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Effects of Quercetin and Resveratrol on Zinc Chloride- and Sodium Metavanadate-Induced Passive Avoidance Memory Retention Deficits in Male Mice

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ABSTRACT: Quercetin and resveratrol are found in a variety of fruits and vegetables and have several biological and pharmacological properties. In this study, the effects of quercetin [50 mg/kg, intraperitoneal (i.p.)] and resveratrol (50 mg/kg, i.p.) on zinc chloride ($ZnCl_2$; 75 mg/kg/d, 2 weeks oral gavage) and sodium metavanadate (SMV; 22.5 mg/kg/d, 2 weeks oral gavage) induced passive avoidance memory retention were investigated in step-through passive avoidance tasks. $ZnCl_2$ was dissolved in saline and SMV was dissolved in drinking water. Mice received $ZnCl_2$ or SMV orally for two weeks and were administered quercetin or resveratrol by i.p. injection on day 14, days 12 and 14, or days 10, 12, and 14. At the end of treatment, animals were trained for one day in a step-through passive avoidance task, then alterations in avoidance memory retention were evaluated after 24, 48, 96, and 168 h. Oral consumption of $ZnCl_2$ and SMV decreased latency time compared with control groups. Both quercetin and resveratrol (50 mg/kg, i.p.) prevented $ZnCl_2$- and SMV-induced avoidance memory retention impairments and did not significantly alter muscle strength, as demonstrated in rotarod tasks. No significant differences were observed between mice who received single, double, or triple doses of quercetin or resveratrol. The results suggest that quercetin and resveratrol may have preventive effects on $ZnCl_2$- and SMV-induced memory impairment in male mice.

Keywords: quercetin, resveratrol, sodium metavanadate, step-through task, zinc chloride

INTRODUCTION

Many compounds in fruit and vegetables such as resveratrol and quercetin exhibit anti-aging properties. Targeting these mechanisms may help alleviate aging-dependent learning and memory deficiencies (Baur and Sinclair, 2006).

Resveratrol is a polyphenol phytoalexin found in the skin of red grapes (Jang et al., 1997; Vinson, 1998). Resveratrol has been shown to inhibit or slow the development of various diseases including cardiovascular disorders, cancer, Alzheimer's disease (AD), and ischemic injuries (Bradamante et al., 2004; Baur and Sinclair, 2006), acting via its antioxidant, anti-inflammatory, and neuroprotective properties (Baur and Sinclair, 2006; Saiko et al., 2008). Furthermore, resveratrol has been shown to reduce toxicity induced by amyloid beta (Aβ) peptides (Han et al., 2004; Anekonda, 2006) and kainic acid (Wang et al., 2004) to prevent cerebral ischemic damage (Wang et al., 2002), improve cognitive function in a senescence-accelerated mouse prone 8 model of AD (Porquet et al., 2013), and improve memory deficit induced by scopolamine (Gacar et al., 2011) or streptozotocin (Sharma and Gupta, 2002). In addition, other studies have illustrated that resveratrol could be a beneficial for treatment of AD (Ono et al., 2008; Turner et al., 2015), with its neuroprotective properties attributed to its antioxidant activity (Poulose et al., 2015).

The flavonoid compound quercetin (3,3',4',5,7-pentahydroxyflavone dihydrate) is found in fruits, vegetables,

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leaves, and grains (Silva et al., 2008) and contains important antioxidant and free radical scavenger activities (Saponara et al., 2002). Quercetin is involved in activation and stimulation of neurogenesis (Tchantchou et al., 2009), and can easily pass through the blood-brain barrier (BBB) to help decrease neurodegenerative alterations and age-related neurocognitive impairment (Manach et al., 2004; Youdim et al., 2004; Rogerio et al., 2007). Moreover, quercetin has shown neuroprotective effects against oxidative stress and Aβ accumulation in *in vitro* and *in vivo* models (Cho et al., 2006; Zhu et al., 2007).

