that the STR is due to the central excitatory effects of morphine.[3]

Meanwhile, it has been reported that 1,3-diphenyl-5-(2-dimethylaminopropionamide)-pyrazole [difenamizole, DFZ][4] and β-(*p*-chlorophenyl)-γ-aminobutyric acid [baclofen][5] have muscle relaxant action. Furthermore, it has been shown that DFZ exerts an inhibitory action on the arousal reaction and evoked muscular discharge following stimulation of the brain stem reticular formation,[6] and baclofen inhibits both mono- and polysynaptic reflexes in the spinal cord.[7] If the STR is ascribed to the effects of morphine on the CNS, it is likely that both DFZ and baclofen in addition to meprobamate and haloperidol may influence the manifestation of the STR.

This possibility was investigated in the present studies using the intracerebral (*i.c.*) injection technique with reference to the effects of DFZ and baclofen on the STR.

Mice used in this study were albino males of ddY strain weighing between 18 and 25 g. A group of ten mice was used in each experiment with the exception of baclofen 0.1 and 0.2 μg/mouse *i.c.* (consisted of twenty animals). Food and water were supplied *ad libitum*. Drugs used in this study were as follows: morphine·HCl (Shionogi and Co., Ltd.), meprobamate (Daiichi Seiyaku Co., Ltd.), haloperidol (Dainippon Pharmaceutical Co., Ltd.), 1,3-diphenyl-5-(2-dimethylaminopropionamide)-pyrazole and its hydrochloride (difenamizole, DFZ) (Takeda Chemical Industries, Ltd.) and β-(*p*-chlorophenyl)-γ-aminobutyric acid and its hydrochloride

1) W. Straub, *Dtsch. Med. Wochenschr.*, **1911**, 1462.
2) R.C. Srimal, K.D. Jaitly, and K.P. Bhargava, *Jpn. J. Pharmacol.*, **15**, 322 (1965).
3) *a*) G. Chen and B. Bohner, *Arch. Int. Pharmacodyn. Ther.*, **125**, 1 (1960); *b*) J.H. Gaddum, "Pharmacology," 5th ed., Oxford University Press, London, 1959.
4) T. Kameyama, K. Oyanagi, K. Sasaki and K. Kisara, *Nippon Yakurigaku Zasshi*, **65**, 529 (1969).
5) T. Kameyama, H. Hori and Y. Hishikawa, The 94th Annual Meeting of Pharmaceutical Society of Japan, Sendai, Apr. 1974.
6) M. Yasuhara, H. Naito, E. Saito, M. Fukagawa, K. Takahashi and M. Kobayashi, *Oyo Yakuri*, **6**, 313 (1972).
7) H. Fukuda, Y. Kudo and H. Ono, *Nippon Yakurigaku Zasshi*, **71**, 13P (1975).

(baclofen) [Ciba-Geigy (Japan) Ltd.]. Morphine·HCl, DFZ·HCl and baclofen·HCl solutions were made up in 0.9% saline immediately prior to use and were adjusted to pH 7.0 with 0.1 N NaOH. The *i.c.* injection was carried out according to the method reported previously.[8] For systemic administration, morphine·HCl was dissolved in saline whereas meprobamate, haloperidol, DFZ as well as baclofen were suspended in a 0.3% carboxymethylcellulose dissolved in isotonic saline. Morphine, 10 mg/kg, *s.c.*, was injected into the back of the neck 15 min after the test drug treatment. The STR was then scored at intervals of 10, 30 and 60 min after the administration of morphine. The tail elevation was graded according to the modified numerical ratings of Juul[9] as follows: 0=0°, 0.5=1—44°, 1.0=45°, 1.5=46—89°, 2.0=90°, 2.5=91—179°, 3.0=180°, above from the horizontal table plane. In addition, the inhibition (%) was calculated from the observation at 30 min after morphine as follows: [(the degree of decline of the mean score of animals treated with drug compared to the mean score of control)/(the mean score of control)]×100. p values were obtained by the Student's t-test. The experiments were programmed in a semi-soundproof room at 23±1° and 55±2.5% relative humidity.

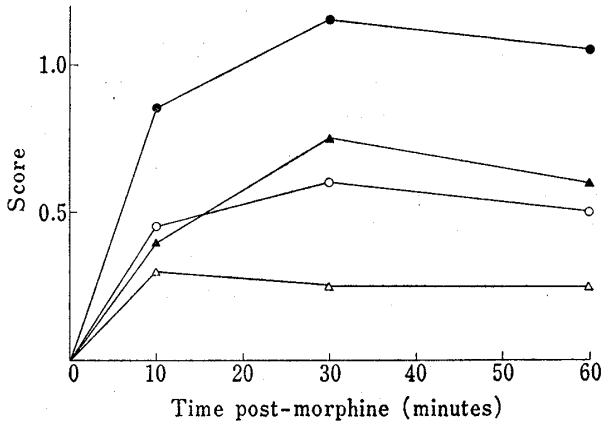

Fig. 1. The Time Course of the Straub Tail Reaction (STR) after the Intracerebral Injection of Morphine in Mice

Each point represents the mean score obtained from ten mice.

