Antidepressant Activity of β-Lactam Antibiotics and Their Effects on the Severity of Serotonin Edema

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 142, No. 7, pp. 82-85, July, 2006
Original article submitted November 29, 2004

Injection of β-lactam antibiotics (reterpen, ceftazidime, and thienam) to mice in doses equivalent to the mean therapeutic doses for humans led to shortening of the duration of behavioral despair in the hanging by the tail test, modified the resistance to serotonin edema, and intensified the exploratory and orientation activity in the open field test. This sum of effects was detected after 10 injections of retarpen and thienam and after single and five-fold administration of ceftazidime. Antidepressant sertraline also shortened the duration of behavioral despair and reduced serotonin edema. An inverse correlation between the duration of behavioral despair and severity of serotonin edema was detected in control mice. The results suggest that β-lactam antibiotics are characterized by antidepressant effect related to changes in serotonin sensitivity.

Key Words: *β-lactam antibiotics; antidepressant effect; serotonin edema*

β-Lactam antibiotics (BLA) are structurally related antibacterial agents characterized by a common mechanism of antibacterial effect and including penicillin [3]. Apart from bactericidal effect, penicillin suppresses the inhibitory GABAergic neurotransmission and amplifies the effects of stimulatory transmitters in the CNS [7]. Modern BLA also increase excitability of neurons [6]. This effect of BLA is traditionally analyzed in the context of their untoward (proconvulsive) side effect. On the other hand, optimal limitation of inhibitory neurotransmission in the CNS under the effect of BLA can improve the resistance to the development of behavioral depressive disorders (BDD) under conditions of long-term stress.

The formation of BDD is largely associated with disorders in the serotonin metabolism in the brain accompanied by shifts in serotonin receptor sensitivity [2,4]. Serotonin receptors 5-HT_{2A} and 5-HT_4 are located not only in CNS, but also on platelets and in the vascular wall. It can be hypothesized that the severity of inflammatory edema after peripheral injection of serotonin to laboratory rodents to a certain measure reflects the sensitivity of cerebral receptors to this monoamine and the resistance of animals to experimental depressogenic exposure.

We analyzed the relationship between the effect of BLA and severity of serotonin edema in mice, their exploratory and orientation activity in the open field test, and "behavioral despair" homologous to human BDD [5].

MATERIALS AND METHODS

The study was carried out on (CBA×C57Bl/6)F_1 mice (18-20 g). Penicillin antibiotic retarpen (benzatine-benzylpenicillin, Biochemie), 3rd-generation cephalosporin ceftazidime (fortum, Glaxo Wellcome), and carbapeneme antibiotic thienam (imipenem with cilastatin, MSD) were used.

Single doses of the antibiotics were extrapolated from the mean daily doses for humans with consideration for the differences in the body surface areas [1]. Retarpen and ceftazidime were injected to mice intraperitoneally once a day in a dose of 400 mg/kg. A single dose of thienam was 200 mg/kg. Three standard protocols were used for each

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BLA: administration for 1, 5, and 10 days. Control animals were injected with equivalent volumes of 0.9% NaCl according to the same protocols.

The resistance to experimental depressogenic exposure was evaluated 24 h after the final injection of BLA by the duration of immobility (behavioral despair) in 6-min hanging by the tail test [5].

Directly after the test the animals were injected (under paw aponeurosis) with 0.05 ml serotonin-creatinine sulfate (Reanal) diluted in 0.9% NaCl to the concentration of 0.5 mg/ml. Sixty minutes after subaponeurotic injection of serotonin and of equivalent volume of 0.9% NaCl into the contralateral paw exarticulation of the talocrural joint was carried out. The severity of inflammatory edema was evaluated gravimetrically and expressed in percents of increment in the weight of the paw injected with serotonin [1]. In this experimental series we studied, along with the effects of BLA, the effects of antidepressant sertraline (Zoloft, Pfizer), a selective serotonin re-uptake inhibitor (SSRI) [2]. Sertraline was injected in a dose of 20 mg/kg corresponding to the mean therapeutic dose for humans standardized by body surface area [1]. The antidepressant was injected intraperitoneally 30 min before hanging by the tail and 36 min before serotonin edema induction.

The effects of BLA on mouse behavior in the open field test were studied in an additional series of experiments [8].

The results were statistically processed using StatSoft Statistica 6 software. The significance of differences was evaluated using Mann—Whitney, Rosenbaum, and Fisher exact tests. Statistical relationships were evaluated by estimating Spearman's coefficient of correlations (r_S). Statistical hypotheses were verified at p=0.05.