Zinc (Zn) is an essential element that plays a central role in various physiological processes, including immune system function and protein synthesis, and is a co-factor for several enzymes (Frassinetti et al., 2006). Zn has numerous structural, catalytic, and regulatory functions in brain maturation, maintenance of mental functions and neurotransmission, and binds to certain receptors at critical periods of brain development (Sandstead et al., 1998; Durczok et al., 2005; Flinn et al., 2005; Boroujeni et al., 2009; Nuttall and Oteiza, 2014; Prakash et al., 2015; Warthon-Medina et al., 2015). The hippocampus has the highest content of Zn in the brain, suggesting that Zn is very important for hippocampal cognitive function and memory formation (Danscher et al., 1975; Greiner et al., 1975; Halas et al., 1983; Frederickson et al., 1987; Chu et al., 2003; Takeda et al., 2005; Boroujeni et al., 2009; Takeda, 2012; Młyniec et al., 2014; Takeda et al., 2015). The hippocampus is part of limbic system and has a major role in spatial learning and memory. Damage of one or both parts of the hippocampus causes behavioral changes and deficits in learning about people, places, and objects (Bannerman et al., 2002; Vitolo et al., 2002; Longoni et al., 2015). Although Zn deficiency can alter spatial learning and memory by changing neurotransmitter content and receptor activity (Halas et al., 1983; Sandstead, 1985; Halas et al., 1986; Golub et al., 1995; Keller et al., 2001; Bitanihirwe and Cunningham, 2009; Kida et al., 2015), excess Zn induces central nervous system (CNS) pathology (Hamadani et al., 2002; Tamura et al., 2003; Flinn et al., 2005; Bitanihirwe and Cunningham, 2009; Suzuki et al., 2015; Contestabile et al., 2016; Tabrizian et al., 2016). Indeed, high levels of Zn can induce apoptosis and cytotoxicity in neural cells (Bitanihirwe and Cunningham, 2009). Thus, the Zn balance is essential for CNS development, normal behavior, and preventing neurological diseases such as AD, epilepsy, amyotrophic lateral sclerosis, and ischemia (Seven et al., 2013; Prakash et al., 2015).

Vanadium (V) is a metal widely distributed in the environment. V can induce toxic effects on different biological systems including the nervous system (Azami et al., 2012), and is involved in weight loss (Sanchez et al., 1998), morphological and biochemical alterations in different organs (al-Bayati et al., 1989), thrombocytopenia (González-Villalva et al., 2006), male reproductive system toxicity (Fortoul et al., 2007), hematological abnormalities (Zaporowska and Wasilewski, 1989), and CNS neurotoxicity (Garcia et al., 2005). In addition, V exposure can reduce visual memory, and induce mood disorders and motor disturbances (Zhou et al., 2007). Indeed, V toxicity impairs learning and spatial memory in animal models (Sanchez et al., 1998; Avila-Costa et al., 2006; Mao et al., 2008), chiefly manifesting as CNS depression and tremors in human (Afeseh Ngwa et al., 2009). Moreover, V exposure in male mice induces hippocampal CA1 damage (Avila-Costa et al., 2006).

The present study was designed to investigate the effects of resveratrol and quercetin as natural pharmacological agents on changes to avoidance memory retention induced by zinc chloride ($ZnCl_2$) and sodium metavanadate (SMV) in male mice by using step-through passive avoidance learning tasks.

MATERIALS AND METHODS

Animals

Animal experiments were approved by the Committee for the Care and Use of Laboratory Animals in the Zabol University (Zbmu.1.REC.1394.150), conducted according to the guidelines for the care and use of laboratory animals of Zabol University of Medical Sciences. Male albino mice (20～25 g) at 8～10 weeks of age were obtained from the Faculty of Pharmacy, Zabol University of Medical Sciences. All animals were maintained under controlled conditions (12-h light/dark cycle at room temperature of 20～22°C) and housed five per cage with free access to standard lab chow and tap water. All animal experiments were carried out during the light cycle. For all experiments, mice were split into groups of 8.

Drugs

$ZnCl_2$ (Merck KGaA, Darmstadt, Germany) and SMV (Merck KGaA) were dissolved in saline (0.9%) and drinking water, respectively, to obtain desirable concentrations. Quercetin and resveratrol were purchased from Sigma-Aldrich Co. (St. Louis, MO, USA). The required amount of resveratrol or quercetin powder was dissolved in 1 mL dimethyl sulfoxide and diluted with normal saline.

