Thus all the animals of the control group died after total replacement of blood by rheopolyglucin, whereas all the animals of the experimental group survived during 4 h of observation after total replacement of blood by a 10% solution of PH-PP. This result can be explained on the grounds that the AOC under investigation can maintain the oxygen supply of the body at an adequate level, and at the same time it possesses a marked hemodynamic action.

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MICRODIALYSIS STUDY OF EFFECTS OF ATYPICAL NEUROLEPTICS AND ANXIOLYTICS ON STRIATAL DOPAMINE RELEASE AND METABOLISM IN CONSCIOUS RATS

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UDC 612.82.015:577.175.82].014.46:615.214.2].085.1

KEY WORDS: cerebral microdialysis; dopamine; metabolites

Cerebral microdialysis in conscious animals is a method of investigating dynamic changes in neurotransmitter release and metabolism in vivo [9]. The method is based on stereotactic implantation of a microdialysis catheter into brain tissue, followed by perfusion and analysis of the dialysate. The concentration of neurotransmitters and their metabolites in the dialysate is determined by their concentration in the extracellular space and it reflects activity of the concrete neurotransmitter system [11]. The basic feature of the method of brain microdialysis which distinguishes it from in vitro methods is that neurochemical processes are studied in the whole brain, with its regulatory mechanisms preserved.

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Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 111, No. 5, pp. 505-507, May, 1991. Original article submitted June 5, 1990.

In the investigation described below the method of brain microdialysis was used to study the effect of several atypical neuroleptic and anxiolytics on the levels of dopamine (DA) and its principal metabolites dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) in the striatum of conscious rats.

EXPERIMENTAL METHOD

Experiments were carried out male Wistar rats weighing 250-300 g. Concentric microdialyzers [8] with a dialysis membrane ("Gambro," West Germany, permeability to 5 kD) 4 mm long and with an external diameter of 0.25 mm. In a preliminary series of experiments the working performance of the microdialyzers was determined in vitro as reflected in their ability to extract (in per cent) the test compounds from the surrounding medium. For DA, with a perfusion rate of 1 μl/min, it was about 20%.

Under pentobarbital anesthesia (40 mg/kg, intraperitoneally) the microdialyzer was implanted in the striatum and secured to the cranial bones. Coordinates were: AP + 0.5, L 3.0, v —7.4. When 18-24 h had elapsed after the operation the rats were put in a cage in which the implanted microdialyzer could be perfused with minimal constraint of the animals. Perfusion was carried out with Ringer's solution (147 mM Na^+, 2.3 mM Ca^{2+}, 4 mM K^+, 155.6 mM Cl^-) at the rate of 1 μl/min. The dialysate was collected every 20 min. Samples were kept at —20°C.

The content of DA, DOPAC, and HVA in samples of dialysate was determined simultaneously by HPLC with electrochemical detection on an LC-304, BAS chromatograph (USA), with "Rheodyne 7125" injector and with 20-μl loops for applying samples. Samples of dialysate were applied without preliminary treatment to a C-18 column (5 μ, 150 × 3 mm). Citratephosphate buffer containing 0.3 mM sodium octylsulfonate, 0.1 mM EDTA, and 7% acetonitrile, pH 3.6, was used as the mobile phase. Detection was carried out electrochemically (LC-4A BAS) at a voltage of +0.7, with the use of an Ag/AgCl comparison electrode. Under the conditions specified the limit of detection of DA was 4 pg.

Collection of samples of dialysate began 1-1.5 h after the beginning of perfusion. After 3 or 4 specimens had been obtained the test substances were injected and the dialysate collected during the next 2 h. The substances were injected intraperitoneally in a volume of 2 ml/kg. Control animals received physiological saline. The preparations were studied in the following doses (mg/kg): ritanserin — 2, risperidone — 1 ("Janssen Pharmaceutica," Belgium), sulpiride — 50 ("Serva," West Germany), buspirone — 10, 5-methoxy-N,N-dimethyltryptamine (MeODMT) — 7.5.

