10. G. N. Kryzhanovskii and V. K. Lutsenko, Neirofiziologiya, No. 7, 3 (1975).
11. G. N. Kryzhanovskii, M. B. Rekhtman, B. A. Konnikov, et al., Byull. Éksp. Biol. Med., No. 1, 23 (1976).
12. G. N. Kryzhanovskii, M. B. Rekhtman, B. A. Konnikov, et al., Byull. Éksp. Biol. Med., No. 2, 147 (1976).
13. G. N. Kryzhanovskii and F. D. Sheikhon, Byull. Éksp. Biol. Med., No. 11, 9 (1968).
14. M. N. Linyuchev, Yu. F. Satrapinskii, and E. A. Khramova, Farmakol. Toksikol., No. 1, 25 (1972).
15. A. N. Panyukov, Vopr. Med. Khimii, No. 1, 88 (1966).
16. V. B. Prozorovskii, Farmakol. Toksikol., No. 5, 553 (1968).
17. Yu. S. Sverdlov, Neirofiziologiya, No. 1, 25 (1969).
18. F. D. Sheikhon and G. N. Kryzhanovskii, Byull. Éksp. Biol. Med., No. 1, 23 (1975).
19. V. B. Brooks, D. R. Curtis, and J. C. Eccles, Nature, 175, 120 (1955).
20. V. B. Brooks, D. R. Curtis, and J. C. Eccles, J. Physiol. (London), 135, 655 (1957).
21. G. N. Kryzhanovsky (G. N. Kryzhanovskii), Prog. Drug Res., 19, 301 (1975).
22. W. Homann, Langenbecks Arch. Klin. Chir., 284, 140 (1956).
23. G. Leonardi, Boll. Ist. Sieroter. Milan., 51, 229 (1972).
24. G. Leonardi, J. Infect. Dis., 128, 652 (1973).
25. G. Leonardi, K. G. Nair, and F. D. Dastur, Prog. Drug Res., 19, 329 (1975).

EFFECT OF CESIUM, LITHIUM, AND RUBIDIUM ON SOME ACTIONS OF MORPHINE

V. M. Bulaev and R. U. Ostrovskaya

UDC 615.212.7:547.943].015.23:615.31:546.35

The effect of cesium, lithium, and rubidium chlorides on the analgesic action of morphine (in the vocalization test) and on the course of dependence on it (by the "two bottle" test) was investigated. The chlorides were shown to reduce both the threshold of the pain response and the duration of analgesia produced by morphine. Cesium chloride was most active in this respect. All the compounds studied reduced the coefficient of morphine preference. The greatest effect was observed with cesium chloride, which reduced the preference coefficient to one-fortieth of the control level.

KEY WORDS: lithium; cesium; rubidium; dependence on morphine.

In the search for substances for the treatment of dependence on opiates compounds belonging to the alkali metal group could be interesting. The effects of some of them, such as lithium salts, have been investigated by several workers. Admittedly, data in the literature on the effect of lithium on the course of morphine dependence are contradictory. Saarnivara and Mannisto [10], for instance, state that lithium reduces the analgesic action of morphine, whereas Weischer and Opitz [11] found that the analgesic effect of codeine also is weakened by lithium. Meanwhile there are reports that lithium can potentiate the analgesic effect of morphine in experimental animals [6] and also its euphoric action in man [5].

The effect of rubidium on the actions of morphine has received less study. During prolonged administration of rubidium the analgesic effect of morphine is reduced [10], but, unlike lithium, rubidium stimulates motor activity induced by morphine [2].

The effect of cesium on the actions of morphine has not been studied. Considering that cesium possesses neurotropic properties [8], it was clearly desirable to undertake a comparative study of the effect of cesium, lithium, and rubidium on the actions of morphine under identical experimental conditions.

Laboratory of Pharmacology of the Nervous System, Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR V. V. Zakusov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 86, No. 7, pp. 42-44, July, 1978. Original article submitted November 23, 1977.

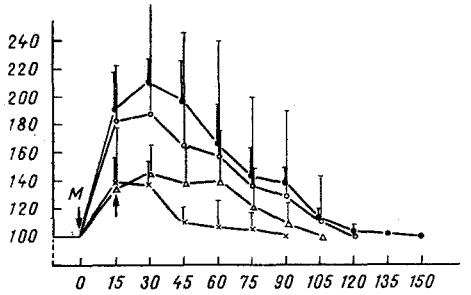

Fig. 1. Effect of cesium, lithium, and rubidium on analgesic action of morphine. 1) Morphine, 2) morphine + lithium, 3) morphine + rubidium, 4) morphine + cesium. Arrows denote time of injection of morphine (M) and of test salts. Abscissa, time (in min); ordinate, threshold of pain response (in %; threshold of response in control 100%).

EXPERIMENTAL METHOD

The effect of cesium, lithium, and rubidium chlorides on the intensity of the analgesic action of morphine was investigated in experiments on rats. A pain response was induced in the animals by electrical stimulation of the tail. Prolonged vocalization [9] served as the criterion of pain. The threshold of the response (in volts) was determined before and every 15 min after intravenous injection of morphine in a dose of 2.5 mg/kg. Aqueous solutions of the chlorides of the metals were injected as a single dose 1 h before morphine was given.

