

IS THERE TREATMENT EFFECT OF VINPOCETINE ON AUTONOMIC DYSFUNCTION IN RATS WITH ALZHEIMER?

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ABSTRACT

Objective: Alzheimer's disease (AD) shows less autonomic dysfunction. There was a lack of response or prolongation of its latency in skin sympathetic response. Vinpocetine is a classic inhibitor of PDE1 activity. Vinpocetine treatment has been shown to enhance performance on cognitive tests in humans. The efficacy of the use of vinpocetine in clinical trials has been controversial. A comparison of multiple studies evaluating vinpocetine use in AD was recently conducted. Our first aim was to assess dysautonomia in rat with AD electrophysiologically, using sympathetic skin response (SSR) test. The second aim of this study, evaluate the effect of vinpocetine treatment on Alzheimer autonomic dysfunction and attention deficiency.

Methods: Rats were divided into four groups: Sham group (Group C, i.p. saline), Alzheimer group (Group A), vinpocetine group (Group V, 5 mg/kg, every other day, i.p.), Alzheimer+vinpocetine group (Group AV). AD was induced in old male rats by AlCl_3 (40 mg/kg i.p.) and D-galactose (90 mg/kg) daily for 6 weeks. Then skin conductance level (SCL), which is an SSR parameter, was measured as tonic (no-stimuli period, 2 minutes) and phasic SSR (simultaneously with 15 auditory stimuli, 10 minutes). Tonic SSR is useful to investigate general states of arousal and alertness, while phasic SSR is useful to study multifaceted attentional processes (related to novelty, intensity).

Results: SCL was a difference among groups (tonic: $F=21.47$, $p\leq 0.000$; phasic: $F=9.86$, $p\leq 0.000$). SCL was statistically lower in Group A than Group C ($p\leq 0.005$) and Group V ($p\leq 0.000$). SCL of Group V was statistically higher than Group C ($p\leq 0.04$), Group A ($p\leq 0.000$) and Group AV ($p\leq 0.000$). SCL of Group AV was lower than Group C's ($p\leq 0.01$).

Conclusion: There was no statistically difference between Group A and Group AV. We concluded that autonomic disturbances accompanied AD and vinpocetine treatment could not ameliorate this disturbance.

Keywords: Autonomic dysfunction, Dysautonomia, Inhibitor, Skin conductance level, Sympathetic skin response.

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INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder associated with cognitive and behavioral dysfunction. It is the leading cause of dementia in the elderly [1]. AD is characterized by the progressive accumulation of amyloid beta peptide, neurofibrillary tangles, and hyperphosphorylated microtubule-associated tau protein. Several regions involved in memory and learning processes in the brain, such as the hippocampus, show neuron apoptosis several years before clinical signs appear [2]. AD also shows less autonomic dysfunction. The majority of patients presented with abnormalities in skin sympathetic response: Lack of response or prolongation of its latency. Idiaquez and Roman also showed less autonomic dysfunction in AD and frontotemporal lobar degeneration [3,4].

In this study, our first aim was to assess dysautonomia in rat with AD electrophysiologically, using sympathetic skin response (SSR) test. One of the most widely used indices of the autonomic nervous system in psychological research has been SSR test or electrodermal activity (EDA), which is usually measured as skin conductance level (SCL) [5]. It is recorded as a change in skin potential or resistance of sweat gland reaction controlled by the sympathetic nervous system. SCL also reflects tonic levels of arousal [6]. SSR has been utilized in research examining attention, emotion, and psychopathology [7-11].

SSR was studied in Alzheimer to the evaluation of clinical and functional assessment of dysautonomia [4], to investigate sudomotor function [3],

and to explore cardiovascular functions [3,12]. They found abnormal SSR test in humans. There are some studies investigate autonomic dysfunction in rats. However, none of them studied with SSR test.

It is now estimated that there are 18-24 million people suffering from AD worldwide. Today there is no cure for this devastating disease. Hence, it is of great interest for researchers to find new treatment that can hinder the disease process. Some drugs may improve the function of intact neurons, but do not inhibit degenerative process leading to neuronal cell death. The alkaloid vinpocetine is a classic inhibitor of PDE1 activity [2]. Vinpocetine treatment has been shown to improve memory retrieval, and enhance performance on cognitive tests in humans [13]. The efficacy of the use of vinpocetine in clinical trials has been controversial.

This is the first study explore autonomic function with SSR in rats with Alzheimer. We also evaluated the effect of vinpocetine treatment on Alzheimer autonomic dysfunction and attention deficiency.

METHODS

This study was carried out in Erciyes University Faculty of Medicine, Physiology Department, Kayseri, Turkey from September 2012 to September 2013. Thirty-two male Sprague-Dawley 19-month-old rats were included in the study. The experiments were performed in laboratories with standardized conditions at $22\pm 2^\circ\text{C}$ and $50\pm 5\%$ humidity. A standard diet and tap water were provided ad-libitum. All rats were bred at the Hakan Çetinsaya Experimental and Clinical

Research Center of Erciyes University and were fed with tap water and Purina rodent chow. The experiments were carried out after receiving approval from the Committee on Ethics in Animal Experimentation at Erciyes University (No. 08-12-85). All animal experiments were conducted at Erciyes University Faculty of Medicine, Department of Physiology in the Laboratory of Brain Dynamics.

Study protocol

Rats were divided into four groups: Sham group (Group C, i.p. saline, N=9), Alzheimer group (Group A, N=9), Vinpocetine group (Group V, 5 mg/kg, every other day, i.p., N=7), Alzheimer+vinpocetine group (Group AV, N=7). AD was induced in old male rats by intraperitoneal administration of AlCl₃ (40 mg/kg body weight) and D-Galactose (90 mg/kg body weight) daily for 6 weeks.

