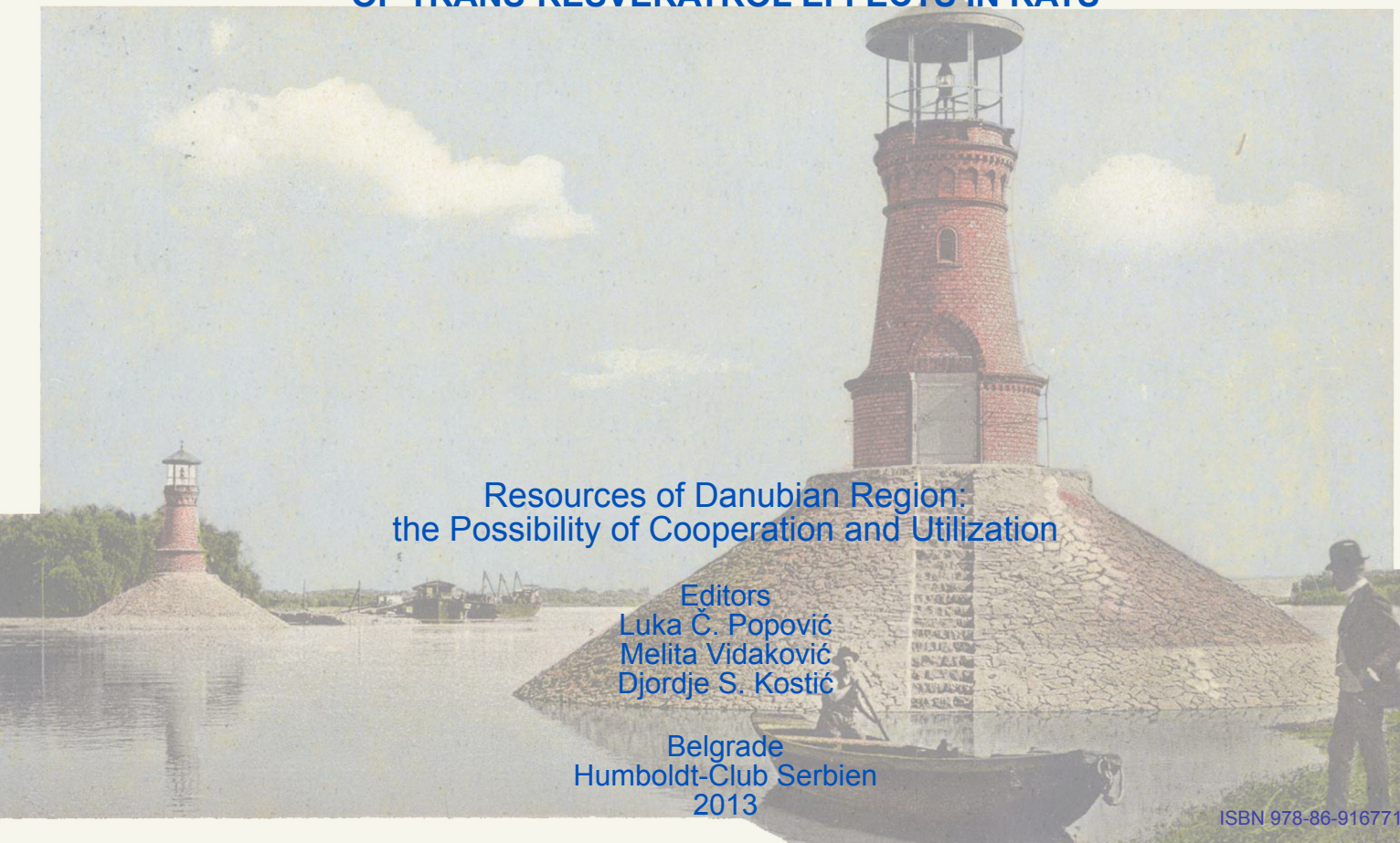
Janko Samardžić
Institute of Pharmacology, Clinical Pharmacology and Toxicology,
Medical Faculty, University of Belgrade
Serbia
Dragan I. Obradović
Institute of Pharmacology, Clinical Pharmacology and Toxicology,
Medical Faculty, University of Belgrade
Serbia
Ljiljana Gojković-Bukarica
Institute of Pharmacology, Clinical Pharmacology and Toxicology,
Medical Faculty, University of Belgrade
Serbia

BEHAVIOURAL CHARACTERISATION OF TRANS-RESVERATROL EFFECTS IN RATS



Resources of Danubian Region:
the Possibility of Cooperation and Utilization

Editors
Luka Č. Popović
Melita Vidaković
Djordje S. Kostić

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Abstract. It has been shown that the trans-isomer of resveratrol demonstrates a variety of pharmacological activities. However, its behavioural profile still remains controversial. The goal of the present study was to examine the influence of trans-resveratrol on memory and depression-like behaviour. We studied the effects of trans-resveratrol on active avoidance learning, forced swimming and locomotor activity. Treatment with trans-resveratrol significantly affected retrieval of avoidance responses. ANOVA showed that resveratrol significantly decreased immobility time at the doses of 10 and 20 mg/kg, and did not show a significant effect on locomotor activity. Our results experimentally support the findings that trans-resveratrol might trigger acute memory-enhancing and antidepressant-like effects.
Keywords: resveratrol, memory, depression, locomotor activity.

