Adrenergic Function and the Development of Analgesic Tolerance to Morphine

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Abstract—Whether or not the suppressive effect of α- and β-adrenergic blockers, phentolamine and propranolol, on the development of tolerance to morphine could be substituted for each other was investigated in mice. Daily co-administration of either one of the blockers with morphine suppressed the development of analgesic tolerance to morphine as far as the treatment was continued without affecting the analgesic effect per se; however, the suppressive effect was lost from the day of the substitution for the other blocker and tolerance developed as rapidly as in the control group treated with morphine alone. Co-administration of both blockers with morphine also maintained the analgesic effect on the 1st day for 10 days, but when the administration of either one or both blockers was eliminated from the 6th day, the development of tolerance was initiated. These results suggest that the mechanisms of α- and β-blockers for the suppression of the development of analgesic tolerance to morphine are different from each other and that adrenergic blockers may produce a specific alteration in the mechanism for the development of tolerance to morphine.

In our previous report (1), we have demonstrated that daily concomitant treatment of adrenergic blockers with morphine, at dose which did not affect the analgesic effect of morphine, completely suppressed the development of analgesic tolerance to morphine as long as the combined treatment was continued, up to 30 days. The effect was specific for adrenergic blockers and neither serotonergic nor cholinergic antagonists possess a similar suppressive effect (preliminary data).

Interestingly, however, the suppressive effect of adrenergic blockers on the development of analgesic tolerance to morphine was common to both α- and β-blockers. This fact stimulated our attention, and in order to clarify the action mechanisms of the adrenergic blockers, in particular, the common ability of both blockers to suppress the development of tolerance to morphine, we studied whether or not the effect of α-blocker is substituted by that of a β-blocker, and vice versa.

Materials and Methods

Animals: Male ddY mice weighing 18–20 g (Ohtsubo Exp. Animals) were housed in a group of 20 animals in a cage. They were kept in a room maintained at 22±1°C and were given normal laboratory diet and tap water ad libitum. After reaching 23 to 25 g, they were used for the experiments.

Drugs: Morphine-HCl (Takeda) and dl-propranolol-HCl (Nakarai) were dissolved in saline, and phentolamine-mesylate (Regitin, Ciba-Geigy) was diluted with saline. They were administered in a volume of 0.1 ml/10 g of body weight, and the dose was expressed in terms of salt. Morphine was administered s.c., and adrenergic blockers were given i.p., 30 min prior to the injection of morphine.

Evaluation of analgesic effect: The analgesic effect of morphine (the response time, a cut-off time of 6 sec) was measured by the
modified Haffner’s method as reported by Takagi et al. (2). The measurement was made every 15 min for the duration of 90 min, and the effect was calculated as the area under the curve (AUC) by plotting the increase of response time (sec) on the ordinate and time intervals (min) on the abscissa.

Assessment of tolerance: The analgesic effect of morphine was determined daily and expressed as percent of the effect obtained in naive control animals. The degree of decrease in analgesic response is indicative of tolerance development to morphine.

Statistical analysis: Statistical significance of the difference between mean values of the measurements was evaluated by Student’s t-test.

Results

1. Substitution of blockers after repeated treatment: Phentolamine and propranolol, at the dose of 10 mg/kg, respectively, did not affect the analgesic effect of morphine in naive animals; and with the daily combined treatment of morphine plus phentolamine or propranolol, the analgesic effect was maintained at the level observed on the 1st day for 10 days. Namely, the development of tolerance to morphine was completely blocked without affecting the analgesic effect. From the 6th day, when the combination of the blockers was exchanged, phentolamine to propranolol and propranolol to phentolamine, tolerance to the analgesic effect of morphine was developed progressively as in the control group.

In the animals rendered tolerant to morphine by 5 daily treatments, the analgesic effect of morphine on the 6th day was not influenced by blockers (Fig. 1).

2. Daily alternative substitution of the

Fig. 1. Effect of co-administration of phentolamine or propranolol with morphine and the substitution of the combination of the blockers on the development of analgesic tolerance to morphine. Mice were daily pretreated with 10 mg/kg, i.p., phentolamine (Δ—Δ, N=20) or propranolol (□—□, N=20) 30 min prior to the injection of 10 mg/kg, s.c., morphine for 5 days. From the 6th day, in a half of the animals of each group, the combination of the blockers was exchanged, phentolamine to propranolol (□—□) or propranolol to phentolamine (Δ—Δ), and the treatment was continued for another 5 days. Control animals received saline instead of blockers (○—○, N=12); and on the 6th day, they were pretreated with 10 mg/kg of, i.p., phentolamine (▲) or propranolol (■). The analgesic effect (the response time, a cut-off time of 6 sec) was measured by the modified Haffner’s method and calculated as AUC (area under the curve) by plotting the increase of response time (sec) against time (min). Development of tolerance was assessed by the decrease percent in AUC in comparison with the value on the 1st day. Figures in parentheses indicate the day after exchange of the blockers. The AUC of the control group on the 1st day was 361±22 (min-sec). Each point shows the mean±S.E. Significantly different from the value on the 1st day, □: P<0.05, closed symbol: ▲<0.01. Significantly different from the value in the animals treated with each blocker and morphine for 10 days, ▲▲P<0.01.
Fig. 2. Effect of daily alternative combination of the blocker with morphine on the development of analgesic tolerance to morphine. Phentolamine (△) or propranolol (□) were alternatively combined with morphine for 9 days. Control animals received saline instead of blockers (○). Each group consists of 16 animals. The AUC of the control group on the 1st day was 347±15 (min-sec). Significantly different from the value on the 1st day, ○: P<0.05, closed symbol: P<0.01. For other details, refer to the footnote of Fig. 1.

