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Resveratrol prevents social deficits in animal model of autism induced by valproic acid

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HIGHLIGHTS

- We performed a prenatal treatment with resveratrol in a rodent model of autism.
- Resveratrol prevented autistic-like social behaviors.
- Bioinformatics analysis suggests weak and unstable interactions between RSV and VPA.
- These results suggest cellular effects instead of a single chemical process.
- Investigation of VPA and RSV common targets may help to clarify autism etiology.

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ABSTRACT

Autism spectrum disorders (ASD) involve a complex interplay of both genetic and environmental risk factors, such as prenatal exposure to valproic acid (VPA). Considering the neuroprotective, antioxidant and anti-inflammatory effects of resveratrol (RSV), we investigated the influence of prenatal RSV treatment on social behaviors of a rodent model of autism induced by prenatal exposure to VPA. In the three-chambered apparatus test, the VPA group showed a reduced place preference conditioned by conspecific and no preference between exploring a wire-cage or a rat enclosed inside a wire cage, revealing sociability impairments. Prenatal administration of RSV prevented the VPA-induced social impairments evaluated in this study. A bioinformatics analysis was used to discard possible molecular interactions between VPA and RSV during administration. The interaction energy between RSV and VPA is weak and highly unstable, suggesting cellular effects instead of a single chemical process. In summary, the present study highlights a promising experimental strategy to evaluate new molecular targets possibly involved in the etiology of autism and developmental alterations implicated in neural and behavioral impairments in ASD.

1. Introduction

Autism spectrum disorders (ASD) comprise a set of developmental disabilities characterized by social impairments, communication difficulties, and restricted and stereotyped patterns of behavior [17]. This group of disorders is attracting great public attention because of their high prevalence, elevated social cost and large impact on the family. The US Center for Disease Control and Prevention estimate the prevalence of autism in the United States to be 1 in 68 children, with boys 4.5 fold more affected than girls [1].

In 1943, a landmark paper describing autism was published by Leo Kanner [11]; however, even after 70 years, the etiology of

Abbreviations: ASD, autism spectrum disorders; DFT, density functional theory; KRG, Korean red ginseng; RSV, resveratrol; SI, Sociability Index in the three-chamber test; SNI, Social Novelty Preference Index in the three-chamber test; VPA, valproic acid; MD, molecular dynamics.

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autism and its molecular basis are not well understood. Genetic studies have revealed a multitude of alterations associated with autism, but the characterized components to date account for only 25% of all cases of autism [15]. On the other hand, environmental factors, like exposure to xenobiotics - e.g. valproic acid (VPA) and thalidomide - can either trigger or contribute to autism development [9].

Considering the association between VPA exposure and ASD in humans [4], an animal model of prenatal VPA administration in rodents was suggested. In the past years, this model has shown to be a reliable research tool, as it presents many morphological and behavioral alterations related to the autism pathophysiology [3,6]. Thus, prevention of complex outcomes, such as behavioral impairments, and investigation of the molecular pathways that underlie these changes in the VPA model can shed light in biological process relevant to autism etiology.

Resveratrol (RSV) is a naturally occurring polyphenolic compound present in grapes, pines, peanuts and red wine [23]. The bulk of an intravenous dose of RSV is mainly converted to sulphate conjugates within approximately 30 min in humans and the serum half-life of total RSV metabolites is approximately 9.2 h [24]. In the last two decades, RSV received special attention from scientific community and has been associated with protective and therapeutic roles in several illnesses [23]. Resveratrol is widely recognized as an anti-oxidant and anti-inflammatory compound besides showing neuroprotective effects [7]. All of these biological activities could be of interest in autism therapeutics [19].

In this context, we investigated preventive effects of RSV in the autistic-like social features of an animal model induced by prenatal exposure to VPA. We performed a three-chamber test to measure social memory and preferences. Additionally, bioinformatics studies were used to evaluate the interaction between VPA and RSV, in order to distinguish whether the effect derivate from a direct molecule-molecule contact or from a broad cellular action.

2. Results

2.1. Behavioral testing

2.1.1. Three-chamber sociability and social novelty test

2.1.1.1. Sociability test. Animals of all groups stayed in the central chamber (known chamber) for only short periods of time, frequently less than 100 s. Thus, the animals were engaged in the exploration of the new environment and its content. The Control rats spent significantly more time in the chamber with the conspecific than in the chamber with the object (mean ± SEM in seconds: 285.14 ± 9.55 and 224.86 ± 12.24, with conspecific and object, respectively; $p < 0.001$). In contrast, VPA-exposed rats showed rather a non-significant tendency to spend more time to the novel object than the conspecific rat. Interestingly, RSV treatment was able to prevent the change induced by VPA (RSV + VPA: 289.5 ± 10.56 and 216.3 ± 21.26; $p < 0.05$) and, in fact the RSV + VPA group showed almost the identical time spent investigating rat 1 and object as the control group. Rats from RSV group behaved similarly to the Control animals, but there was no statistical difference between the times spent in the chamber with the rat and the chamber with the object. These data show that the VPA group animals seem to avoid the rat in favor of the object, an atypical behavioral pattern that was prevented by RSV prenatal treatment (Fig. 1A).

