Differential Roles of the Adrenal Gland in the Suppression of Morphine Antinociceptive Tolerance Development by α- and β-Adrenergic Blockers

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ABSTRACT—Concomitant treatment with phentolamine, an α-blocker, or with propranolol, a β-blocker, suppressed the development of morphine tolerance in sham-operated (Sham) mice. In adrenalectomized (ADX) mice, daily morphine developed tolerance as well as in the Sham group, and concurrent phentolamine suppressed the development of tolerance, whereas such suppression by propranolol was abolished. Supplemental treatment of ADX mice with dexamethasone did not restore the suppressive effect of propranolol. These results suggest that different mechanisms underlie the prevention of tolerance development by α- and β-blockers, and that adrenal cortex does not seem to participate in the suppression by β-blockers.

It is well-established that adrenergic function plays an important role in the production of antinociception by morphine and the development of tolerance to the effect (1–4). Recent studies in our laboratory have shown that α- and β-adrenergic blockers co-administered with morphine suppress the development of antinociceptive tolerance to morphine without affecting the antinociceptive effect as shown on the initial day (5). Furthermore, α- and β-adrenergic blockers mainly act on the supraspinal area in suppressing the development of tolerance (6). However, it has been reported that bilateral adrenalectomy causes a significant increase in α-adrenoceptor-mediated potentiation of β-adrenoceptor-stimulated cAMP accumulation in rat brain and attenuates the vasopressor responses by stimulation of postjunctional α2-adrenoceptors in pithed rats (7, 8), suggesting the possibility that adrenal function, in addition to the direct central mechanisms (6), are involved in the suppression by α- and β-blockers of tolerance development.

On the other hand, we have also reported that concurrent footshock exposure abolished the development of analgesic tolerance to morphine and have demonstrated that the adrenal glucocorticoids play an essential role in the suppression by exposure to footshock stress (9).

In the present study, it was examined how the adrenal function participates in the suppression by α- and β-adrenergic blockers of the development of morphine tolerance in the adrenalectomized (ADX) animals.

Male ddY strain mice weighing 18–20 g were purchased and housed in groups of 10 animals in plastic cases with free access to food and water. They were kept in ambient room temperature, 22 ± 1°C, and after reaching 23–26 g, they were employed for the experiments. Adrenalectomy or sham operation was performed by bilateral dorsal incisions under
ether anesthesia. Both ADX and sham-operated (Sham) mice were given 0.9% NaCl as drinking water, with normal laboratory diet, and allowed 14 days to recover from the surgical trauma.

Morphine-HCl (Takeda Pharm. Co., Osaka) and dl-propranolol (Nacalai Tesque, Kyoto) were dissolved in saline, and phentolamine mesylate (Regitin®, Ciba-Geigy, Switzerland) and dexamethasone sodium phosphate (Decadron®, Banyu Pharm. Co., Tokyo) were diluted with saline. Adrenergic blockers, 10 mg/kg, respectively, were daily given i.p. at 30 min prior to the s.c. injections of morphine, 10 mg/kg. Dexamethasone, 500 μg/kg for supplemental doses, was administered s.c. twice a day (9:00 and 17:00) from 24 hr after the adrenalectomy throughout the experimental period. Morphine was administered 1 hr after the dexamethasone injection of on the test days.

The antinociceptive effect was measured by the modified Haffner's method (10), using a 6-sec cut-off time to avoid tissue damage. Measurements were made every 15 min after the administration of morphine for a period of 90 min. The antinociceptive effect was expressed as the area under the curve (AUC), which was obtained by plotting the increase in response time (sec) on the ordinate and the time interval (min) on the abscissa.

The antinociceptive effect of morphine alone or in combination with phentolamine or propranolol was determined daily for 5 days. The decrease in analgesic response was considered an indication of the development of tolerance. The results were expressed as the mean ± S.E. Following a two-way analysis of variance for repeated measures of the overall data to assess statistical significance, differences between the individual mean values in different groups were analyzed by the Dunnett's test. The difference was considered to be significant at P < 0.05.

In the Sham mice, daily injections of morphine, 10 mg/kg, s.c., gradually developed tolerance; however, the concomitant treatment with morphine and the α-blocker phentolamine, 10 mg/kg, i.p., or with the β-blocker propranolol, 10 mg/kg, i.p., suppressed the development of morphine tolerance without affecting the antinociceptive effect as shown on the 1st day (Fig. 1, left panel). In ADX mice, daily morphine developed tolerance as well as in the Sham group, and the prevention of the development of morphine tolerance by concurrent phentolamine was observed. However, the suppression by concurrent propranolol was abolished by adrenalectomy (Fig. 1, middle panel). The antinociceptive effect of morphine on the 1st day was significantly potentiated by the adrenalectomy. The supplemental treatment of ADX mice with dexamethasone, 500 μg/kg, s.c., did not prevent the suppression by propranolol of tolerance development which was shown in Sham mice (Fig. 1, right panel).

We have previously reported that the suppressive effect of exposure to footshock on the development of morphine tolerance in naïve mice cannot be found in ADX mice, and such suppression is restored in ADX mice by prednisolone, suggesting an essential role of adrenal glucocorticoids in the mechanism (9). In this experiment, the suppression by propranolol of the development of morphine tolerance in Sham mice was abolished by adrenalectomy, whereas that by phentolamine was not affected. This may suggest that α- and β-adrenoceptor mediating mechanisms play mutually different roles in the suppression of tolerance development. The differential mechanism between α- and β-adrenoceptors in the suppression is supported by our earlier findings that the suppressive effect of an α-blocker cannot be maintained by the substitution with a β-blocker, and vice versa (5). Although the neurochemical mechanism through which the suppression by a β-blocker, but not that by α-blocker, was nullified by adrenalectomy is uncertain, it is suggested that besides the direct central mechanism, which is suggested by i.c.v. administered blockers (6), adrenal functions are also related to the suppression in response to propranolol and, to a lesser extent, in response to phentolamine.
Dexamethasone did not produce the supplemental effect on the deficiency of glucocorticoids in ADX mice treated with morphine and propranolol. Thus, in contrast to footshock exposure, it seems unlikely that the abolishment of suppression by propranolol is due to a lack of humoral glucocorticoids caused by adrenalectomy. This also suggests that exposure to footshock stress and administration of the blocker prevent the development of morphine tolerance by distinct mechanism.

On the other hand, adrenalectomy increase $\beta$-adrenoceptor-stimulated cAMP through the activation of $\alpha$-adrenoceptors in rat cerebral cortex (8). Thus, it cannot be excluded that the function of $\alpha$- and $\beta$-adrenoceptors in the CNS may be altered by adrenalectomy through the mediation of the changes in the peripheral sympathetic neuronal system and/or pituitary-adrenal axis.

In conclusion, we demonstrated, using ADX mice, that different mechanisms underlie the prevention of the development of tolerance to morphine by $\alpha$- and $\beta$-blockers, and that adrenal cortex function does not seem to participate in the suppression by $\beta$-blockers of the development of tolerance to morphine.

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