Mean values of the concentration of DA, DOPAC, and HVA in 3 or 4 samples of dialysate before injection of the drugs were taken as 100% (basal level). The results were subjected to statistical analysis by the Wilcoxon—Mann—Whitney test.

EXPERIMENTAL RESULTS

The basal levels of DA, DOPAC, and HVA in samples of striatal dialysate from conscious rats were 0.026 ± 0.003, 4.7 ± 0.028, and 2.845 ± 0.215 ng/20 μl (n = 15).

Risperidone, sulpiride, and buspirone, which are antagonists of D_2 DA receptors, were found to increase the DA, DOPAC, and HVA concentrations in the extracellular space (Table 1). This effect is a general property of preparations in whose receptor spectrum D_2 antagonism is represented, and it has been described for sulpiride [13] and buspirone [1]. In the present investigation it was shown for the first time by microdialysis that the new atypical antipsychotic risperidone also possesses the same property [4]. Ritanserin, a selective antagonist of 5-HT_2 serotonin (5-HT) receptors, in the dose studied, which does not affect D2 receptors [5], did not affect DA release, while raising the DOPAC and HVA levels, but by a much lesser degree than risperidone, sulpiride, and buspirone. The fact that ritanserin has no effect on DA release in the striatum is rather unexpected, for it was shown in [8] to have an activating effect on the spike discharge of DA-containing neurons in the substantia nigra and ventral region of the tegmentum mesencephali, unconnected with any effect on DA receptors. However, it was demonstrated by intracerebral microdialysis that DA release in the striatum is modulated mainly by presynaptic DA autoregulators, and may not be dependent on spike activity of DA neurons [13], although that is also an essential condition for intensification of DA release by neuroleptics [12]. On the other hand, experiments to study effects of selective agonists and antagonists of D_1 and D_2 receptors [14], and of preparations blocking DA reuptake and releasing DA from the various intraneuronal pools [15], and also the absence of correlation between the levels of DA and its

TABLE 1. Effect of Preparations on DA, DOPAC, and HVA Levels in Striatal Dialysates from Conscious Rats (M ± m)

Preparation	Period of perfusion (interval 20 min)								
	basal level			level after injection of preparation					
				DA					
Risperidone	112±7	96±3	92±5	119±11	143±15*	145±16*	143±13	159±20	165±14**
Sulpiride	100±2	89±5	111±5	163±12**	162±21*	170±23*	158±10*	167±12**	160±18*
Buspirone	89±8	103±6	109±6	115±4*	122±5	130±8*	125±7	119±9	108±8
Ritanserin	96±4	102±6	102±6	100±8	95±8	90±11	104±15	100±14	105±13
MeODMT	107±3	93±4	100±3	109±9	92±8	95±3	102±8	92±7	91±10
				DOPAC					
Risperidone	98±2	101±2	101±2	130±6*	180±10**	212±11**	244±13**	246±12**	245±12**
Sulpiride	98±1	101±1	101±1	127±5**	157±6**	185±6**	201±8**	218±8**	225±9**
Buspirone	97±4	97±5	107±2	172±8**	231±15**	269±19**	315±25**	343±22**	340±28**
Ritanserin	102±9	97±5	101±5	117±4**	120±5**	128±7**	123±4**	127±9**	125±6**
MeODMT	103±2	100±1	96±1	106±2	102±2	98±3	93±3	93±3	94±3
				HVA					
Risperidone	99±4	101±3	100±2	113±4	150±12**	195±15**	241±20**	259±22**	275±28**
Sulpiride	95±3	101±2	104±2	121±3**	144±5**	168±7**	191±6**	212±11**	230±13**
Buspirone	91±6	98±5	112±2	151±9**	207±16**	245±23**	309±24**	354±28**	373±38**
Ritanserin	102±3	97±4	101±3	120±5	125±7	128±7	128±7	126±9	130±6*
MeODMT	101±2	101±2	98±1	103±3	103±2	108±2	105±3	105±3	103±3

Legend. Effect given as a percentage of basal level (first three periods of perfusion). Effect of each preparation was studied on 6-8 animals. *$p < 0.05$, **$p < 0.01$ compared with control.