Introduction

Resveratrol (3,5,4'-trihydroxy-trans-stilbene), a natural non-flavonoid polyphenol antioxidant, exists as two geometric isomers: cis- and trans-. The trans-isomer of resveratrol is the active ingredient of Poligonum cuspidatum, a plant traditionally used in the Far East, and it is also found abundantly in the skin of red grapes and red wine (Bai et al., 2010). It has been shown that more stable trans-resveratrol demonstrates a variety of pharmacological activities including antioxidant, anti-inflammatory and vasodilatatory effects, neuroprotective properties and amelioration of learning and memory impairment (Gojkovic-Bukarica et al., 2008; Ranney et al., 2009; Xu et al., 2010). However, its behavioural profile still remains controversial.

Extracts of many plants are increasingly proposed as an integral part of the clinical treatment of neuropsychiatric diseases and particularly mood disorders, due to higher compliance and fewer side effects in patients (Thachil et al., 2007). Clinical depression represents a global health problem and at any time point 2-3 % of the population suffers from the disease (Moussavi et al., 2007). Current guidelines of depression pharmacotherapy are mainly focused on the modulation of monoamine neurotransmitter systems. However, data from epidemiological studies shows that 20-40 % of patients treated with conventional antidepressants remain resistant to therapy (Souery et al., 2006), and 50 – 80 % of patients experience a recurrence (Wiliams et al., 2010), indicating the need for intensive biological and behavioural studies and possible revision of the existing hypotheses.

In the literature, there is much more data and studies on the effects of resveratrol on cardiovascular system and peripheral tissues, while the effects of mental function and behaviour are less understood.

The central nervous system (CNS) represents a very important target for the effects of resveratrol, since the polyphenols easily pass the blood-brain barrier (Baur et al., 2006; Xu et al., 2010).

The goal of the present study was to examine the influence of trans-resveratrol and compare its dose-response effects on memory, spontaneous locomotor activity and depression-like behaviour.

Material and methods

Experiments were carried out on male Wistar rats (Military Farm, Belgrade, Serbia) weighing 180–230 g. The rats were housed in transparent plastic cages, six animals per cage, and had free access to pelleted food and tap water before and after drug administration. The animals were placed in a room kept at a temperature of 22 ± 1 °C, relative humidity 40–70%, and 12/12-h light/dark period (lights on at 0630 h).

All handling and testing took place during the light portion of the cycle. The animals were used only once throughout the study, with 6 rats in a treatment group. All procedures in the study were confirmed to EEC Directive 86/609 and approved by the Ethical Committee on Animal Experimentation of the Medical Faculty in Belgrade.

The effects of resveratrol were observed with the active substance trans-isomer of resveratrol, which is the reference to the literature most often used in these studies (Orallo, 2006). The control group received the solvent (dimethyl sulfoxide, DMSO), and the experimental groups received trans-resveratrol in increasing doses (5, 10, and 20 mg/kg).

The substances were administered intraperitoneally (i.p.) in the lower right quadrant of the abdomen, before the testing of active avoidance learning, spontaneous locomotor activity and behaviour in the forced swim test.

Active avoidance test (AA)

AA test was performed in automated two-way shuttle boxes and programming recording units (Campden Instruments, Sileby, UK). In the first part of the study, the active avoidance test was elaborated by 100-trial 2-day sessions, and in the second part the influence of trans-resveratrol on the acquisition rate was checked in a procedure lasting five consecutive days, with 50 trials per day.

Measurement of spontaneous locomotor activity (SLA)

Immediately after receiving the treatment or solvent, single rats were placed in a clear Plexiglass chamber (40 x 25 x 35 cm). Activity under dim red light (20 lux) was recorded for a total of 30 min, without any habituation period.

Forced swim test (FST)

FST was performed in a glass cylinder, 45 cm high, 20 cm diameter filled with water up to a height of 30 cm, with a temperature of 21-23 °C. Male Wistar rats were exposed to two swimming sessions (an initial 15-min pretest session, followed 24 h later by a 5-min test session).