Fig. 3. Effect of co-administration of phentolamine plus propranolol with morphine and omission of either one or both blockers on the development of analgesic tolerance to morphine. Mice were pretreated with phentolamine plus propranolol (○—○, N=42) 30 min before morphine injection. From the 6th day, in some animals, the co-administration of phentolamine (□—□, N=9), propranolol (△—△, N=9) or both blockers (○—○, N=9) were omitted. Control animals received saline instead of blockers (○—○, N=18). Figures in parentheses indicate the day after omission of the blockers. The AUC of the control group on the 1st day was 315±22 (min-sec). Significantly different from the value on the 1st day, △: P<0.05, closed symbol: P<0.01. Significantly different from the value in the animals treated with both blockers and morphine for 10 days (N=15), *P<0.05, **P<0.01. For other details, refer to the footnote of Fig. 1.
blockers: Daily alternative combination of phentolamine or propranolol with morphine gradually developed tolerance from the 3rd day, regardless of the nature of the blockers on the 1st treatment (Fig. 2).

3. Co-administration of both blockers and omission of one of them: Co-administration of both phentolamine and propranolol with morphine had no influence on the analgesic effect of morphine, while it completely suppressed the development of tolerance to morphine during the combined treatment for 10 days. From the 6th day, when the co-administration of either one or both blockers was omitted, tolerance developed as in the control animals treated with morphine alone (Fig. 3).

Discussion

As has been reported, both phentolamine and propranolol, an α- and β-adrenergic blocker, respectively could suppress the development of tolerance to the analgesic effect of morphine when it was administered daily in combination with morphine. The suppressive effect of phentolamine or propranolol on the development of tolerance to morphine could not be substituted by each other. Namely, in the animals treated with morphine plus either one of the blockers, the development of analgesic tolerance to morphine was completely suppressed; however, substitution of the blocker for the other one could not maintain the suppressive state, and tolerance developed as rapidly as in the case of the control animals treated with morphine alone. Similarly, daily alternative combination of the blockers with morphine progressively developed tolerance to morphine. Furthermore, simultaneous combination of both blockers with morphine also suppressed the development of tolerance to morphine, but the omission of either one or both blockers resulted in the loss of the tolerance blocking effect.

These results may suggest that the mechanisms of α- and β-blockers for the suppression of the development of tolerance to morphine are different from each other. Furthermore, the preceding treatment with either one or both blockers with morphine would produce a profound and specific alteration in the action mechanism to develop tolerance to morphine, since we have suggested that the analgesic effect of morphine may be dissociable from its tolerance and dependence liability (3, 4). The present results also support the previous findings and clearly demonstrated that the development of tolerance to morphine was suppressed by the combined treatment with adrenergic blockers without affecting the analgesic effect. The apparent analgesic effect maintained at the control level during combined treatment with phentolamine or propranolol was not attributed to the potentiation by the blockers of the morphine effect since the reduced analgesic effect of morphine in tolerant animals was not potentiated by blockers.

Hypersensitivity or up-regulation of the receptors is expected after repeated administration of the blockers, and it has been reported that the clinically observed "propranolol withdrawal syndrome" is due to β-adrenergic hypersensitivity after abrupt discontinuation of propranolol treatment (5). Actually, Aarons et al. (6) have demonstrated the increase in the density of β-adrenergic receptors after 5 daily propranolol administrations in human erythrocytes. In our preliminary study, we found that the analgesic effect of morphine was significantly reduced in the animals pretreated with phentolamine or propranolol for 5 days. This result may suggest that up-regulation of adrenergic receptors or function produces reduction in the analgesic effect of morphine.

On the other hand, there is much data on the changes in catecholaminergic function after chronic treatment with morphine (7, 8), and the hypersensitivity of the noradrenergic or dopaminergic function has been proposed as a possible mechanism for morphine tolerance and dependence (9, 10).

On the contrary, however, in the present experiments, daily combined treatment of adrenergic blockers with morphine completely suppressed the development of tolerance to morphine, although the up-regulation of adrenergic receptors by the repeated administration of blockers with morphine was expected. Thus, the mechanisms of the suppressive effect of adrenergic blockers on the development of analgesic tolerance to morphine could not be explained by the specific alterations in the functions of adrenergic
receptors.

We have reported that both $\alpha$- and $\beta$-adrenergic blockers, even drugs which act on the respective receptor subtypes, suppressed the development of tolerance to morphine without affecting the catecholamine content in the brain (1). Namely, the fact suggested the importance of the equilibrated state of adrenergic functions rather than the brain level of catecholamines in the mechanism for the development of tolerance to morphine. The results obtained here also revealed that the changes in the equilibration of the adrenergic function, which plays a key role in brain function, may produce an unbalance of the network of various nervous systems in the CNS and interfere with the development of tolerance to morphine.

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References