Morphine and Antibodies to μ-Opiate Receptors in Ultralow Doses: Effect on Oxygen Consumption

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The degree of oxygen consumption in rats was determined after intraperitoneal injection of morphine in a single dose of 5 mg/kg. Some animals were injected with morphine and perorally received morphine or antibodies to μ-opiate receptors in ultralow doses obtained by the technology of potentiation. Potentiated substances significantly reduced oxygen consumption intensified after morphinization. Potentiated morphine decreased the intensity of oxygen consumption to the level observed in intact animals. Our results indicate that morphine in ultralow doses modulates the action of this compound in toxic concentrations (bipathic phenomenon) and produces the normalizing effect. Potentiated antibodies to μ-opiate receptors modulated the effect of morphine, which indicates that they are involved in the development of opium dependence.

Key Words: *oxygen consumption; morphine; ultralow doses; antibodies; μ-opiate receptors*

A socially important problem of addictions determines the search for new substances capable of modulating the development of dependences. During combination treatment biologically active substances in ultralow doses (ULD) obtained by the technology of potentiation modulate the effect of these compounds in high doses (bipathic phenomenon) [5].

Substances in ULD modulate the effects of morphine. The influence of potentiated morphine (PM) on various types of animal's behavior [2,4] and modification of morphine-produced changes during bipathic treatment were evaluated [3].

New medicinal preparations containing antibodies to S100 protein and morphine are used for the therapy of patients with alcohol and opium withdrawal syndromes, respectively [4]. Therefore, substances in ULD hold much promise for treatment of addictive disorders.

It is important to determine the mechanisms that underlie the influence of exogenous and endogenous compounds in ULD at various stages of addictions and evaluate anti-addictive activity of new substances.

Administration of opiates to rodents causes muscle rigidity [1,9], which is followed by the development of catalepsy after treatment with increasing doses of these compounds [10]. The increase in muscle tone should be accompanied by intensification of oxygen consumption in the muscle tissue and decrease in oxygen content in the expired air. These changes may be recorded on an oxygen analyzer. The increase in oxygen consumption by resting animals treated with morphine may reflect progressive muscle rigidity or cataleptic effect of morphine.

Here we studied the effects of PM (bipathic phenomenon) and potentiated antibodies against μ-opiate receptors (PAB-μR, screening for activity of new substances) on changes in oxygen consumption produced by single treatment with morphine.

MATERIALS AND METHODS

Experiments were performed on male Wistar rats weighing 200-250 g and obtained from the nursery of the Novosibirsk State Medical Academy. The animals were kept in cages (2 specimens per cage) under the natural light/dark cycle and had free access to water and food.

Morphine hydrochloride was injected intraperitoneally in a dose of 5 mg/kg, which causes muscle rigidity [9] and intensifies oxygen consumption in rats [8]. This dose corresponds to a neurotoxic dose (TD) of more than TD_{50} that produces narcotic intoxication [3]. Some rats were injected with morphine and perorally received morphine hydrochloride and polyclonal antibodies against μ-opiate receptors in ultralow doses obtained by the technology of homeopathic potentiation. Potentiated antibodies to morphine (PAB-M) were administered in dilutions of C30 and C200. Antibodies against PAB-μR were given in mixture

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C30+C200. The animals perorally received 500 µl aqueous solution of potentiated substances. Control animals were intraperitoneally injected with isotonic NaCl and perorally received distilled water. Each group included 9 rats.

The animals were placed in a cylindrical semi-transparent chamber (height 18 cm, diameter 8 cm) 20 min after treatment. Air was pumped through the chamber at a flow rate of 0.8 liter/min. A Spirolit device connected to a measuring-and-computational complex served as an oxygen analyzer. Oxygen consumption was recorded for 15 min. The results were averaged at 3-min intervals.

The data were analyzed by standard statistical methods.

RESULTS

Control and treated rats initially displayed irregular behavioral activity in the experimental chamber, but then became still and fell asleep. The degree of oxygen consumption decreased by the end of observations ($p<0.01$).

In morphine-treated rats the degree of oxygen consumption surpassed the control (Table 1). It was probably associated with the increase in muscle tone produced by exogenous and endogenous opiates [1,9,10].

Combination treatment with PM and morphine in allopathic doses markedly reduced oxygen consumption (compared to animals receiving only morphine, Table 1). Treated rats did not differ from the control, which indicates that morphine in homeopathic doses modifies the effect of this compound in standard concentrations.

The rats receiving morphine and PAB-µR were intermediate in the intensity of oxygen consumption between control and morphine-treated animals. From the 4th minute after treatment the degree of oxygen consumption in these rats markedly surpassed the control ($p<0.01$). However, the intensity of oxygen consumption in rats receiving morphine and potentiated antibodies was lower than in morphinized animals (Table 2).

Our results show that PM and PAB-µR modify the effect of morphine and attenuate its influence on physiological functions, *e.g.*, those regulated by the extrapyramidal brain system. Probably, morphine affects dopamine metabolism in the corpus striatum. Therefore, single systemic administration of morphine increases the content of dopamine metabolites in this structure [7]. Potentiated preparations produce the normalizing effect under these conditions. It may suggested that PM and antibodies against PAB-µR bind to opiate receptors and modify their state, which contributes to changes in the interaction between morphine and receptors. PAB-µR affecting only the certain type of receptors produce more specific changes than PM.

These properties of potentiated preparations probably contribute to modification of various effects produced by morphine (*e.g.*, euphoric action underlying reinforcement of addictive behavior) [11]. If so, potentiated preparations hold promise to treat opium dependence in the stage of remission or decrease the efficiency of drug consumption.

TABLE 1. Oxygen Consumption in Animals ($M\pm m$, rel. U)

Group (n=9)	Time, min				
	3	6	9	12	15
Control	250±11	209±11	198±6	192±8	190±10
Morphine	290±11^{+}	276±13*	264±12*	258±11*	253±14**
Morphine and PM (C30)	205±14^{+}	181±11	182±11	178±11	167±15
Morphine and PM (C200)	218±17	200±14	183±13	176±12	191±14

Note. *$p<0.01$ compared to other groups; $^{+}p<0.05$ compared to the control.

TABLE 2. Oxygen Consumption in Animals ($M\pm m$, rel. U)

Group (n=9)	Time, min				
	3	6	9	12	15
Control	236±14	191±8	180±12	158±10	147±5
Morphine	322±19	319±23	317±17	290±17	238±13
Morphine and PAB-µR	274±20	250±17**	229±13*	219±11*	211±7

Note. *$p<0.01$ and **$p<0.05$ compared to the morphine group.

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