The Effect of Serotoninergic 1A Agonists on Rotating Behavior in Rats with Raphe Lesions

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UDC 615.357:577.175.823].015.21.076.9

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, № 2, pp. 157-159, February, 1993
Original article submitted July 7, 1992

Key Words: *serotoninergic agonists; rotations; nuclei raphe; lesions*

It is well known that the motor expression of an emotional state is determined by the interaction between the serotoninergic (5-HT) and dopaminergic (DA) neurotransmission in the mesostriatal and mesolimbic systems. Buspirone, an agonist of the 5-HT_{1A} receptors and an antagonist of the D_2 presynaptic receptors, produces a significant effect on 5-HT neurons in the raphe nuclei and on DA neurons in the substantia nigra (SN). Buspirone and an agonist of the other 5-HT_{1A} receptors, 5-methoxy-N,N'-dimethyltryptamine (5-MeODMT), have shown the ability to restore rat behavior disturbed by L-dioxyphenylalanine in acute stress situations, the effect of the two anxioselective preparations being of equal intensity but of diverse behavioristic pattern [1].

The complex pharmacological action of buspirone, its complex effect on the locomotor control of neurons in the median and dorsal nuclei raphe [3], and the selective participation of the latter in the realization of the stress response [5] were taken into consideration, the effect of buspirone and 5-MeODMT on rotating activity being investigated under conditions of disturbed interaction of 5-HT and DA neurotransmission in the mesostriatal and mesolimbic systems of the brain.

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MATERIALS AND METHODS

The experiments were carried out on male Wistar rats weighing 210-230 g. The operations were performed under ether. A stereotactic introduction of isolated and paired Nichrome electrodes with a diameter of 0.2 mm and free ends of 0.5 mm was performed according to the atlas [4], unilaterally into the medial nucleus raphe (MNR) and/or dorsal nucleus raphe (DNR) (A=0.16, L=0.3, H=5; A=0.35, L=0.2, H=7.5 mm from the surface of the brain for DNR and MNR, respectively). Lesions were induced by a direct current of 1 mA during 15 sec. After a postoperative interval of 14 days, the rats with unilateral lesions of the DNR, MNR, or both were tested for the induction of 5-MeODMT-dependent rotating behavior. Animals with a rotating rate of less than 0.5 turn per minute were eliminated from the experiment. Experimental groups comprising 28-30 animals with each type of lesion and groups of animals undergoing sham operation were formed from the rest of the rats. Four-five rats were included in the experiment testing each dose of substance. Automatic registration of the number of rotations was performed simultaneously in 4-5 animals placed in specially constructed rotometers. The intensity of

0007-4888/93/0002-0153$12.50

TABLE 1. Effect of Raphe Lesions on Rat Locomotor Activity

Experimental conditions (lesions)	Number of meters within intervals			Total during 15 min
	0-5 min	6-10 min	11-15 min	
Sham operation (control)	4.73	3.30	1.60	9.63
Unilaterally, DNR	5.17	0.99*	0.33*	4.49*
Unilaterally, MNR	6.60*	4.40	0.55*	11.55*
Unilaterally, DNR and MNR	10.34*	9.13*	2.09*	21.56*

Note: here and in Table 2 *: $p<0.05$.

motor activity was measured in the freely rotating drums. Registration (in meters) was performed automatically during periods of 15 min separated by intervals of 5 min. Buspirone (Bristol Myers) and 5-MeODMT (Sigma) were introduced intraperitoneally. The number of turns in an hour and the presence of stereotyped reactions were tested. After the end of the experiments, the brains of the rats were subjected to histological investigation. The results were processed statistically using the Wilcoxson-Mann-Whitney test.

RESULTS

Unilateral lesions in the DNR and MNR were verified histologically. Unilateral lesions induced in the nuclei raphe elicited diverse changes of motor function assessed on the freely rotating drums (Table 1). The lesions in MNR induced an increase, while the destruction of DNR caused a decrease of activity. The most marked rise of motor activity was observed after the simultaneous destruction of DNR and MNR. These results concerning a different influence of the DNR and MNR on the DA neurons of the SN and, consequently, on motor function, are in agreement with previously obtained data [3, 6].

Unilateral lesions of the cell bodies in DNR and MNR induce a supersensitive denervation of the postsynaptic 5-HT_{1A} receptors localized in the zones of the corresponding projections of the SN and corpus striatum [2]. 5-MeODMT, a 5-HT_{1A} receptor agonist, induces stable contralateral rotations in rats with lesions of DNR, MNR, and both nuclei (Table 2). However, stereotyped reactions of head shaking, shifting from one front paw to the other, and slowing of the rotation rate appeared beginning from a 5-MeODMT dose of 5 mg/kg (lesions of the DNR or MNR) and from a dose of 1 mg/kg (lesions of both nuclei), this correlating with previously reported data [7]. The effect of 5-MeODMT depended upon the localization of the lesions in the nuclei. The greatest intensity of rotation was observed against the background of MNR lesions and the lowest intensity after partial destruction of both nuclei. This is in disagreement with the level of motor activity noted on the drums, the minimum activity being observed after DNR destruction and the maximum activity discovered after destruction of both nuclei. The high control level of rotations in rats with lesions of both nuclei exceeded 1.9 and 3 times, respectively, the same values found in rats with lesions only of MNR or DNR. The maximum rotation rate was induced by a fourfold decrease of the 5-MeODMT dose. Taking into account published data attesting to a significant increase of the number of 5-HT_{1A} binding sites and elevated values of the dissociation constants after destruction of the nuclei raphe [2], we assumed that a considerable number of supersensitive 5-HT_{1A} receptors were present in animals with lesions of this type. These factors provide a possible explanation for the high motor activity in such animals tested in a stress situation on a freely rotating drum.

