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EFFECT OF OPIATE RECEPTOR AGONISTS AND ANTAGONISTS ON MATERNAL AGGRESSION IN RATS

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KEY WORDS: maternal aggression; opiate receptor agonists and antagonists; computerized etiologic pharmacology.

Convincing results indicating involvement of the opiate systems of the brain in the regulation of affective behavior, of intraspecific attachment and sociability have recently been obtained [1, 3-5]. Data on the role of the opiate systems in integration of maternal behavior and, in particular, aggression in lactating females, remain very limited. Accordingly, the aim of the present investigation was to study the effects of opiate-positive and negative drugs on the structure of behavior of lactating females relative to a strange male and offspring.

EXPERIMENTAL METHOD

Experiments were carried out on 54 lactating female rats weighing 250-350 g during the two weeks after giving birth. Intraspecific behavior of the mothers was analyzed 20 min after intraperitoneal injections of physiological saline or the appropriate drug. For this purpose, a strange male was placed in the cage in which the female and her offspring were kept constantly, and the behavior of the female toward the male and the offspring was assessed for a period of 5 min. The data were recorded and analyzed statistically by methods of computerized etiologic pharmacology [2, 3], using the "Étograf-ÉVM" complex. The behavior of the lactating females was described by means of a discrete stationary mathematical model [3]. Matrices of statistical probabilities of diadic transitions of behavioral elements were represented by directional graphs. Nonparametric tests were used for rapid analysis of the effects of the drugs. Morphine, buprenorphine, tifluadom ("Sandoz"), and bremazocine ("Sandoz") were used as agonists of opiate systems, and naloxone and naltrexone (both from "Endo Laboratories") as antagonists.

EXPERIMENTAL RESULTS

The μ-agonist morphine and also buprenorphine (Table 1) induced a dose-dependent reduction of aggression of the female toward the male. Buprenorphine facilitated individual behavior and nonagonistic forms of intraspecific interactions (such as sociability toward the male, active and passive contacts with the offspring) a little. Buprenorphine changed not only the probability of appearance of elements of intraspecific behavior, but also their order and interdependence, i.e., the program of behavior, as was shown by computer analysis of the behavior graph (Fig. 1). Elements of aggressive and ambivalent interaction (attacks,

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TABLE 1. Effect of Opiate Receptor Agonists on Intraspecific Behavior of Lactating Female Rats

Drugs, doses, mg/kg	Categories and elements of behavior			
	aggression		sociability toward male	contacts with offspring
	attacks	threats		
Buprenorphine				
0,01	−0,05 ▽	+0,05 △	+0,01 △	+0,09 △
0,1	−0,10 ▼	−0,46 ▼	+0,03 △	+0,22 ▲
0,5	−0,11 ▼	−0,53 ▼	0	−0,10 ▽
Morphine				
11	−0,07 ▼	−0,05 ▽	0	0
5	−0,09 ▼	−0,15 ▽	+0,01 △	+0,09 △
10	−0,11 ▼	−0,25 ▼	−0,02 ▽	+0,20 △
Tifluadom				
0,01	−0,04 ▼	−0,09 ▼	0	+0,32 △
0,1	−0,06 ▼	−0,06 ▽	−0,02 ▽	+0,31 △
Bremazocine				
0,01	−0,02 ▽	−0,08 ▽	−0,03 ▽	+0,06 △
0,1	−0,03 ▼	−0,21 ▼	0	−0,02 ▽

TABLE 2. Effect of Opiate Receptor Antagonists on Intraspecific Behavior of Lactating Female Rats

Drugs, doses, mg/kg	Categories and elements of behavior			
	aggression		sociability toward male	contacts with offspring
	attacks	threats		
Naloxone				
0,1	−0,02 ▽	−0,07 ▽	−0,05 ▼	+0,07 △
1	−0,05 ▼	−0,06 ▼	−0,02 ▽	+0,24 △
5	−0,04 ▼	−0,11 ▼	−0,03 ▼	+0,45 ▲
Naltrexone				
0,5	−0,04 ▽	−0,03 ▽	0	+0,02 △
1	−0,07 ▽	+0,05 △	−0,02 ▽	+0,14 △
5	−0,09 ▼	−0,11 ▽	−0,01 ▽	+0,23 ▲

Legend. Here and in Table 2: +) or −) attached to numbers indicates direction of effect; numbers indicate difference of statistical probabilities (control subtracted from experimental values; triangle) increase, triangle upsidedown) decrease in value of parameter, ▲▼) significant changes at the $p < 0.05$ level by Wilcoxon's test.

threats, circulation), which predominated in the behavior of the control animals, were distinguished on the graph as separate associations of elements, joined by highly probable connections of mutual sequences of transitions (Fig. 1a). After injection of buprenorphine (0.1 mg/kg, Fig. 1b), significant changes took place in the structure of the stochastic connections in complex elements of aggressive and ambivalent interaction, and predominance of diadic transitions of nonaggressive elements of behavior was observed, including intraspecific sociability toward the male. A tendency to "sit in the nest" (an indication of facilitation of passive contacts with the offspring) became the principal transitional element. A change both in the structure of behavior (Fig. 1) and in the probabilities of appearance of behavioral elements (Table 1) after buprenorphine clearly reflected activation of nonaggressive forms of intraspecific contacts.

