Participation of the Nucleus Reticularis Gigantocellularis in the Morphine-Induced Elevation of Plasma Corticosterone in Rats

Shiroh KISHIOKA, Sadako TAMURA, Yoshiyuki IGUCHI, Masanobu OZAKI and Hiroyuki YAMAMOTO
Department of Pharmacology, Wakayama Medical College, Wakayama 640, Japan

Accepted May 8, 1985

Abstract—The effects of morphine, adrenocorticotropic hormone (ACTH) and formalin on plasma corticosterone levels were investigated in the nucleus reticularis gigantocellularis (NRGC)-lesioned rats. ACTH (1.0 U/kg) or formalin (6.4%, 0.2 ml/rat) elevated plasma corticosterone in both sham-lesioned and NRGC-lesioned rats at the same degree, while morphine (10 mg/kg) also elevated plasma corticosterone in sham-lesioned rats, the elevation of which was significantly reduced by NRGC-lesioning. These findings suggest that the NRGC is involved in the corticosterone-increasing effect of morphine, but not involved in the effect of ACTH or formalin.

The nucleus reticularis gigantocellularis (NRGC), including the nucleus reticularis paragigantocellularis, of the medulla oblongata is one of the sensitive sites in the production of morphine analgesia in rats (1). Recently, it was made clear that morphine analgesia induced by systemic injection was depressed by NRGC-lesioning (2).

There are many investigations into the effects of morphine on the hypothalamo-pituitary-adrenal system demonstrating that morphine increased the plasma corticosterone concentration in naive rats (3) and that no elevation of plasma corticosterone was elicited by morphine in rats showing tolerance to the morphine analgesic effect (4). It has been found that the increase in plasma corticosterone was induced by morphine abstinence (4–6). Moreover, morphine analgesia was increased by adrenalectomy without any influence on the development of tolerance to and dependence on morphine (7). These findings suggest a relationship between the hypothalamo-pituitary-adrenal function and the morphine actions, but the details of this interaction remain unknown.

It seems to be of interest to investigate whether the site involved in the production of the morphine analgesic effect is the same as that in the increasing effect of morphine on plasma corticosterone.

The purpose of the present study is to examine the effects of NRGC-lesioning on the stimulating effect on the hypothalamo-pituitary-adrenal system of morphine, compared to the said effects on the increase in plasma corticosterone due to adrenocorticotropic hormone (ACTH) and formalin which is one of the non-specific stressful manipulations.

Sprague Dawley male rats, initially weighing 275–325 g, were used. They were housed in groups of two in hanging wire cages in an air-conditioned (23–24°C) and light-controlled (lights on from 08:00 to 20:00 daily) room. Food (CA-1, Clea Japan Inc.) and water were available ad libitum.

The NRGC of the rats was bilaterally lesioned by a direct current via a monopolar electrode (0.5 mA for 40 sec) under pentobarbital anesthesia. No abnormality in motor activity was observed in NRGC-lesioned rats. In rats serving as surgical controls (sham lesioned), the electrode was inserted into the NRGC, but no current was passed. The animals were allowed to recover for 13–16 days following surgery before their response to stresses were tested. At the end of every experiment, the brains were
removed and the lesioned site and its size were identified histologically according to the atlas of Fifkova and Marsala (8). When the position of lesioning was not exactly located in the NRGC, it was designated as a deviated lesioning. The size of the lesioned area on days 13–16 after surgery was about 13% of the NRGC area at the level of P10. The typical position and extent of the lesions are portrayed in Fig. 1.

Experiments were performed between 10:00 and 12:00, when the basal corticosterone level is low. Morphine (10 mg/kg, morphine hydrochloride, Takeda Chem.), ACTH (1.0 U/kg, ACTHAR, Armour Pharmaceutical Comp.) or formalin (0.2 ml of 6.4% solution per rat, Katayama Chem.) was subcutaneously injected 30 min before the blood sampling which was done by cardiopuncture under a large dose of pentobarbital (600–900 mg/kg, i.p.). Plasma corticosterone was estimated fluorimetrically using the method of Zenker and Bernstein (9).

In the data, each column and vertical bar indicates the mean±S.E.M. Statistical evaluation was made using Student’s t-test. \( P<0.05 \) was considered significant.

Plasma corticosterone levels after injection of saline, morphine, ACTH or formalin are shown in Fig. 2.

