Korean J. Ginseng Sci.
Vol. 13, No. 2, 239–241(1989)

Effect of Ginseng Total Saponins on the Development of Acute and Delayed Types Tolerance to Morphine

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(Received October 12, 1989)

Abstract□Naloxone partially antagonized the analgesic effect of a large dose of morphine and inhibited the development of an acute type tolerance. Ginseng total saponins did not antagonize the analgesia of a large dose of morphine but inhibited the development of acute and delayed types tolerance. The morphine analgesia and the development of acute type tolerance were affected by the opioid receptor antagonist, naloxone, but the development of acute type tolerance was not. Ginseng total saponins partially inhibited the development of the delayed type tolerance that was not inhibited by naloxone, but also partially suppressed the development of the acute type tolerance that was completely inhibited by naloxone. These results imply that the partial inhibition of the development of the acute and delayed types tolerance by ginseng total saponins is not mediated by the opioid receptors.

Keywords□antagonist, morphine, naloxone, ginseng total saponins, acute and delayed types tolerance

Introduction

A single large dose of morphine produce profound analgesia accompanied with the development of tolerance and physical dependence. The tolerance develops acutely within 24 hours, acute type tolerance, and the degree is further intensified and reaches its peak on the 5th day, delayed type tolerance, and gradually disappeared. Partial or complete blocking of morphine analgesia by naloxone inhibited the development of acute type tolerance, but could not prevent the development of delayed type tolerance[1]. The complete and sustained blockade of opioid receptors by naloxone can not modify the development of delayed type tolerance, and these facts may demonstrate the participation of the mechanism which is not mediated by opioid receptors, and may indicate the development of tolerance which is essentially unrelated to the analgesic effect of morphine[2]. Further, it was reported that ginseng total saponins antagonize the analgesia of a small dose of morphine[3,4] and inhibite the development of morphine tolerance[5-7].

The present study was undertaken to determine whether ginseng total saponins inhibits the development of acute type tolerance and/or delayed type tolerance.

Materials and Methods

Male mice of the ICR strain weighing 12-15 g were purchased and housed as a group of ten mice in a plastic cage. They were kept in a room maintained at an ambient temperature of 22 ± 1 °C and given normal laboratory diet and tap water *ad libitum*. After reaching 18-22 g, they were employed for the experiments. The following compounds were used; morphine-HCl (Dae-Won Pharm. Co.), naloxone-HCl (Sigma, U.S.A.), ginseng total saponins (gift from Korea Ginseng and Tobacco Research Institute).

On the first day, they were treated as follows; Group 1 received morphine 50 mg/kg s.c., group 2 had naloxone 10 mg/kg i.p. 30 min before the mor-

phine injection, group 3 had ginseng total saponins 100 mg/kg i.p. four hours before the morphine injection, and group 4 had ginseng total saponins 200 mg/kg four hours before the morphine injection.

The analgesic effect (a response-time, 2 sec and a cut-off time, 10 sec) was measured by the tail flick method of D'Amour and Smith[8]. Mice of each group were further divided into three sub-groups. To evaluate the degree of tolerance, the analgesic effect of a test dose of morphine 5 mg/kg s.c. was measured on the 2nd, 5th and 10th days.

Results and Discussion

A single dose of 50 mg/kg of morphine produced a marked analgesia lasting about 3.5 hours (group 1). Naloxone pretreatment, 10 mg/kg, 30 min before the morphine injection, partially antagonized the analgesic effect of morphine (group 2). But 100 mg/kg and 200 mg/kg of ginseng total saponins did not antagonize the morphine analgesia (group 3 and 4). Morphine tolerance developed on the second day, reached its peak on the fifth day and then gradually declined. Therefore, the degree of tolerance was determined on the second fifth and tenth days. The development of tolerance on the 2nd day was completely inhibited in the group treated with naloxone on the 1st day. On the other hand, the pretreatment with 100 mg/kg or 200 mg/kg of ginseng total saponins, 4 hours before the morphine injection, did not modify the morphine analgesia. The development of acute type tolerance on the second day, was partially inhibited in the groups treated with ginseng total saponins on the first day. Delayed type tolerance was also inhibited by ginseng total saponins on the fifth day.