On the other hand, the effect of buspirone did not depend upon the lesions introduced in DNR, MNR, or both nuclei; the relative dose-dependent increase of

TABLE 2. Effect of Buspirone and 5-MeODMT in Rats with Unilateral Raphe Lesions

Type of lesions	Substance, mg/kg	Number of contralateral rotations	Relation to control
Dorsal	physiological saline	14.6	–
	5-MeODMT, 0.5	43.8*	3.0
	5-MeODMT, 2.0	88.3*	6.1
	5-MeODMT, 5.0	57.8*	4.0
	buspirone, 0.5	18.2	1.3
	buspirone, 1.5	23.5*	1.6
	buspirone, 4.0	40.2*	2.8
Medial	physiological saline	28.6	–
	5-MeODMT, 0.5	106.3*	3.7
	5-MeODMT, 2.0	228.0*	8.0
	5-MeODMT, 5.0	95.0*	3.3
	buspirone, 0.5	32.4	1.1
	bupirone, 1.5	40.1*	1.4
	buspirone, 4.0	82.4*	2.9
Dorsal and medial	physiological saline	45.2	–
	5-MeODMT, 0.25	59.3	1.3
	5-MeODMT, 0.5	115.0*	2.5
	MeODMT, 1.0	21.2	0.5
	buspirone, 0.5	57.0	1.3
	buspirone, 1.5	84.9*	1.9
	buspirone, 4.0	92.8*	2.1

the number of rotations vis-a-vis the control was the same as that induced by 5-MeODMT. This is probably connected with a partial agonism of buspirone to the 5-HT_{1A} receptors, because buspirone is known to diminish the serotoninergic syndrome caused by 8-oxy-2-(di-n-propylamino)-tetraline (a selective agonist of 5-HT_{1A} receptors) [8]. A blocker of the D_2 autoreceptors, buspirone has a modulatory effect on DA synthesis and promotes local release of DA from the dendrites of SN, by activation of the supersensitive somatodendritic 5-HT_{1A} postsynaptic receptors. Evidently, inhibition of hyperpolarization during the transmission of impulses to SN is hindered by buspirone blocking the somatodendritic D_2 autoreceptors, DA release being induced in the ipsilateral striatum. A buspirone-induced DA release can be observed in the corpus striatum itself, this compensating on the whole for the specific disturbances of 5-HT neurotransmission. Such a combined action of buspirone on the DA autoreceptors and 5-HT_{1A} receptors in rats with unilateral lesions of DNR and MNR is achieved not only in the mesostriatal, but also in the mesolimbic structures, where the anxiolytic effect of the preparation is mainly realized.

REFERENCES

1. N. A. Bondarenko, N. A. Bondarenko, L. Baran, *et al.*, *Byull. Eksp. Biol. Med.*, **110**, № 12, 629 (1990).
2. T. P. Blackburn, B. Cox, C. G. Heapy, *et al.*, *Europ. J. Pharmacol.*, **71**, 343 (1981).
3. V. Hillegaart and S. Hjorth, *Ibid.*, **160**, 303 (1989).
4. J. F. R. Konig and R. A. Klippel, *The Rat Brain*, Baltimore (1963).
5. E. H. Y. Lee, H. H. Lin, and H. M. Yin, *Neuroscience Letters*, **80**, 115 (1987).
6. H. Rommelspacher and S. Strauss, *J. Neural Transmis.*, **49**, 51 (1980).
7. P. Slater, *Pharmacol. Biochem. Behav.*, **13**, 817 (1980).
8. J. Traber and T. Glaser, *Trends Pharmacol. Sci.*, **8**, 432 (1987).

Effects of N-Acetylaspartic Acid on the Brain after Frontal Lobectomy in Rats: Antiamnestic Effect and Influence on Monoamine Content

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UDC 616.89−008.464−089:616.831.311−089.87]−092.9−07

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 115, № 2, pp. 159−161, February, 1993
Original article submitted September 1, 1992

Key Words: *N-acetylaspartate; frontal lobectomy; antiamnestic effect; monoamines*

N-acetylaspartic acid (AcAA) is a neurospecific substance found in diverse regions of the CNS, its concentration in the brain tissue being inferior only to that of glutamic acid, along with which it is produced by enzymolysis of the N-acetylaspartylglutamate dipeptide. The latter is considered to be a possible excitatory neurotransmitter [5, 8]. It has been established that AcAA is able to accelerate spatial learning in a water maze, to improve performance of the conditioned passive avoidance response (CPAR) disturbed by transcorneal electroshock or by the injection of the NMDA-receptor antagonist MK-801, and also to prevent the natural extinction of the habit [3].

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0007−4888/93/0002−0155$12.50