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Genotoxicological Safety Assessment of a New Antiparkinsonian Substance ((1r,2r,6s)-3-methyl-6-(Prop-1-en-2-yl)cyclohex-3-ene-1,2-diol)

[1]Maxim V. Trushin, [2]Oleg V. Ardashov, [2]Konstantin P. Volcho,
[1]Irina A. Arkharova and [2]Nariman F. Salakhutdinov

[1]Kazan Federal University, Kazan, Russia
[2]Vorozhtsov Novosibirsk Institute of Organic Chemistry,
Russian Academy of Sciences, Novosibirsk, Russia

Abstract: Parkinson's disease (PD) is a neurodegenerative condition of unknown etiology. This article is devoted to special genotoxicological testing of a new substance with antiparkinsonian activity. It was assessed using *Allium cepa*-test system. As a result of study of the effect (1R, 2R, 6S)-3-methyl-6-(prop-1-en-2-yl) cyclohex-3-ene-1,2-diol in cell model object (*Allium cepa*) we revealed two distinctive features of the effects of substance-itotoxic effect and no increase in the frequency of genetic disorders with increasing concentration of the substance. In general, the tested substance seems safe.

Key words: Parkinson's disease · Treatment · Diol · Genotoxicological safety · Mutations

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative condition of unknown etiology. It displays a progressive character with substantial physical, emotional and social implications. Pharmacological treatment is the main option of PD management but it should be individualized accordingly to the personal needs of the patient.

All treatments may be divided into three main groups: surgical, special physical training and pharmacological therapies. The first consists of deep brain stimulation (DBS) as a gold standard for PD neurosurgery [1-3]. It helps to manage pharmacologically refractory neurological symptoms and there are a few various targets for DBS-mainly ventral posterolateral nucleus of the thalamus and pedunculopontine nucleus [4-7]. However, the question is how many nuclei should be stimulated simultaneously? There is also an issue of laterality. Finally, postoperative risks are real [8-10] and DBS may mainly be considered for patients with refractory history toward drugs. Special physical training together with speech training presents an important addition to pharmacological therapy [11-13].

Special pharmacological treatment concerns a management of motor symptoms (like tremor, rigidity, akinesias, dyskinesias, fluctuations) as well as nonmotor symptoms (sleep disorders and others). A few comprehensive reviews were devoted to pharmacological treatment of PD and all advantages and disadvantages were discussed [14-16]. About 5 years ago, scientists from Vorozhtsov Novosibirsk Institute of Organic Chemistry of Russian Academy of Sciences (Novosibirsk, Russia) reported on a synthesis of a new substance with antiparkinsonian activity that were proved in PD models and special features of the compounds were also reported [17-23]. This article is devoted to special genotoxicological testing of one of these substances.

MATERIALS AND METHODS

(1R,2R,6S)-3-methyl-6-(prop-1-en-2-yl)cyclohex-3-ene-1,2-diol was synthesized in Vorozhtsov Novosibirsk Institute of Organic Chemistry, Russian Academy of Sciences, Novosibirsk, Russia. The possible genotoxicological safety of the substance was assessed using *Allium cepa*-test system. Onion bulbus (Stuttgarter Riesen) were obtained commercially and were placed in small jars with the tested solutions of the substance. We tested from 0.1 to 1% concentrations of (1R,2R,6S)-3-methyl-6-(prop-1-en-2-yl)cyclohex-3-ene-1,2-diol for 3-5 days. For the negative control it was used a distilled water. When roots were appeared, they were cut of and fixed with solution containing 96% ethanol and acetic acid (in proportion 3:1). 2 h later, fixed roots were placed into staining solution (2% acetocarmine). Later, root tips were squashed in slides and visualized with AxioLab A1 microscope (Carl Zeiss, Germany).

Corresponding Author: Dr. Maxim Trushin, Kazan Federal University, 420008 Kazan, Russia.

RESULTS AND DISCUSSION

In effect was analyzed (1R, 2R, 6S)-3-methyl-6-(prop-1-en-2-yl) cyclohex-3-ene-1,2-diol in onion cells. In general, we visualized over 14,500 cells. The results of this work are presented in Table 1 and Figs 1 and 2.

In the control and experimental variants, we were detected the following types of genetic abnormalities-C-metaphase (showing propensity to aneuploidy), micronuclei (containing aborted genetic material at the genomic changes) and lobulated nucleus (describing the process of cell death) (Figure 2).