metabolites in the extracellular space [6], are evidence of differences in mechanisms of regulation of DA synthesis, metabolism, and release. For instance, it was shown in [15] that most of the DOPAC arises from intraneuronal metabolism of unreleased, de novo synthesized DA. It can be tentatively suggested that the spike activity of DA neurons is more closely connected with DA synthesis than with its release from terminals. This view is confirmed by comparison of effects of buspirone, risperidone, and sulpiride on DA, DOPAC, and HVA levels (Table 1). Buspirone potentiated DA release by a lesser degree than risperidone or sulpiride, although it was much more effective in relation to DOPAC and HVA. Agonists of 5-HT_{1A} receptors, which includes buspirone, inhibit activity of 5-HT neurons in the dorsal nucleus raphe [10]. It has been suggested that this effect is due to stimulation of somatodendritic 5-HT_{1A} receptors. Considering the ability of 5-HT neurons to inhibit DA neurons [3], it can be postulated that buspirone, which disinhibits them, determines the greater DA-synthesizing activity, reflected in an increase in levels of DA metabolism. This kind of effect is probable for ritanserin, which blocks postsynaptic 5-HT_2 receptors on DA neurons. However, the possibility cannot be ruled out that buspirone may affect intraneuronal DA metabolism, for despite an increase in DA release, it reduces the DA concentration in the tissues [1]. This effect has not been described for any of the known antagonists of D_2 receptors.

MeODMT, an unselective agonist of 5-HT_1 receptors, did not affect striatal DA, DOPAC, and HVA levels. Unlike buspirone, which is a complete agonist of presynaptic and a partial agonist of postsynaptic 5-HT_1 receptors, MeODMT is a complete agonist of postsynaptic 5-HT receptors, as shown by its ability to induce a 5-HT syndrome in intact rats and contralateral rotations in rats denervated unilaterally with 5,7dihydroxytryptamine [2]. Buspirone does not possess such effects. Despite inhibition of 5-HT neurons [7], the absence of any effect of MeODMT on DA release may be linked with complex interaction with 5-HT neuronal mechanisms.

The results described above, obtained by intracerebral microdialysis in conscious rats, enable both the neurochemical profile of the tested preparations in vivo and the dynamics of the effect in unrestrained animals can be assessed.

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IN VITRO AND IN VIVO STUDIES OF ANTIMUTAGENIC PROPERTIES OF BIOGINSENG IN MAMMALIAN CELLS

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UDC 575.224.6

KEY WORDS: bioginseng; Chinese hamster cells; Ehrlich's ascites tumor cells; chromosomal aberrations; sister chromatid exchanges; antimutagenic properties

In certain industries the level of mutagens still remains quite high. The possibility of accidents at chemical factories or atomic power stations, accompanied by massive discharge of mutagens into the environment, likewise cannot be ruled out. Hence the great urgency for a search for antimutagenic agents and, in particular, those possessing not only antimutagenic, but also other beneficial properties besides. Ginseng is used on quite a wide scale as an adaptogen, influencing biosynthetic, neurohumoral, and bioenergetic processes at all stages of formation of protection against stress and its aftereffects [1]. Emergency mobilization of plastic and energy-yielding resources of the cell under the influence of the panaxosides contained in ginseng has led to the suggestion that these plant glycosides probably have an antimutagenic action.

The aim of the investigation described below was to study the possibility of reducing the frequency of chromosomal aberrations arising under the influence of mutagens by preliminary addition of bioginseng to the culture medium for cells in vitro or its injection into an animal in vivo.

EXPERIMENTAL METHOD

To study the antimutagenic properties of ginseng we chose a preparation obtained from a culture of callus cells of ginseng, known as bioginseng. The technology of producing bioginseng has been worked out at the All-Union Research Institute of Biotechnology and has been introduced at a number of factories. The biomass of the ginseng tissue culture has been shown to be stable with respect to its biochemical parameters, and closely similar in composition to the native route

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 0007-4888/91/0005-0658$12.50 ©1991 Plenum Publishing Corporation