Relationship between the Antiaggressive Properties of Buspirone and the Time of Day

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Buspirone administered in the morning or evening completely suppressed the interspecies aggressiveness of isolated rats expressed as attacks on and bites of mice; muricidal behavior (killing of mice) was blocked by the drug only if it was administered in the evening. Electrolytic destruction of serotonin-containing structures of the midbrain levels the phase dependence of the antimuricidal properties of buspirone.

Key Words: *buspirone; aggression; suture nuclei; serotonin receptors*

Buspirone is a new-generation anxiolytic differing from the benzodiazepine tranquilizers [2]. Its anxiolytic action is associated with its effects on the pre- and postsynaptic serotonin receptors of the first type of the A subtype (S_{1A}) [13]. Antiaggressive properties of buspirone and other S_{1A}-receptor agonists have been described [7,10]. The S_{1A} receptors appear to play an important role in the regulation of aggressive behavior. Experimental data indicate patent changes of this form of behavior in the course of the day and changes in the binding capacity of the S_{1A} receptors [9,12]. This study was aimed at finding out whether the antiaggressive properties of buspirone depend on the time of its administration.

MATERIALS AND METHODS

An experimental model of pathological aggression was created by combining destruction of the nuclei of the midbrain suture and social deprivation for 2 weeks or by social deprivation alone. The experiments were carried out with 26 outbred male rats weighing 230 to 270 g, in which the dorsal and medial nuclei of the midbrain suture were destroyed electrolytically, 28 intact rats, and 10 sham-operated animals of the same weight. The suture nuclei were destroyed by preimplanted nichrome electrodes [1] with a device for electrolysis at a 1-1.5 mA current for 20 sec with polar alterations. In the sham-operated animals the electrodes were implanted at the same sites, but embedded at a depth of 4 mm from the bone. The rats were kept under a standard photoregimen and fed standard diets with free access to food and water. On day 2-3 after the operation the animals were isolated. Aggressive behavior was assessed on day 14 of isolation before and 20 and 60 min after the injection of buspirone (intraperitoneally in a dose of 5 mg/kg of an 0.1% aqueous solution or in the right brain ventricle in a dose of 5 μg in 5 μl of normal saline) or its solvent. Buspirone was provided by Prof. T. A. Voronina, Head of the Psychopharmacology Laboratory at the Research Institute of Pharmacology, Russian Academy of Medical Sciences. One group of animals was administered the drug at 9 o'clock in the morning, the other at 7 o'clock in the evening. Intact animals were isolated for longer periods (21-30 days). The aggressiveness of the rats was assessed from their behavior toward mice put in the cage. The latency of the first aggressive act, the total duration of aggression, and the number of attacks during 10 min of observation were recorded. The serotonin content in the brain was measured fluorometrically using orthophthalic aldehyde [2] and expressed in μg/g wet tissue. The experimental data

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were statistically processed using the sign test and Wilcoxon's test [6]. The data on animals in which morphological control revealed complete or partial destruction of suture nuclei were selected for analysis [4].

RESULTS

Our studies demonstrated that social isolation of rats alone caused aggression in 30% cases, expressed as attacks, bites, and killing of mice (muricidal behavior). Disorders in the transmitter systems of the limbic formations of the brain responsible for the emotional motivation of this form of behavior cause rats to become pathologically aggressive after isolation. The majority of scientists consider that changes in serotonin metabolism and in the affinity and number of serotonin receptors play a crucial role in this process [8,11].

Intraperitoneal injection of solvent in the same volume as the buspirone dose did not change the parameters of aggressive behavior, regardless of the time of injection (Table 1).

After a morning injection of buspirone the aggressiveness of rats in the form of bites and attacks was completely eliminated, whereas muricidal behavior remained unchanged. Similar effects of buspirone on the manifestations of rat aggressiveness are reported by other workers, who carried out experiments at approximately the same times of day [7,10]. In contrast to the morning administration, the evening injection of buspirone completely suppressed all types of aggression.

Hence, a manifest phase dependence of the antimuricidal effect of buspirone was observed in isolated rats, whereas the suppression of other forms of aggression by the drug did not depend on the time of its administration. Evidently the sensitivity of the S_{1A} receptors to the agonist is higher in the evening than in the morning. This is in line with reports about the circadian time of the highest binding capacity of the S_{1A} receptors with the agonist [9,12].

The second series of experiments was carried out with isolated rats in which the nuclei of the midbrain suture had been destroyed. Electrolytic destruction of the suture formations caused a more pronounced drop of the serotonin content in the brain stem (from 1.2±0.08 μg/g in isolated rats with intact suture nuclei to 0.76±0.04 μg/g, $p<0.05$) in comparison with sham-operated animals (0.93±0.05 μg/g), in which electrodes were implanted, but nerve tissue was not exposed to electrolysis. Pronounced aggres-

TABLE 1. Effect of Buspirone (5 mg/kg, Intraperitoneally) on the Aggressiveness of Isolated Rats