Thus, as a result of study of the effect (1R, 2R, 6S)-3-methyl-6-(prop-1-en-2-yl) cyclohex-3-ene-1,2-diol in cell model object (*Allium cepa*) we revealed two distinctive features of the effects of substance-mitotoxic effect and no increase in the frequency of genetic disorders with increasing concentration of the substance. The first effect may suggest that the (1R,2R,6S)-3-methyl-6-(prop-1-en-2-yl) cyclohex-3-ene-1,2-diol can influence the development and growth of the test organism. Indeed, with increasing concentrations of the substances we observed worsening of the dynamics of root growth of onions. Roots became yellowish and harder compared to the control. A number of genetic disorders are not increased with increasing concentration of the substance. Moreover, when the concentration of the substance was increasing, we detected some reduction in the frequency of genetic disturbances (Fig. 2). It is likely that this was due to

Table 1: Changes in the mitotic index in onion cells induced by exposure to (1R, 2R, 6S)-3-methyl-6-(prop-1-en-2-yl) cyclohex-3-ene-1,2-diol.

Experimental variant	Number of cells under study	Values for mitotic index, %
Control	2933	8.3
0.1%	2154	4.2
0.2%	2141	0
0.3%	2481	0
0.5%	2010	0
0.7%	1111	0
1%	1700	0

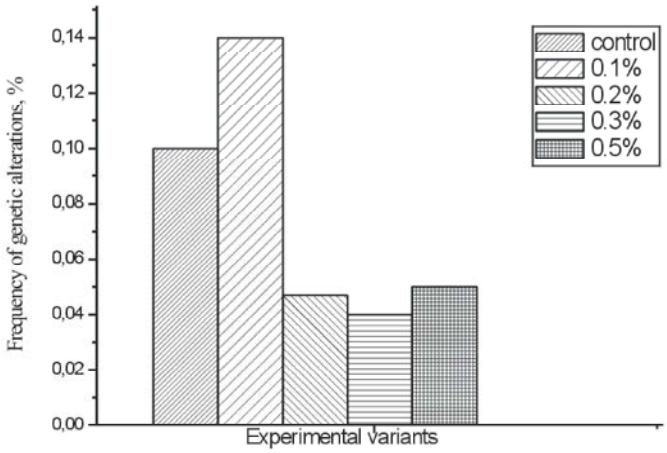

Fig. 1: Frequency of genetic alterations in the cells due to exposure bow (1R, 2R, 6S)-3-methyl-6-(prop-1-en-2-yl) cyclohex-3-ene-1,2-diol. Note: at concentrations of 0.7 and 1% genetic abnormalities were not detected.

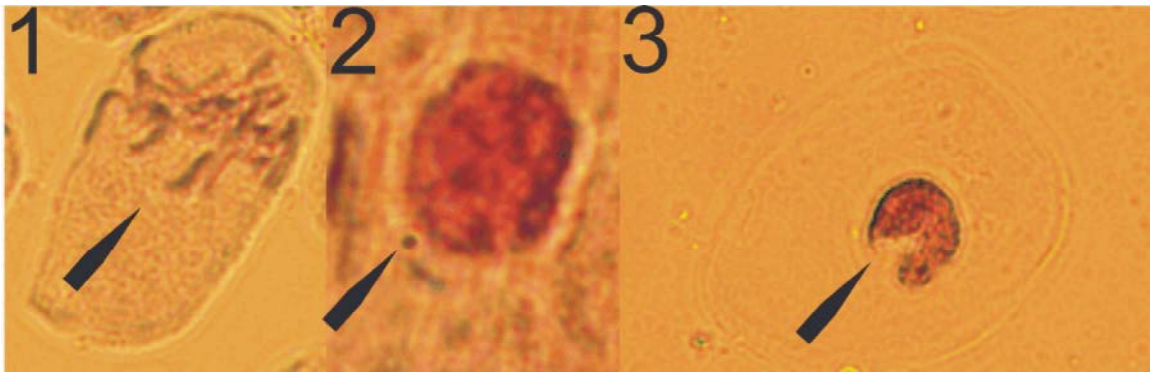

Fig. 2: Examples of genetic alterations in the cells of onion. 1 – C-metaphase, 2 – microkernel, 3 – lobulated nucleus.

inhibition of cell division-reducing the frequency of chromosomal and nuclear irregularities at the normal values of the mitotic index could indicate antimutagen effect of the substance. However, it should be clarified in special experiments. Also, utilizaion of, for example, 1-1.5 cm onion roots at the beginning of the experiment would clarify the true values of genetic abnormalities at a higher concentrations of the substance (till 1%).

So, (1R,2R,6S)-3-methyl-6-(prop-1-en-2-yl) cyclohex-3-ene-1,2-diol seems safe from the genotoxicological point of vew.

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