The effect of cesium, lithium, and rubidium chlorides on the course of morphine dependence was studied in mice by the "two-bottle test" [4]. Dependence was produced by giving the animals only a solution of morphine in increasing concentrations (from 0.3 to 1 mg/kg) to drink by a modified method of McMillan et al. [7]. These workers showed that administration of morphine for 2 weeks in increasing concentrations (up to 1 mg/kg) causes the animals to become physically dependent on morphine, as confirmed by the development of a withdrawal syndrome after administration of naloxone to the animals.

Experiments were carried out on mice divided into four groups (10 mice in each group). For 25 days the animals were given morphine as the sole fluid to drink. On the 26th day the mice of groups 1, 2, and 3 were given intraperitoneal injections of cesium, lithium, and rubidium chlorides in doses of 210, 210, and 150 mg/kg respectively; the animals of group 4 (controls) received an injection of distilled water. Immediately after injection of the compounds the animals were offered morphine solution and water, and during the next 5 days their consumption was determined under free choice conditions. The coefficient of preference was calculated as the ratio between the volume of morphine solution and the total volume of fluid consumed (M/M + W). At the end of this time the animals were again given morphine solution as the only fluid to drink (in a concentration of 1 mg/kg) for 2 days, after which they were again offered the choice between morphine solution and water, in order to determine the degree of recovery of preference.

EXPERIMENTAL RESULTS AND DISCUSSION

Morphine (in a dose of 2.5 mg/kg intravenously) caused a more than twofold rise in the threshold of the pain response; the mean duration of the analgesic effect in this case was 2.5 h. The maximal rise in the threshold of the pain response was observed 20-30 min after injection of morphine. These times coincided with the peak of the morphine concentration in the rat brain after intravenous injection in this dose [3]. As Fig. 1 shows, cesium, lithium, and rubidium chlorides weakened the analgesic action of morphine by reducing both the threshold of the pain response and the duration of analgesia. Of the three compounds tested, cesium chloride showed the greatest ability to weaken morphine analgesia.

The same compound also was more active as regards its influence on preference for morphine, as measured by the "two-bottle test." In animals not compelled to take morphine the mean coefficient of preference was 0.11 (the mean daily consumption of morphine solution was 5 ml and of water 40 ml); after the development of dependence it increased to 0.8, evidence of marked preference for morphine. Preference was reduced in

the animals receiving the test salts. In the case of cesium chloride the coefficient of preference was 0.14 on the 1st day, 0.02 on the 2nd, and 0.1 on the 3rd and 4th days. Evidence of the significance of the effect of cesium in reducing morphine dependence was given by an increase in the coefficient almost to its initial level (0.65) after the animals had been given morphine solution for 2 days as the sole drinking fluid. A decrease in the degree of preference was produced also by both lithium and rubidium: In the animals of these series the coefficient of preference was reduced on the 1st day to 0.22 and 0.25 respectively; later, in series II, the initial level of consumption of morphine and water was quickly restored, whereas in series I the coefficient of preference remained low for a further 3 or 4 days.

These results indicate that cesium, lithium, and rubidium chlorides have an antimorphine action, for they reduce the intensity of morphine analgesia and the degree of preference for morphine. According to both tests used, cesium chloride was most active in this respect.

The mechanism of the effects described above is not yet clear. According to Byck's hypothesis [1], lithium affects the mechanism of binding of encephalin with opiate receptors. Whether or not this applies also to rubidium and cesium, and whether or not this mechanism is related to their antimorphine action is not yet clear. Despite the absence of any clear notions of the causes of the effect described above, the facts themselves are interesting from the standpoint of the possible use of these compounds, especially cesium salts, in the treatment of morphine dependence. The correlation observed between the ability of these salts to reduce morphine analgesia and to reduce the degree of preference for morphine may serve as the basis for an experimental study of substances with antimorphine action.

LITERATURE CITED

1. R. Byck, Lancet, 2, 72 (1976).
2. B. Carrol and P. Sharp, Science, 172, 1355 (1971).
3. D. Dahlstrom, G. Paalzow, and L. Paalzow, Life Sci., 17, 11 (1975).
4. B. Fernandez and J. Ternes, Bull. Psychonom. Soc., 5, 331 (1975).
5. D. Jasinski, J. Nutt, C. Haertzen, et al., Science, 195, 582 (1977).
6. J. Jensen, Acta Pharmacol. (Copenhagen), 35, 395 (1974).
7. D. McMillan, F. Waddell, and C. Cathcart, J. Pharmacol. Exp. Ther., 190, 416 (1974).
8. F. Messina and J. Krantz, Am. J. Pharmacol., 145, 17 (1973).
9. G. Paalzow and L. Paalzow, Psychopharmacologia (Berlin), 45, 9 (1975).
10. L. Saarnivara and P. Mannisto, Arch. Int. Pharmacodyn., 222, 282 (1976).
11. M. Weischer and K. Opitz, Arzneimittel-Forsch., 20, 1046 (1970).