CORRELATION BETWEEN ANALGESIC ACTION OF NARCOTIC ANALGESICS AND THEIR ABILITY TO INDUCE BEZOLD'S TRIAD

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All the analgesics investigated (morphine, trimeperidine, methadone, hydrocodon, dionin) evoke a Bezold–Jarisch reflex in rats. A high degree of correlation is found between the analgesic activity and ability of these substances to evoke this reflex and also to produce tachyphylaxis. The total serotonin content in the brain was unchanged under the influence of morphine.

Many attempts have been made to link the mechanism of analgesia with interference by the analgesic in processes requiring the participation of mediators and neurohormones [2, 6, 8, 12, 15]. The role of catecholamines in the analgesic effect has been demonstrated [1, 2]. However, the role of serotonin in the mechanism of analgesia has not been adequately studied. Meanwhile facts described in the literature (the tranquilizing action of morphine, similar to the effect of reserpine, the ability to excite parasympathetic centers which is common to both of them, and the ability of morphine and other analgesics to liberate serotonin from certain depots [3, 6, 9, 13]) indicates that a link may exist between the analgesic effect and changes in serotonin metabolism under the influence of morphine.

In the investigation described below the analgesic activity of a number of narcotic analgesics was compared with ability to evoke the Bezold–Jarisch reflex which, according to data in the literature, is connected with the serotonin liberating activity of analgesic drugs [5].

EXPERIMENTAL METHOD

Experiments were carried out on albino rats weighing 120-180 g. The analgesic activity of morphine, methadone, trimeperidine, hydrocodon, codeine, and dionin was studied. The criterion used to assess analgesic activity was the mean effective dose (ED_{50}), depressing pain sensitivity during electrical stimulation of the tail with a voltage twice the threshold level [4].

TABLE 1. Content of Serotonin (in μg/g fresh weight) in Various Parts of Rats' Brain before and after Action of Morphine

Parts of brain	Before action of morphine	After action of morphine
Cortex	0,71 (0,55±0,87)	0,95 (0,51±1,39)
Diencephalon	0,38 (0,31±0,44)	0,48 (0,20±0,76)
Mesencephalon and medulla	0,48 (0,33±0,46)	0,69 (0±1,44)
Cerebellum	0,08 (0,06±0,09)	0,27 (0±0,55)

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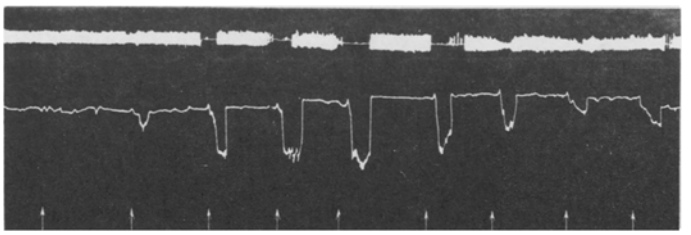

Fig. 1. Bezold–Jarisch reflex and development of tachyphylaxis following administration of methadone. Kymogram of acute experiment on rat. From top to bottom: respiration, arterial pressure; arrows indicate times of injection with doses of methadone.

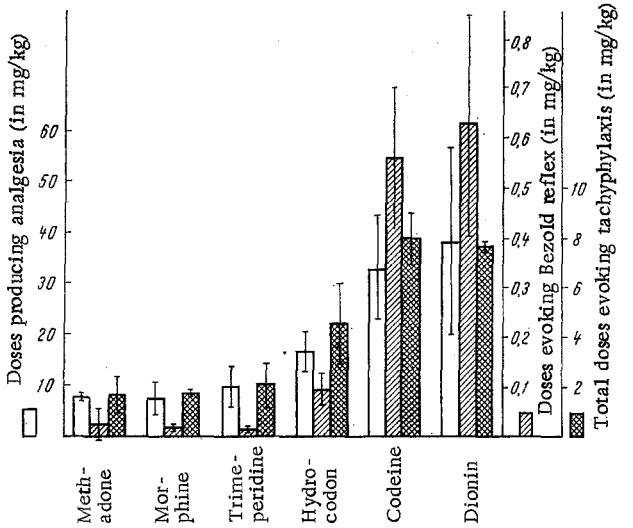

Fig. 2. Comparison of doses of investigated analgesics evoking analgesia, tachyphylaxis, and a Bezold–Jarisch reflex.

Ability of the analgesics to evoke the Bezold–Jarisch reflex was assessed in experiments on rats anesthetized with urethane (1 g/kg). The arterial pressure (in the abdominal aorta) was recorded by a mercury manometer, and respiration by a Marey's capsule. The analgesics were injected intravenously in increasing doses (0.005-3 mg/kg). The following doses were determined: the smallest dose of analgesic producing apnea, hypotension, and bradycardia, and the dose at which, during subsequent administration of the drug by the adopted scheme, one of the components of the reflex was completely absent because of the development of tachyphylaxis (Fig. 1).

The content of serotonin in the rats' brain was investigated 30 min after intraperitoneal injection of morphine in a dose of 20 mg/kg. Serotonin was extracted from the brain tissue with acetone and determined quantitatively by a biological method using a strip of rat's stomach as described by Vane [16].