Experimental conditions	Types of aggression	Time of day	Before injection			After injection		
			latency, sec	number of aggressive acts	duration of aggression, sec	latency, sec	number of aggressive acts	duration of aggression, sec
Control (isolation+H_2O)	Attacks, bites (n=15)	9.00	100.0±42.1	3.6±1.9	19.0±6.8	83.0±40.1	1.4±0.4	8.4±3.8
		19.00	98.6±50.1	1.6±0.6	9.4±4.1	65.8±32.8	2.2±1.0	9.4±2.1
Isolation+ buspirone	Attacks, bites (n=6)	9.00	79.6±27.9	4.9±0.8	11.7±2.1	0.0*	0.0*	0.0*
		19.00	107.0±43.1	3.1±0.9	10.0±2.5	0.0*	0.0*	0.0*
	Muricide (n=8)	9.00	19.1±10.0	1.8±0.8	12.6±2.9	20.0±10.1	1.0±0.001	6.4±1.0
		19.00	8.0±2.2	1.0±0.006	1.0±0.005	0.0*	0.0*	0.0*
Isolation+ destruction of suture nuclei+ H_2O	Muricide (n=8)	9.00	124.6±57.6	5.8±3.0	11.4±4.1	25.0±8.2	5.9±2.2	10.4±2.7
		19.00	9.5±5.4	3.0±1.2	3.8±1.2	33.3±12.0	2.6±1.6	5.3±2.0
Isolation+ destruction of suture nuclei+ buspirone	Muricide (n=9)	9.00	23.8±1.8	1.0±0.00	9.1±2.5	224.1±78.2*	0.7±0.1*	7.8±2.6
		19.00	21.3±6.5	2.8±1.0	7.4±3.1	337.5±100.7*	0.7±0.3*	5.8±0.5
Isolation+ destruction of suture nuclei+ normal saline in brain ventricle	Attacks, bites (n=6)	9.00	123±36.9	12.4±3.8	15.6±4.1	240.6±61.9	13.6±2.02	15.8±2.3
		19.00	154±71.8	4.0±0.8	13.0±3.9	551±49.0*	0.2±0.1*	0.6±0.3*
	Muricide (n=5)	9.00	57.2±12.5	1.0±0.001	6.0±2.1	15.0±4.1	1.0±0.0001	8.5±4.1
		19.00	4.5±2.1	1.0±0.001	1.5±0.3	5.7±3.1	1.0±0.001	1.7±0.4
Isolation+ destruction of suture nuclei+ buspirone in brain ventricle	Attacks, bites (n=6)	9.00	162.4±42.8	22.4±8.1	27.1±8.3	130±32.6	17.8±7.1	25.2±10.5
		19.00	75.0±23.8	9.7±2.5	13.0±2.9	586.7±26.8*	1.6±0.9	1.6±0.9*
	Muricide (n=6)	9.00	27.5±9.9	1.7±0.7	8.3±4.1	64.5±20.7	1.7±0.5	11.3±4.5
		19.00	35.5±15.5	2.0±0.8	4.0±2.5	51.3±25.8	2.0±1.1	3.8±1.1

Note. *$p<0.05$ vis-a-vis initial value.

sion was observed in 80% of animals with destroyed nuclei, and 80% of these demonstrated killer activity. In the group of sham-operated animals the number of aggressive rats did not differ from that in the group of isolated animals with the midbrain intact.

Intraperitoneal injections of the solvent in both phases of the day did not appreciably change the aggressiveness of animals with destroyed suture nuclei. On the other hand, injection of buspirone was followed by a marked prolongation of the latency of the first aggressive act and a decrease in the number of attacks, pointing to a weakening of aggressiveness in the rats (Table 1). In contrast to the case with the previous experimental series, this effect of buspirone was observed during both phases of the day, but in the morning a complete suppression of muricidal behavior was observed in only 25% of operated animals, whereas in the evening it was observed in 50%.

Therefore, in the second series as opposed to the first, the antimuricidal effects of buspirone were boosted in the morning and weakened in the evening in animals with destroyed suture nuclei (Table 1).

Hence, electrolytic injury to serotonin-containing structures of the midbrain levels the manifest phase dependence of the antimuricidal activity of buspirone in isolated rats. This evidently reflects the changes occurring in the daily pattern of sensitivity of the S_{1A} receptors of the limbic formations, striatum, and cortex to the agonist [7,9,10,12].

In order to check this hypothesis, in a third series of experiments we studied the effect of buspirone on the aggressive behavior of rats with destroyed suture nuclei upon injection of the drug into the right brain ventricle. Administered via such a route, buspirone was ineffective against any form of aggression (Table 1). Evidently, the S_{1A} receptors of the forebrain, at least of the striatum, are little involved in the regulation of both muricidal behavior and other manifestations of aggressiveness caused by isolation.

The results indicate that the pathological aggressiveness developing after social deprivation may be regulated by the postsynaptic the S_{1A} receptors of the limbic system, the S_{1A} autoreceptors of the suture nuclei playing the crucial role here. It is possible that social deprivation is associated with two types of pathological aggressiveness of different origin. One of them is expressed as attacks and bites and is regulated mainly by the S_{1A} receptors of the limbic system, while the other (muricidal behavior) is regulated by S_{1A} autoreceptors of the suture nuclei. The suture structures appear to be directly involved in the regulation of the diurnal fluctuations in the muricidal behavior of isolated rats.

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