RESULTS

All BLA modified the duration of behavioral despair in the hanging by the tail test (Table 1). Retarpen and ceftazidime significantly shortened the period of mouse immobility, which attested to antidepressive effects of these antibiotics [5]: the degree of this effect depended on the protocol of injections. Retarpen significantly decreased the duration of behavioral despair after 5 and 10 injections, ceftazidime after 1 and 5 injections. The most pronounced antidepressant effect was observed after 5 injections of both these BLA. The use of this protocol shortened the immobility period 3.5 times after retarpen and 2.6 times after ceftazidime. A single injection of thienam prolonged the immobility period by 78%, while 10 injections of this antibiotic had a significant antidepressant effect (Table 1).

The studied BLA had opposite effects on the severity of serotonin edema at different protocols of treatment in the majority of cases (Table 1). Retarpen and ceftazidime exhibited the most pronounced antidepressant effects. Single injection of retarpen reduced serotonin edema, while 10 injections increased animal sensitivity to phlogogenic effect of serotonin. Single injection of ceftazidime promoted serotonin edema, while 5 and 10 injections of this BLA produced a significant antiinflammatory effect. Only 10 injections of thienam modified (increased) the edemogenic effect of serotonin. These data suggest that BLA should be regarded as modulators of sensitivity to the phlogogenic effect of serotonin. Analysis of correlations between the duration of behavioral despair and severity of serotonin edema in control mice (r_S=-0.516, p=0.033) showed that after local injection of serotonin the severity of edema reflects the resistance of animals to the depressogenic effect and presumably can serve as a marker of sensitivity to this monoamine at the cerebral level. This hypothesis is supported by the decrease of serotonin edema from 34.72±5.33% in the control (n=10) to 19.90±2.33% (n=9, p=0.017) after injection of 20 mg/kg sertraline. In parallel with this effect, this SSRI representative reduced the duration of behavioral despair from 157.8±6.87 sec in control (n=10) to 50.44±2.60 sec (n=9, p=0.008). Changed sensitivity to serotonin after long-term treatment with SSRI is an important mechanism of their antidepressant activity [2,4]. Presumably, shifts in serotonin sensitivity promote the development of antidepressant effect during the course of BLA treatment.

Retarpen, ceftazidime, and thienam significantly increased spontaneous exploratory, orientation, and motor activities of animals in the open field test (Table 1). Ten injections of retarpen and thienam activated mouse behavior in the open field, shortened the duration of behavioral despair, and modify the sensitivity to the edemogenic effect of serotonin. The same regularity was observed after single and 5-fold administration of ceftazidime. These results indicate that stimulation of mouse behavior with BLA in these modes of treatment is associated with changed serotonin sensitivity and concomitant antidepressant effect of antibiotics.

In many cases BLA stimulated animal behavior in the open field without modifying serotonin sensitivity and/or behavioral despair. This was observed after single injection of retarpen, 5 injections of thienam, and 10-day treatment by ceftazidime. Prolongation of immobility in the hanging by the tail test after single injection of thienam was not paralleled by changes in open field behavior and

TABLE 1. Effects of β-Lactam Antibiotics on Duration of Mouse Immobility in Hanging by the Tail Test, Open Field Behavior, and Severity of Serotonin Edema (*M*±*m*)

