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Evidence for the dissociation of morphine analgesia, tolerance and dependence

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A single large dose of morphine produced profound analgesia accompanied by the development of tolerance and physical dependence. The tolerance developed acutely within 24 h and was further intensified, reaching a peak on the 5th day, then gradually disappeared. Partial or complete masking of morphine analgesia by naloxone inhibited the development of the acute, but could not prevent the development of the delayed, tolerance. These results suggest there are two kinds of tolerance and that the analgesic effect is separate from tolerance. Similarly, treatment with morphine produced physical dependence which was precipitated by naloxone, Unlike tolerance, dependence did not develop when morphine analgesia was completely masked by naloxone. The findings provide for the dissociation or morphine analgesia, tolerance and dependence.

It has been thought that the analgesic effect of narcotic drugs could not be separated from their ability to produce tolerance and dependence. In particular, the parallel appearance of tolerance and dependence suggested that both phenomena had common mechanisms. However, evidence has been accumulated which indicates the possible dissociation of analgesic effect from tolerance and/or dependence (Cox et al 1968; Jacquet 1979; Miksic et al 1980; Kaneto et al 1983) and also tolerance from dependence liability (Wüster et al 1982; Johnson & Duggan 1984). We report here evidence that morphine analgesia, tolerance and dependence may be dissociated from each other.

Material and methods

Male mice of ddY strain, 25–27 g, in groups of 20 animals having free access to normal laboratory diet and tap water were housed in a temperature controlled room.

On the 1st day, they were treated as follows: Group 1 received morphine, 50 mg kg^{-1} s.c.; group 2, had naloxone, 10 mg kg^{-1} i.p. 30 min before the morphine injection and group 3 had 3 injections of naloxone, 10 mg kg^{-1} i.p. 5 min before, 1 and 2 h after morphine. The analgesic effect (the response time, a cut-off time of 6 s) was measured by a modified Haffner's method (Takagi et al 1966). Animals of each group were further divided into 3 sub-groups. To evaluate the degree of tolerance, the analgesic effect of a test dose of morphine, 10 mg kg^{-1} s.c., was measured on the 2nd, 5th and 10th day. The measurement was made every 15 min for 90 min. The effect was calculated by plotting the increase of response time (s) against time and the AUC was expressed as percent of the effect obtained in saline-treated controls. Separate groups of animals were treated as described above on the 1st day. They were divided into 3 sub-groups and challenged with naloxone, 10 mg kg^{-1} i.p. on the 2nd, 5th and 10th day, respectively. The degree of physical dependence was assessed by scoring the withdrawal signs according to Kaneto et al (1973). Observation of the withdrawal signs was started immediately after naloxone injection, and the 10 min observation was repeated 3 times with a 20 min intermission. The relative intensity of the physical dependence was expressed as the sum of the withdrawal scores of 3 observation periods. Naloxone did not precipitate any withdrawal signs in the saline-treated controls. Each sub-group consisted of at least 20 animals.

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Results and discussion

As shown in Fig. 1a, a single dose of 50 mg kg^{-1} s.c. of morphine produced a marked analgesia lasting about 3·5 h (Group 1). Naloxone pretreatment, 10 mg kg^{-1} i.p., 30 min before the morphine, partially antagonized the analgesic effect, especially initially (Group 2). The analgesic effect of morphine was completely suppressed by three injections of naloxone given at 5 min before, 1 and 2 h after morphine (Group 3).

In the preliminary experiments, we found that after a single dose of morphine, 50 mg kg^{-1} s.c., tolerance developed on the 2nd day, reached its peak on the 5th day then gradually declined. So, in this study, the degree of tolerance and physical dependence were determined on the 2nd, 5th and 10th day. Development of tolerance on the 2nd day was completely inhibited in both groups treated with naloxone on the 1st day (Fig. 1b). The inhibition was attained in the group which was treated with a single injection of naloxone 30 min before the analgesic effect was partially antagonized. We have reported previously (Kaneto et al 1983) that the latter part of the duration of morphine analgesia was partially antagonized by naloxone, while the development of tolerance on the 2nd day was completely inhibited. Thus, for the development of tolerance on the 2nd day, full expression of morphine analgesia at the initial treatment is essential. In group 3, the analgesic effect of morphine was completely masked by naloxone on the 1st day, tolerance developing to the same extent as in