In sham-lesioned rats, morphine, ACTH or formalin injection caused significant rises of plasma corticosterone levels. ACTH or formalin injection also elevated corticosterone levels in NRGC-lesioned rats, and there was no significant difference between the corticosterone levels of the sham-lesioned group and those of the NRGC-lesioned group. However, in the case of morphine injection, elevation of plasma corticosterone level in NRGC-lesioned rats was significantly lower than that in the sham-lesioned group, although the plasma corticosterone level was significantly increased by morphine in the NRGC-lesioned group. When the lesion was deviated from NRGC, the increase in plasma corticosterone level was greater than that in the NRGC-lesioned group by morphine injection.

The basal level of plasma corticosterone was not affected by NRGC-lesioning.

Yamamoto et al. (4) reported that analgesic doses of morphine caused the elevation of plasma corticosterone level dose-dependently, which was not detected in morphine tolerant rats. Kokka et al. (5) and Suzuki et al. (10)
demonstrated that the rise of plasma corticosterone level by morphine was antagonized by naloxone. ACTH or formalin also increased plasma corticosterone level dose-dependently (3).

It was also confirmed that morphine, ACTH or formalin injection elevated the plasma corticosterone level in sham-lesioned rats. While NRGC-lesioning had no effect on the elevation of plasma corticosterone level induced by ACTH or formalin, the plasma corticosterone increase induced by morphine was significantly reduced by NRGC-lesioning and was less reduced by deviated lesioning than by NRGC-lesioning. Morphine analgesia was markedly reduced by NRGC-lesioned rats and was moderately inhibited by deviated lesioning (2). Plasma corticosterone increase and analgesia by morphine in NRGC-lesioned rats were about 12% and 50% of the control, respectively.

These results suggest that the NRGC is one of the sites participating in both morphine analgesia and morphine induced increase in plasma corticosterone and that the site involved in the elevation of plasma corticosterone induced by morphine may be different from that involved in the increase induced by formalin.

References

1 Takagi, H.: The nucleus reticularis paragiganto-locellularis as a site of analgesic action of morphine and enkephalin. Trends Pharmacol. Sci. 1, 182–184 (1980)

2 Kishioka, S., Iguchi, Y., Ozaki, M. and Yamamoto, H.: Effect of electrical lesioning of nucleus reticularis gigantocellularis of rat medulla oblongata on morphine analgesia. Folia Pharmacol. Japon. 82, 475–484 (1983) (Abs. in English)

3 Kuki, M.: Hypothalamo-pituitary adenocortical (HPA) function in the morphine dependent rat. Folia Pharmacol. Japon. 75, 215–225 (1979) (Abs. in English)

4 Yamamoto, H., Mikita, S., Yano, I., Masuda, Y. and Murano, T.: Studies on the physical dependence liability of analgesics. 2nd report: Relationship between transformation of intramitochondrial structures in adenocortical cells and corticosterone biosynthesis in morphine addicted rats. Japan. J. Pharmacol. 23, 217–225 (1973)

5 Kokka, N., Garcia, J.F. and Elliott, H.W.: Effects of acute and chronic administration of narcotic analgesics on growth hormone and corticotrophin (ACTH) secretion in rats. Prog. Brain Res. 39, 347–360 (1973)

6 Kishioka, S., Iguchi, Y., Ozaki, M. and Yamamoto, H.: Morphine tolerance and dependence liability in NRGC destructed rats. Folia Pharmacol. Japon. 83, 269–280 (1984) (Abs. in English)

7 Wei, E.: Morphine analgesia, tolerance and physical dependence in the adrenalectomized rat. Br. J. Pharmacol. 47, 693–699 (1973)

8 Fišková, E. and Marsál, J.: Stereotaxic atlas for the cat, rabbit and rat. In Electrophysiological Methods in Biological Research, Edited by Bureš, J., Petráš, M. and Zachar, J., p. 653–731, Academia, Prague (1967)

9 Zenker, N. and Bernstein, D.E.: The estimation of small amounts of corticosterone in rat plasma. J. Biol. Chem. 231, 695–701 (1958)

10 Suzuki, T., Shimada, M., Yoshii, T., Akiba, I. and Yanaura, S.: Effect of morphine on plasma corticosterone concentration in rats. Folia Pharmacol. Japon. 80, 195–202 (1982) (Abs. in English)