The duration of immobility (seconds) was scored during the 5-min test session and the rat was considered immobile whenever it floated passively in the water and only made movements necessary to keep its head above the water line. The time of struggling (seconds) during the 5-min test session consists of explosive muscular movements against the apparatus wall, in an attempt to escape from the cylinder.

Statistical analysis

All numerical data presented in the figures were given as the mean ± S.E.M. an alpha level of 0.05 was used for all statistical tests. In all the experiments, a digital camera recorded the behaviour of the animals, and data was analyzed by one-way ANOVA, followed by Dunnett's test.

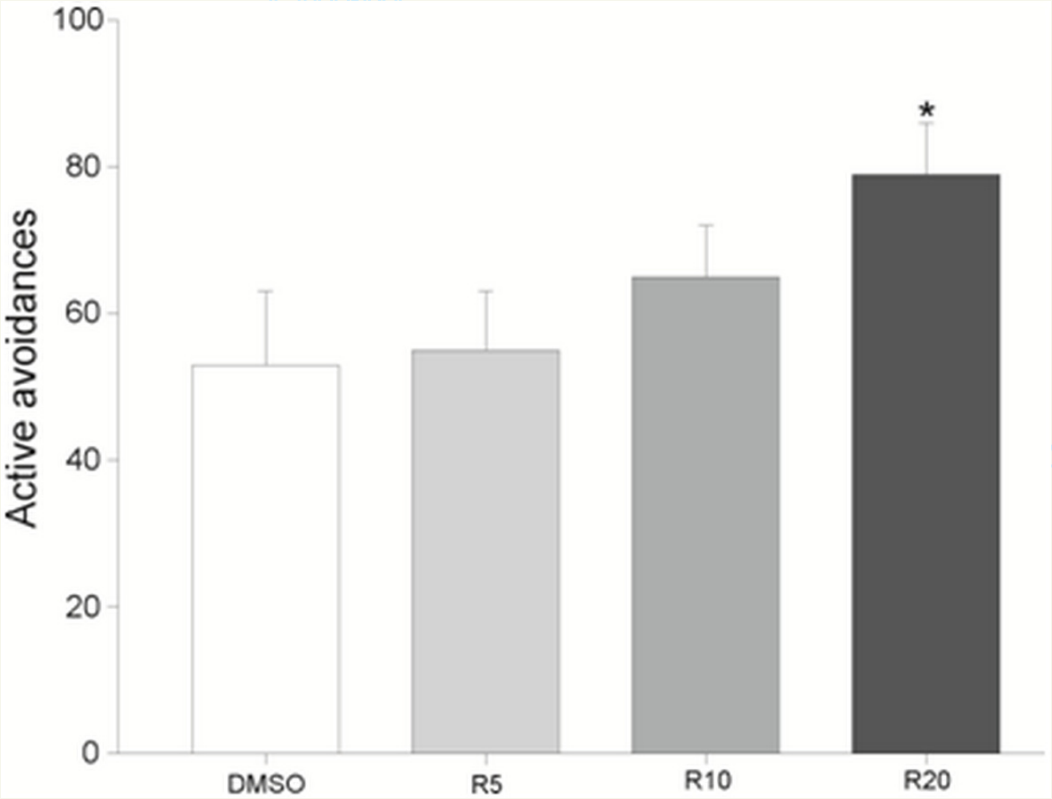

Figure 1.
Effects of resveratrol (R: 5, 10, 20 mg/kg) on active avoidance retrieval;
* p< 0.05 compared to solvent group (DMSO).

Results

Treatment with trans-resveratrol significantly affected retrieval of avoidance responses on the second day of shuttle box testing. Dunnett's test indicated that the trans-resveratrol avoidance-facilitatory dose was 20 mg/kg (**Figure 1**). However, it did not induce significant differences in acquisition rate during 5 days training.