SSR recordings

SSR was measured using the MP30 system (MP30; Biopac Systems Inc., Santa Barbara, CA) and the physiological recordings took place in a dimly lit, electrically and acoustically shielded experimental room. Before the recordings, rats were subjected to a habituation period of 5 minutes. SSR was recorded, employing a constant voltage technique and sampling the absolute, direct current skin conductance at the rate of 20 samples per second, from the plantar surface of the posterior extremities of each rat using Ag/AgCl electrodes. Animals were conscious during recording, and multipurpose gel was used between the skin and the electrodes. Electrodes were connected to the MP30 system. The incoming signals of skin response were converted to digital signals through an MP30 data acquisition unit and processed with off-line analysis [5].

Tonic SSR

A period of 2 minutes was allowed at the start of recording to register non-specific SCL ($\mu\text{mho}/\text{cm}^2$) during a no-stimuli period. Tonic SSR is useful to investigate general states of arousal and alertness.

Phasic SSR

The 15 auditory stimuli were presented at the end of the tonic EDA period (no-stimuli period). All were 1-s, 90 dB, 1000-Hz tones with 50-ms rise and fall times. They occurred at pseudo-random intervals ranging from 30 to 65 seconds, averaging 45 seconds. The mean SCL values were calculated also off-line for phasic SSR. Phasic SSR is useful to study multifaceted attentional processes (related to novelty, intensity).

Statistical analyses

Values were expressed as means \pm SE. Data from SSR recordings analyzed with the ANOVA test for comparison of the 4 groups and the *post-hoc* Scheffe test was used for comparison of 2 groups. Differences were considered to be significant with a $p < 0.05$. All the statistical analyses were performed using the SPSS 16.0 for Windows software.

RESULTS

Table 1 indicates the mean SCL values in all groups. SCL was a difference among groups (tonic: $F=21.47$, $p \leq 0.000$; phasic: $F=9.86$, $p \leq 0.000$). SCL was statistically lower in Group AD than Group C ($p \leq 0.005$) and Group V ($p \leq 0.000$) in tonic and phasic recordings. SCL of Group V was statistically higher than Group C ($p \leq 0.04$), Group A ($p \leq 0.000$) and Group AV ($p \leq 0.000$) for tonic recordings. Tonic SCL of Group ADV was lower than Group C's ($p \leq 0.01$) (Fig. 1). There was no statistically difference between Group AD and Group ADV.

DISCUSSION

This is the first study investigating therapeutic effect of vinpocetine on sympathetic activity and autonomic dysfunction in AD. We found that vinpocetine was increased SSRs, but it was not therapeutically efficacious on Alzheimer's autonomic function.

The use of vinpocetine in animal models suggests that vinpocetine has a role to play in restoring neuronal plasticity (learning and memory

Table 1: Descriptives of SCL values of groups (mean \pm SE)

Skin conductance level	Group C (n=7)	Group AD (n=6)	Group V (n=7)	Group ADV (n=7)
Tonic	10.70 \pm 0.28	6.6 \pm 0.59	13.8 \pm 0.58	7.07 \pm 4.36
Phasic	9.63 \pm 0.35	5.25 \pm 0.48	10.93 \pm 0.98	6.66 \pm 1.20

SCL: Skin conductance level, Group C: Sham group; Group AD: Alzheimer group, Group V: Vinpocetine group; Group ADV: Alzheimer+Vinpocetine group, SE: Standard error

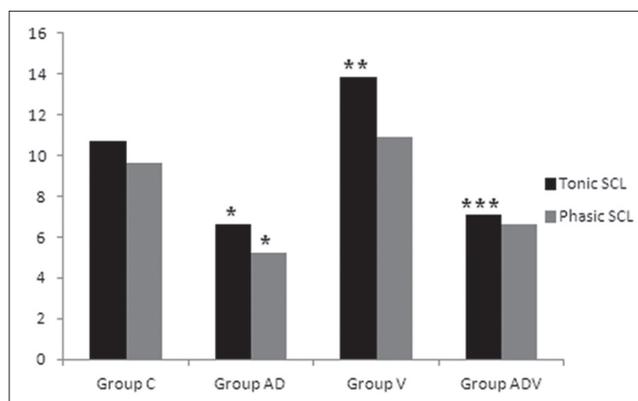


Fig. 1: Comparison of SCL values of groups. *Different from Group C and Group V; **versus Group ADV and Group C; ***versus Group C, SCL: Skin conductance level, Group C: Sham group, Group AD: Alzheimer group, Group V: Vinpocetine group, Group ADV: Alzheimer+vinpocetine group

in particular) in different conditions. However, the findings from clinical trials are still controversial, and more studies are needed. It is conceivable that one reason for this discrepancy is the great difference in the dosage used in basic science studies and the ones used in clinical trials. Most studies performed in animal models used doses between 10 and 20 mg/kg [14,15]. These doses translated to humans would result in approximately 1,000 mg, which would be roughly a 20-fold increase in the current doses used in clinical trials [16-18].

We found only one study related with vinpocetine and sympathetic system. Gaál and Molnár found that vinpocetine produces a significant and dose-dependent increase in the firing rate of locus coeruleus neurons [19]. They also claimed that vinpocetine increases the activity of ascending noradrenergic pathways and this effect can be related to the cognitive-enhancing characteristics of the compound.

CONCLUSION

We concluded that autonomic disturbances accompanied AD and vinpocetine treatment could not ameliorate this disturbance.

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