The analgesic activity of each drug was studied on 20 rats: ED_{50} was calculated by the method of least squares. The ability of each analgesic to evoke a Bezold reflex was determined on 5 rats, and the effect of morphine on the serotonin content in the brain on 10 animals.

EXPERIMENTAL RESULTS

All the drugs studied evoked a Bezold reflex, manifested by hypotension, bradycardia, and apnea. The reflex origin of the reaction was confirmed by the fact that division of the vagus nerves was followed by disappearance of Bezold's triad. A characteristic feature of the reflex following administration of the narcotic analgesics was its disappearance during repeated administration of the drugs (tachyphylaxis).

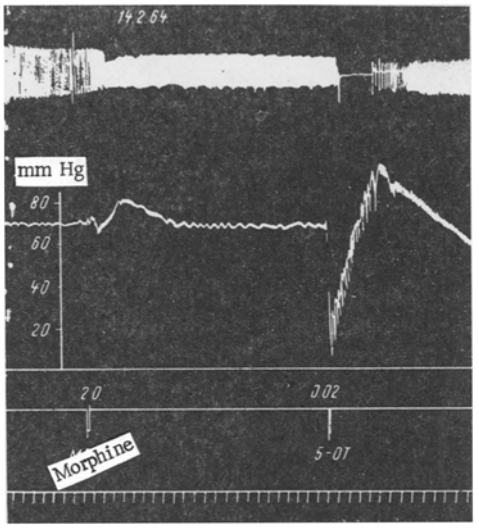

Fig. 3. Absence of Bezold–Jarisch reflex following injection of morphine into a preliminarily reserpinized rat. From top to bottom: respiration, arterial pressure, zero line, marker of injection, time marker (5 sec).

The rate of development of tachyphylaxis following administration of the various substances differed depending on the total dose of drug received by the animal. For instance, the reflex evoked by methadone (Fig. 1) disappeared after administration of a total dose of 1.56 mg/kg of this drug, compared with a total dose of dionin of 7.61 mg/kg.

The minimal doses of the analgesic evoking a Bezold–Jarisch reflex also differed. A reflex was observed following injection of methadone, morphine, and trimeperidine in a dose of 0.01 mg/kg; minimal doses of dionin and codeine evoking the reflex were 0.5 mg/kg. Hydrocodon occupied an intermediate position. Depending on the total doses producing tachyphylaxis, all the investigated analgesics could be clearly divided into two groups: drugs easily producing tachyphylaxis (methadone, morphine, and trimeperidine) and drugs evoking this effect in higher doses (codeine, dionin).

The ability of the analgesics to evoke the reflex triad correlated with their analgesic activity. ED_{50} for methadone, morphine, and trimeperidine did not differ significantly from each other, but were significantly smaller than ED_{50} for codeine and dionin (Fig. 2). Hydrocodon as an analgesic again occupied an intermediate position between them. The coefficients of correlation calculated by Spearman's nonparametric method [14] were 0.94 (comparison of doses producing analgesia and the investigated reflex) and 0.97 (comparison of doses producing analgesia and tachyphylaxis), respectively.

The ability of the tested analgesics to evoke a Bezold reflex with rapidly developing tachyphylaxis is evidently a specific property of these drugs. Evidence of this was given by the fact that nonnarcotic analgesics either do not evoke a Bezold reflex (analgin) or they evoke such a reflex but do not exhibit crossed tachyphylaxis with morphine (sodium salicylate), indicating that the Bezold reflex develops by a different mechanism in the last case.

It can be assumed that the existence of correlation between the pain-relieving activity of the analgesics and their ability to evoke a Bezold reflex is attributable to the common nature of the mechanisms lying at the basis of these types of activity. Accordingly, an investigation was carried out to study the nature of the reflex evoked by the analgesics. The rapidly developing tachyphylaxis indicates that the Bezold reflex may develop as the result of liberation of an endogenous substance. Morphine and other analgesics have been shown to be capable of liberating serotonin [3, 7, 9], and also catecholamines [1, 2]. However, catecholamines do not evoke a Bezold reflex, whereas serotonin does so in minimal doses [5]. It was natural, therefore, to postulate that the ability of analgesics to evoke a Bezold reflex is due to their serotonin-liberating activity. To test this hypothesis, experiments were carried out on reserpinized rats (2 doses, each of 5 mg/kg body weight, given intraperitoneally 24 and 48 h before the experiments). The kymogram (Fig. 3) shows that in rats preliminarily receiving reserpine, morphine does not evoke the Bezold triad even in large doses, whereas the reflex to serotonin is completely preserved. The ability of reserpine to produce a sharp decrease in the content of serotonin in its various depots is well known [10, 11]. Disappearance of the Bezold–Jarisch effect in rats preliminarily treated with reserpine can be explained in the same way.

However, the hypothesis that both types of activity studied are based on liberation of serotonin is contradicted by the fact that morphine, as Table 1 shows, caused no significant change in the total serotonin content in the brain, even at the height of the analgesic effect. The pain-relieving action of the narcotic analgesics is probably due to a change in the content of free serotonin, and not of the total or bound serotonin of the brain. A similar situation has been described for catecholamines [1, 2].

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