Antibiotic		Serotonin edema, %	Duration of immobility, sec	Motor activity (number of sectors)	Orientation reaction (rearings)	Exploratory behavior (peeping through holes)
Retarpen, 400 mg/kg						
day 1	control	44.4±3.2 (9)	89.11±12.02 (9)	68.90±4.65 (10)	14.20±2.46 (10)	5.80±1.22 (10)
	experiment	30.28±2.63* (8)	86.33±15.32 (9)	102.78±8.90* (9)	26.67±2.87* (9)	18.56±1.43* (9)
day 5	control	29.57±3.98 (10)	133.80±10.04 (10)	98.90±9.17 (10)	33.70±3.52 (10)	19.20±2.48 (10)
	experiment	28.37±3.81 (9)	38.63±8.67* (8)	91.44±9.25 (9)	36.33±3.71 (9)	22.67±2.81 (9)
day 10	control	26.72±1.25 (10)	114.40±6.56 (10)	105.9±2.9 (10)	22.90±0.88 (10)	19.10±1.29 (10)
	experiment	34.91±2.05* (9)	79.78±4.48* (9)	126.9±3.6* (10)	32.40±1.32* (10)	25.40±1.01* (10)
Ceftazidime, 400 mg/kg						
day 1	control	26.31±2.21 (10)	158.50±21.72 (10)	57.00±4.54 (10)	17.40±1.68 (10)	10.40±1.05 (10)
	experiment	32.81±2.38* (8)	126.75±19.24* (8)	64.00±4.66 (8)	23.88±2.83* (8)	17.00±2.92 (8)
day 5	control	47.16±5.24 (8)	116.75±21.39 (10)	74.71±6.98 (14)	22.50±3.59 (14)	13.71±2.58 (14)
	experiment	33.03±3.02* (9)	44.8±5.5* (8)	52.71±4.38* (16)	14.44±2.68 (16)	7.81±1.61 (16)
day 10	control	54.95±4.26 (9)	153.78±14.64 (9)	68.14±1.92 (7)	17.29±1.77 (7)	6.14±0.67 (7)
	experiment	33.20±4.43* (8)	113.25±21.21 (8)	71.78±4.95 (9)	22.22±1.81(9)	18.33±2.27* (9)
Thienam, 200 mg/kg						
day 1	control	41.93±5.60 (5)	50.00±7.57 (6)	64.00±6.86 (11)	18.36±3.80 (11)	11.36±3.03 (11)
	experiment	39.29±4.10 (6)	89.17±9.69* (6)	58.80±6.25 (10)	25.90±3.77 (10)	18.30±3.12 (10)
day 5	control	34.96±1.34 (8)	162.63±14.61 (8)	39.70±6.54 (10)	5.60±1.09 (10)	3.20±0.88 (10)
	experiment	37.29±1.22 (10)	127.10±11.33 (10)	58.93±6.15* (14)	19.64±1.98* (14)	14.29±2.11* (14)
day 10	control	40.71±5.49 (6)	185.80±32.68 (5)	46.71±4.52 (17)	16.06±2.88 (17)	10.76±1.84 (17)
	experiment	27.47±3.73* (10)	113.6±13.5* (10)	61.35±6.20* (17)	26.47±2.71* (17)	17.00±1.86* (17)

Note. The number of animals is shown in parentheses. *$p<0.05$ compared to the control.

in the severity of serotonin edema. It seems that serotoninergic processes are not the only target of the psychotropic effect of BLA.

The stimulatory effect of BLA on behavior is probably related to limitation of GABAergic inhibition in CNS [6,7]. It is also possible that BLA-induced blockade of GABA subtype receptors on serotoninergic neurons of raphe nuclei increases axonal release of serotonin and, similarly to SSRI, modifies the sensitivity of serotonin receptors. This modulation of serotoninergic processes is regarded as a mechanism of antidepressant effect [2,4].

The findings do not permit us to attribute the antidepressant effect of the studied BLA to their antibacterial spectrum [3]. This can be seen from identical periods of attaining the maximum antidepressant effect after a course of treatment with BLA with the predominant effect on gram-positive cocci (retarpen) and gram-negative enterobacteria (ceftazidime). On the other hand, single injection of BLA with the widest spectrum of antibacterial activity (thienam) produces a pronounced depressogenic effect. Presumably, this was a result of pronounced bacteriolysis of enteric microflora and concomitant development of endotoxemia. This dictates further studies of the psychotropic effects of BLA with consideration for their effects on not only neuromediator processes, but also on the intestinal microflora composition, with evaluation of the blood level of bacterial LPS.

REFERENCES

1. I. A. Volchegorskii, I. I. Dolgushin, O. L. Kolesnikov, and V. E. Tseilikman, *Experimental Simulation and Laboratory Evaluation of Adaptive Reactions* [in Russian], Chelyabinsk (2000).
2. A. B. Smulevich, *Depressions in Somatic and Mental Diseases* [in Russian], Moscow (2003).
3. L. S. Strachunskii and S. N. Kozlov, *Modern Antibacterial Chemotherapy. Manual for Physicians* [in Russian], Moscow (2002).
4. P. Celada, V. Puig, M. Amargos-Bosch, *et al.*, *J. Psychiatry. Neurosci.*, **29**, No. 4, 252-265 (2004).
5. L. Steru, R. Chermat, B. Thierry, and P. Simon, *Psychopharmacology*, **85**, 367-370 (1985).
6. M. Sugimoto, I. Uchida, T. Mashimo, *et al.*, *Neuropharmacology*, **45**, No. 3, 304-314 (2003).
7. A. Tsuda, M. Ito, K. Kishi, *et al.*, *Neurochem. Res.*, **19**, No. 1, 1-4 (1994).
8. M. L. Weischer, *Psychopharmacology*, **50**, 275-279 (1976).