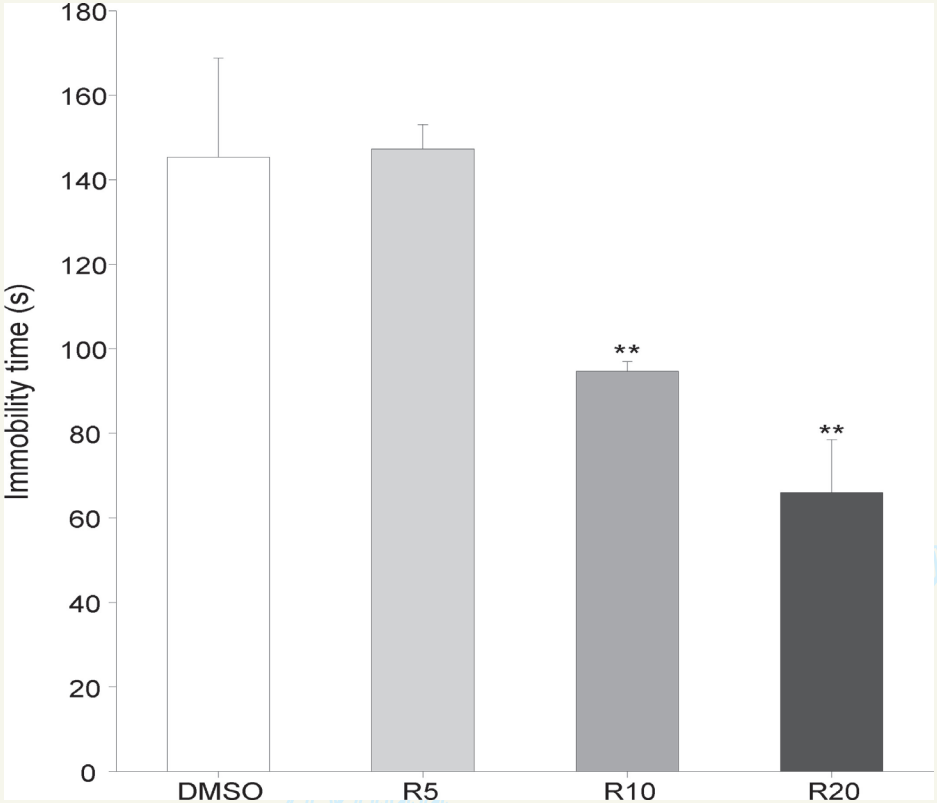

Figure 2.
Effects of resveratrol (R: 5, 10, 20 mg/kg) on the immobility time of the animals in forced swim test; ** p< 0.001 compared to solvent group (DMSO).

ANOVA did not show a significant effect of treatment on the locomotion and rearing of the animals during 30 min of monitoring of spontaneous locomotor activity ($F(3,20)=1.68$, $p>0.05$).

In FST, ANOVA indicated statistically significant effects of resveratrol ($F(3,20)=50.95$, $p<0.001$). Dunnett's analysis showed that resveratrol significantly decreased immobility time at the doses of 10 and 20 mg/kg, exerted acute antidepressant-like effects (**Figure 2**). However, it did not induce significant differences in time of struggling behaviour during the test (data not shown).

Discussion

The active avoidance test measures the ability of animal to avoid an aversive event and provides a way to study neurobiology of associative learning and memory (Grauer et al., 2009). Resveratrol, at the dose of 20 mg/kg, clearly facilitates retrieval of memory task imposed to rats in two-way active avoidance paradigm. The improvement of the performance in the retention session exerted by resveratrol was not caused by changes in motor activity, as there were no significant variations in locomotor parameters. However, all paradigms which involve aversive events also have an emotional component, and they are strongly connected to motivation and depression-like behaviour. Several studies have proposed that depression and memory are not just related to each other, but motivation would, in fact, be a necessary step for memory formation (Mathews, 1990).

The forced swim test is a valuable behavioural research model of depression in rodents and also an important tool to study neurobiological mechanism involved in antidepressant activity (Xing et al., 2011). In the present study, decreased immobility was clearly observed with resveratrol (10 and 20 mg/kg), exerted acute antidepressant-like effects, but there was no effect on struggling time, confirming that these effects were not confounded by change in motor function. However, when it comes to the mechanism of action, it still remains unknown whether resveratrol realized antidepressant effects via modulation or neurotransmission and inhibitition of monoamine oxidase (MAO), or it was some other mechanism.

It has been recently recognized the role of neuroinflammation and pro-inflammatory cytokines in the neurobiology of mood disorders, and the potential use of anti-inflammatory agents in the treatment of depressive symtoms (Bay-Richter et al., 2011; Lindqvist et al., 2009). Since it has been shown that resveratrol has a strong anti-inflammatory potentional, these properties could be essential in the clarifying of the central effects of resveratrol. The recent preclinical studies also suggest that free radicals may be involved in the development of mood discorders, particulary depression, due to its prooxidative effects of relatively high sensitive cells of CNS (Eren et al., 2007; Herkel et al., 2007). Molecular studies have shown that resveratrol, as a powerful antioxidant, inhibits the activity of MAO in astroglial cells and may have an important role in protecting neurones from oxidative stress (Salmina et al., 2009; Schulz et al., 2000). The overall effect of resveratrol may thus reflect better performance based on both anti-inflammatory and antioxidant potentials.

Conclusion

Our results experimentally support the findings that besides to cardiovasular effects, resveratrol produces significant effects in the central nervous system. Under certain circumstances, trans-resveratrol produces acute memory-enhancing and antidepressant-like effects, and these behavioural effects are not confounded by locomotion influences. The study is going to be extended in the characterizing the repeated dose administration of resveratrol and clarifying the probable central mechanism of its action.

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We declare that we have no conflict of interest.

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