It has been believed that the analgesic effect of narcotic drugs could not be separated from their liability to produce tolerance and dependence. Especially, the parallel appearance of tolerance and dependence may suggest that common mechanisms underlie both phenomena. Recently, evidence is being accumulated indicating the possible dissociation of analgesic effect from tolerance and/or dependence[9]. Kaneto *et al.*[2] reported evidence that morphine analgesia and tolerance were dissociated with

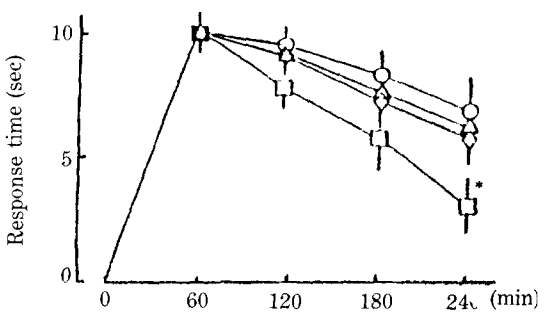

Fig. 1. Antagonism of morphine analgesia by naloxone or ginseng total saponin (GTS).
The analgesia was measured every 60 min for 240 min by tail flick test. On the 1st day, mice were treated as follows: Group 1, Morphine 50 mg/kg (s.c.) (○-○). Group 2, naloxone 10 mg/kg (i.p.) was given 30 min prior to the administration of morphine (□-□). Group 3 and 4, GTS 100 mg/kg (△-△) and 200 mg/kg (i.p.) (◇-◇) were given 4 hours prior to the administration of morphine. *: $p<0.05$, compared with that of morphine control. Each point is the mean ± S.E. of at least 10 mice

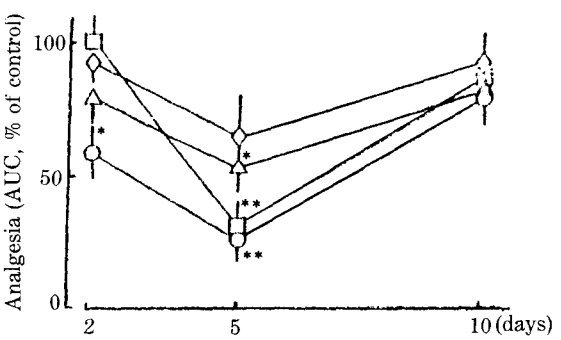

Fig. 2. Inhibition of acute and delayed types tolerance by naloxone or GTS.
The analgestic effect of morphine 5 mg/kg was measured every 30 min for 120 min by tail flick test. The analgesic effect was calculated as area under the curve (AUC) and expressed as percent of control. Group 1, Sal. + morphine 50 mg/kg (○-○), Group 2, naloxone 10 mg/kg + mor. 50 mg/kg (□-□), Group 3 and 4, GTS 100 mg/kg (△-△) or 200 mg/kg (◇-◇) + mor. 50 mg/kg. *: $p<0.05$, **: $p<0.01$, compared with that of morphine 50 mg/kg control.

each other.

Naloxone could not inhibit the development of delayed type tolerance but ginseng total saponins could partially inhibit the development of acute and delayed types tolerance to morphine.

It has been suggested that drugs which affect the cholinergic mechanism must modify the acute and chronic actions of morphine[10,11] Acetylcholine supersensitivity has been implicated in the development of morphine tolerance[12,13].

Recently Watanabe *et al.*[14] reported that ginseng saponins affected the cholinergic system to inhibit the development of morphine tolerance without the direct action of opioid receptors on the guinea-pig ileum preparations. Furthermore, We found that ginseng saponins had a non-opioid mechanism on electrically evoked contractions of guiea-pig ileum and the result was consistent with the studies reported by Watanabe *et al.*[14]

Therefore, we can not exclude any possible cholinergic involvement in the inhibition of the development of morphine acute and delayed types tolerance by administration of ginseng total saponins.

In conclusion, ginseng total saponins partially inhibited the development of the delayed type tolerance that was not inhibited by naloxone, but also partially suppressed the development of the acute type tolerance that was completely inhibited by naloxone. These results implicate that the partial inhibition of the development of the acute and delayed types tolerance by ginseng total saponins is not mediated by opioid receptors.

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