The analysis of exploration time, defined as time sniffing near the enclosed rat or the object and actively interacting with it (Fig. 1B), shows that rodents from both Control and RSV groups preferentially interact with a conspecific than an object (Control: 232.29 ± 10.42 and 117.43 ± 11.67; $p < 0.001$. RSV: 247.43 ± 38.8 and 91.57 ± 19.01; $p < 0.05$. Rat and object, respectively).

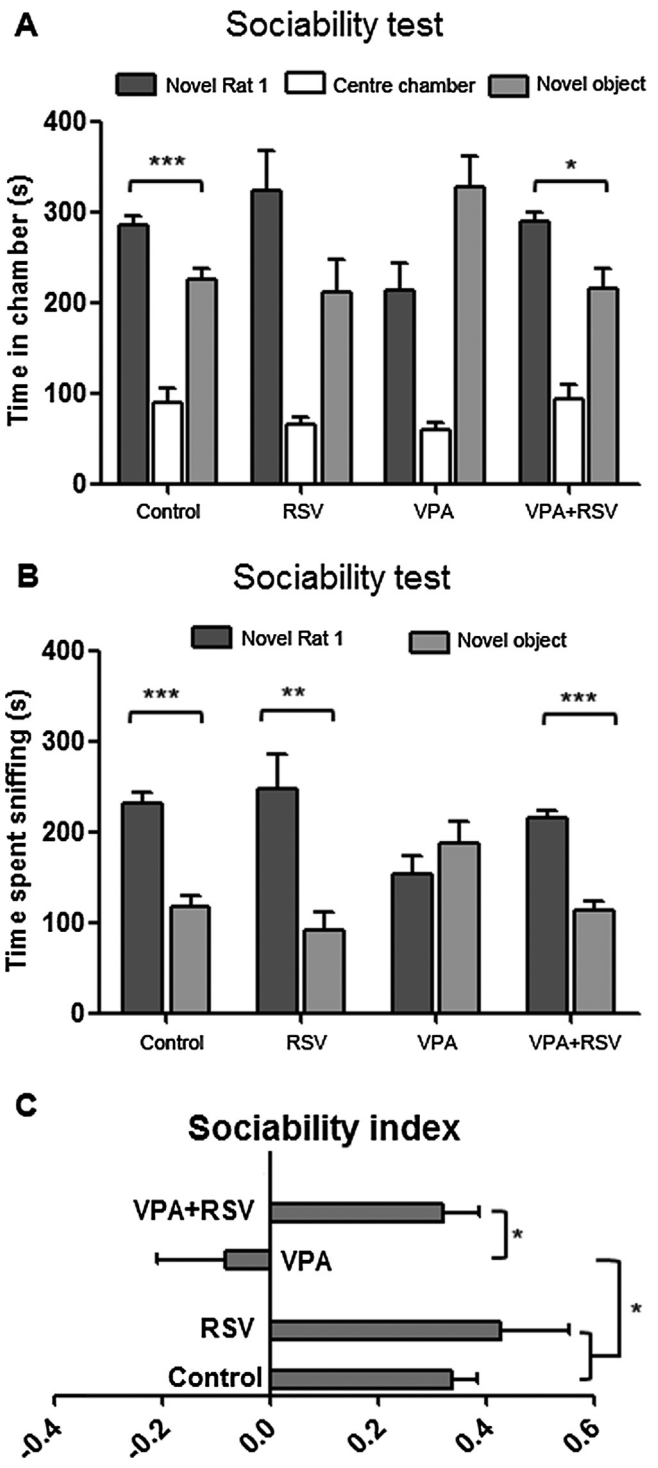

Fig. 1. RSV administration prevents the sociability deficit present in the VPA model of autism in rats. After 5 minutes of acclimatization, male rats were allowed to explore all chambers for 10 min. (A) Time spent in chambers. (B) Time spent exploring novel rat 1 or novel object. (C) Sociability Index. *$p < 0.05$. **$p < 0.01$, ***$p < 0.001$. $n_{Control} = 7$, $n_{RSV} = 7$, $n_{VPA} = 19$, $n_{VPA+RSV} = 10$.

The VPA animals showed no difference between the contact times with the novel rat and the object (147.17 ± 21.54 and 189.44 ± 25.11), which clearly shows decreased sociability. The RSV treatment was again able to counteract the VPA effect by restoring the preference for the novel rat (214.5 ± 9.02 and 112.4 ± 11.43; $p < 0.001$).