A similar tendency was exhibited also by morphine.

The κ-agonists tifluadom and bremazocine (Table 1) reduced aggression toward the male; unlike the μ-agonist, however, they activated the tendency of the females to avoid contact with the male and to sit passively in the nest (tifluadom), or to avoid interaction with the offspring (bremazocine).

Antagonists of opiate receptors (naloxone and naltrexone) in small doses did not induce significant changes in aggression (Table 2). High doses led to suppression of all forms of contact with the male and to stimulation of elements of passive behavior in the nest, possibly as a result of blocking not only of μ-, but also of other types of opiate receptors. By contrast with agonists of opiate receptors, the antagonist did not cause facilitation of nonaggressive forms of intraspecific contacts with the male.

Thus μ-agonists (buprenorphine), unlike κ-agonists (trifluadom) have a more selective inhibitory action on maternal aggression. The μ- and κ-opiate systems probably have different roles to play in the integration of maternal behavior. Activation of μ-opiate systems led to a more selective change in intraspecific interactions, inhibiting aggression, but stimulating nonagonistic contacts to some degree. By contrast with this, activation of κ-opiate systems caused nonspecific reduction of maternal aggression and stimulated passive-defensive behavior. The results are evidence that opiate (mainly μ-receptor) systems of the brain are involved in the integration of maternal behavior and, in particular, of the aggression of lactating females.

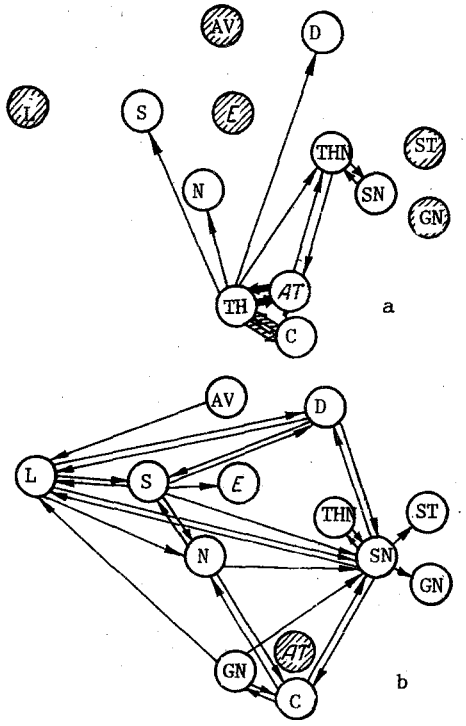

Fig. 1. Graphs of diadic transitions of behavioral acts in experiments with physiological saline (a) and after buprenorphine (0.1 mg/kg) (b). Empty circles – highly probable forms of behavior, obliquely shaded circles – improbable forms. AT) Attack, TH) threat, D) defense, C) circulation, AV) avoidance, N) nuzzling male, SN) sitting in nest in contrast with offspring, G) grooming in nest, ST) standing up on hind limbs in nest, THN) threatening in nest, L) locomotion, S) sitting, E) eating. Symbols used to indicate statistical probabilities of transitions: thin arrow $p < 0.01$, broad broken arrow $0.01 < p < 0.03$; broad solid arrow $p > 0.03$.

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EFFECT OF TUFTSIN ON LEUCYL AMINOPEPTIDASE ACTIVITY OF SUBCELLULAR COMPONENTS OF THE CEREBRAL CORTEX

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The neurotransmitter and neuromodulator role of different peptides is responsible for interest in the enzymes of their metabolism, which participate in the synthesis and breakdown of these peptides. The investigation described below was conducted on leucyl aminopeptidase (LAP), an aminopeptidase of the arylamidase class which degrades enkephalins; it is present in the tissues of many mammals and changes its activity in a number of pathological processes (encephalitis, cataracts, brain tumors) [12, 15].

The tetrapeptide tuftsin is a natural endogenous factor which incorporates four amino acids (Thr-Lys-Pro-Arg), it passes readily through the blood-brain barrier, and a fragment of it (Lys-Pro-Arg) is a component of enkephalins (substance P, neurotension), which regulate

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