△—△, 2 μg. ○—○, 20 μg
●—●, 40 μg. ▲—▲, 50 μg.

When each dose of morphine (*i.c.*) was injected, as shown in Fig. 1, the maximal

Table I. Effects of Central Muscle Relaxants on the Straub Tail Reaction (STR)

Drugs	Dose (mg/kg)	Route	Score (mean±S.E.)	Inhibition (%)	p-Value
Saline		*i.p.*	1.5±0.1		
Meprobamate	100	*i.p.*	0.8±0.2	47	<0.01
Haloperidol	5	*i.p.*	0.7±0.2	53	<0.001
	10	*i.p.*	0.2±0.1	80	<0.001
Difenamizole	10	*i.p.*	0.9±0.1	40	<0.001
	15	*i.p.*	0.6±0.1	60	<0.001
	30	*i.p.*	0.5±0.1	67	<0.001
Baclofen	5	*i.p.*	0.3±0.1	80	<0.001
	10	*i.p.*	0.1±0.1	93	<0.001
Saline		*i.c.*	1.4±0.1		
Difenamizole	100[a]	*i.c.*	0.8±0.1	43	<0.001
	200[a]	*i.c.*	0	≧100	—
Baclofen	0.1[a]	*i.c.*	0.7±0.2	50	<0.001
	0.2[a]	*i.c.*	0.6±0.1	57	<0.001

Each drug was administered 15 min before morphine 10 mg/kg, *s.c.* Intensity of the STR (mean±S.E.) was assessed according to the scoring system described in methods. The mean control level in these experiments was 1.5±0.1 (systemic administration of the vehicle+morphine 10 mg/kg, *s.c.*) or 1.4±0.1 (central administration of the vehicle+morphine 10 mg/kg, *s.c.*). Each inhibition (%) was constructed using the mean values for intensity (expressed as a percentage of vehicle treated control values). *a*) μg/mouse.

8) T.J. Haley and W.G. McCormick, *Brit. J. Pharmacol Chemother.*, **12**, 12 (1957).
9) A. Juul, *Arch. Int. Pharmacodyn. Ther.*, **62**, 69 (1939).

reaction of the STR was obtained at a dose of 40 μg/mouse. However, the STR induced by the higher dose of morphine 50 μg/mouse, was mitigated as compared to the 40 μg/mouse of morphine. Morphine 100 μg/mouse, proved to be lethal.

On the other hand, the STR was elicited in all mice tested when injected with morphine 10 mg/kg, *s.c.* Meprobamate, haloperidol, DFZ and baclofen, respectively, in the doses shown in Table I, showed a significant inhibition of the STR induced by morphine. Moreover, the STR was noticeably inhibited in mice injected *i.c.* with DFZ or baclofen. Especially, the dose of the latter required for this inhibition was as low as approximate one-thousandth of that by systemic administration.

The STR may be partly due to the central excitatory effects of morphine since this reaction was observed by *i.c.* administration of morphine. It has been stated that DFZ (*i.p.*) acts on the reticular formation in the brain stem[6] and has muscle relaxant activity in the rotarod, traction and inclined plane tests.[4] In the meantime, Fukuda, *et al.*[7] have shown that baclofen have an inhibitory action on the spinal reflex in rats. It is further noted that meprobamate acts on the polysynaptic pathways of the CNS and the muscle relaxant action of haloperidol results from the inhibitory action on a higher center of animals. In the present experiment, the STR induced by morphine 10 mg/kg, *s.c.* was markedly inhibited by DFZ and baclofen when injected *i.c.* or *i.p.* It was also shown, unlike the results reported by Srimal, *et al.*,[2] that the STR was suppressed by the relatively low dose of meprobamate and haloperidol which believed to have a central muscle relaxant action. From these findings, it would be reasonable to speculate that DFZ and baclofen inhibit the STR through the mediation of the CNS in mice.

Acknowledgement We wish to acknowledge our indebtedness to Mr. Y. Komori for invaluable technical assistance.

Faculty of Pharmaceutical Sciences,
Meijo University
Tenpaku-ku, Nagoya, 468, Japan

Tsutomu Kameyama
Toshitaka Nabeshima
Makoto Ukai

Received December 27, 1976

[Chem. Pharm. Bull. 25(7)1839—1841(1977)]

UDC 547.551.52.03.08 : 615.31.011.3.033

Transmucosal Fluid Movement and Its Effect on Rectal Sulfanilamide Absorption in Rat

Sulfanilamide absorption from the rectum in rats was studied using the recirculating perfusion method with perfusion solutions having different levels in tonicity by changing concentration of sodium chloride and revealed that the absorption was influenced by the apparent transmucosal bidirectional fluid movements.

Keywords——drug absorption; recirculating perfusion method; rectal absorption of drug; rectum; sulfanilamide; sulfanilamide absorption; transmucosal fluid movement

Studies concerning the effect of transmucosal fluid movement on drug absorption from rat gastrointestinal tract using the method of recirculating perfusion[1] with perfusion solutions

1) L.S. Schanker, D.J. Tocco, B.B. Brodie, and C.A.M. Hogben, *J. Pharmacol. Exptl. Therap.*, **123**, 81 (1958).