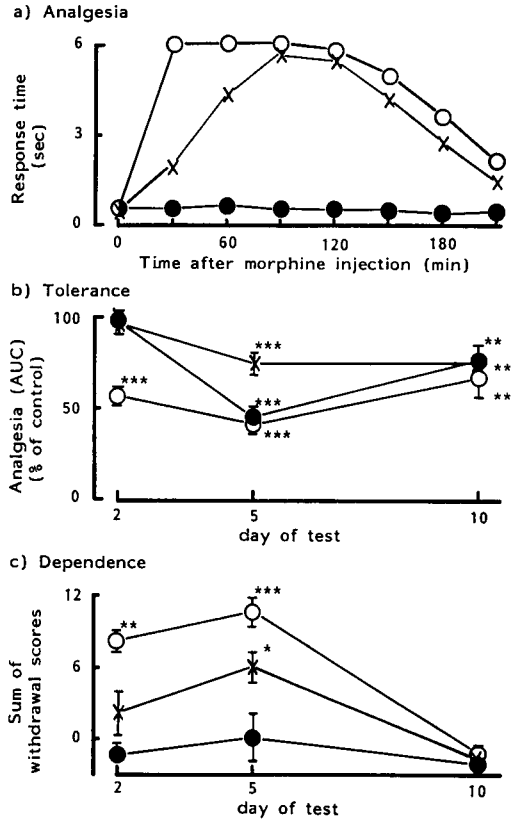

Fig. 1. (a) Analgesia, (b) tolerance and (c) dependence after a single dose of morphine in mice of ddY strain. On the 1st day, they were treated as follows: Group 1, morphine, 50 mg kg^{-1} s.c. (○—○). Group 2, naloxone, 10 mg kg^{-1} i.p., was given 30 min before morphine injection (×—×). Group 3, 3 injections of naloxone, 10 mg kg^{-1} i.p., 5 min before, 1 and 2 h after morphine administration (○—○). Values are the mean, and the vertical bars indicate the s.e. Significantly different from control, $*P < 0.05$, $**P < 0.01$, $***P < 0.001$ (Student's t-test).

group 1 on the 5th day. Here we confirmed our previous finding that after a single dose of morphine two kinds of tolerance, acute and delayed, developed to its analgesic effect. The acute kind could be prevented by partial or complete inhibition of the morphine effect by co-administered naloxone, but the delayed effect was insensitive to naloxone. The fact that complete masking of morphine analgesia by naloxone could not prevent the development of delayed type tolerance may indicate the existence of a mechanism unrelated to morphine analgesia.

The degree of tolerance on the 5th day was greater in group 3 than in group 1 (Fig. 1). Thus the apparent analgesia, calculated as area under the curve at the initial treatment, is not the determinant factor for the degree of delayed tolerance. After the peak on the 5th day, however, no difference was observed between the three groups in the degree of tolerance.

When the animals in group 1 were challenged with naloxone on the 2nd day there were various withdrawal signs such as jumping, falling, backward locomotion, and rearing. On the 5th day, parallel with the progress of tolerance, a higher degree of physical dependence was noted. However, naloxone failed to precipitate any withdrawal signs on the 10th day. A similar tendency was evident but less marked in group 2 and no withdrawal signs were precipitated by naloxone in group 3 (Fig. 1c). A high degree of tolerance in the absence of physical dependence, as demonstrated in group 3, indicates the difference in the underlying mechanisms of the two phenomena.

In the animals treated with a single or three repeated injections of naloxone on the 1st day, the test dose of morphine, 10 mg kg^{-1} s.c., produced the same degree of analgesia as in naive or saline-treated control animals on the 2nd and 5th day (data not shown). Thus, the evidence presented clearly demonstrates the possibility of the dissociation of morphine analgesia, tolerance and dependence.

REFERENCES

Cox, B. M., Ginsberg, M., Osman, O. H. (1968) Br. J. Pharmacol. 33: 245–256

Jacquet, Y. F. (1979) Trends Neurosci. 2: 140–143

Johnson, S. M., Duggan, A. W. (1984) Eur. J. Pharmacol. 97: 305–308

Kaneto, H., Koida, M., Nakanishi, H., Sasano, H. (1973) Japan. J. Pharmacol. 23: 701–707

Kaneto, H., Hirota, N., Yamazaki, A. (1983) Life Sci. 33: 353–356

Miksic, S., Schearman, G. T., Lal, H. (1980) Subst. Alcohol Actions/Misuse 1: 281–285

Takagi, H., Inukai, T., Nakama, M. (1966) Japan. J. Pharmacol. 16: 287–294

Wüster, M., Schulz, R., Herz, A. (1982) Life Sci. 31: 1695–1698