Step-through avoidance learning tasks

Details of the passive avoidance apparatus were described previously (Ader et al., 1972). In this study, each mouse was placed in the light chamber, and the door was opened after 10 s. The time taken for the mouse to cross into the dark chamber was recorded as the latency time (300 s was determined as the cut-off point). Electric shocks

(0.2 mA intensity for 2 s) were administered to the grid floor of the dark compartment. All training and testing trials were carried out at a similar time during the morning. During the retention test sessions, no electric shocks were applied.

Rotarod tests

Motor coordination and balance were tested using rotarod apparatus. Animals were initially placed on a rotating drum (rotation speed of 0～40 rpm) of rotarod and trained to walk. The speed of the device could be adjusted by changing the position of a belt. The rotary rod began to rotate at a speed of 5 rpm, reaching a maximum rotational speed of 20 rpm. Mice were placed on the drum of the rotarod for a maximum of 300 s, and the amount of time each mouse could maintain its balance was recorded. This experiment was repeated three times for each mouse (Rabiei and Rafieian, 2014).

Experiments

***Experiment 1*:** Fresh solutions of $ZnCl_2$ in normal saline were prepared daily. $ZnCl_2$ (75 mg/kg/d) or saline (controls) was administered via oral gavage needles once a day for two weeks. In addition, quercetin or resveratrol were administered by intraperitoneal (i.p.) injection on days 14, 12, and 14, or 10, 12, and 14 of treatment. Avoidance memory retention tests were carried out at day 14 (in mice not administered quercetin or resveratrol) and after 24, 48, 96, and 168 h after training trials (in mice administered quercetin or resveratrol). For all animals, muscle strength was assessed using rotarod tasks.

***Experiment 2*:** Fresh solutions of SMV in drinking water were prepared daily. SMV (22.5 mg/kg/d) or saline (controls) was administered via oral gavage needles once a day for two weeks. In addition, quercetin or resveratrol were administered by i.p. injection on days 14, 12, and 14, or 10, 12, and 14 of treatment. Avoidance memory retention tests were carried out at day 14 (in mice not administered quercetin or resveratrol) and at 24, 48, 96, and 168 h after training trials (in mice administered quercetin or resveratrol). For all animals, muscle strength was assessed using rotarod tasks.

Statistical analysis

Data were analyzed using GraphPad Prism version 5.0 (GraphPad Software, San Diego, CA, USA). We performed one-way analysis of variance (ANOVA) followed by Newman-Keuls post hoc test to compare results of our behavioral studies. Values were considered statistically significant at $P<0.05$.

RESULTS

Effects of quercetin or resveratrol on $ZnCl_2$-induced passive avoidance memory retention impairments in step-through tasks

Pre-training oral administration of $ZnCl_2$ (75 mg/kg/d) for 14 consecutive days significantly decreased step-through latency times (s) during the retention tests. In addition, quercetin (50 mg/kg, i.p.; Table 1) and resveratrol (50 mg/kg, i.p.; Table 2) prevented $ZnCl_2$-induced avoidance memory retention impairment and did not significantly alter muscle strength, as demonstrated in rotarod tasks (data not shown). Quercetin (single, double, and triple doses) significantly inhibited $ZnCl_2$-induced memory retention impairments (measured 24, 48, 96, and 168 h after training trials) in step-through avoidance tasks. However, there were not significant differences between single, double and triple doses of quercetin or resveratrol. For resveratrol-treated mice, those that received resveratrol (on days 10, 12, and 14 of $ZnCl_2$ treatment) showed better responses at 48, 96, and 168 h after the training trials.

Effects of quercetin or resveratrol on SMV-induced passive avoidance memory retention impairments in step-through tasks

Pre-training oral administration of SMV (22.5 mg/kg/d) for 14 consecutive days significantly decreased step-through latency times (s) during the retention tests. In addition, quercetin (50 mg/kg, i.p.; Table 3) and resveratrol (50 mg/kg, i.p.; Table 4) prevented $ZnCl_2$-induced avoidance memory retention impairment and did not significantly alter muscle strength, as demonstrated in the

Table 1. Effects of quercetin on $ZnCl_2$-induced passive avoidance memory retention alterations in step-through tasks

	24 h	48 h	96 h	168 h
Control	291.10±6.36	260.00±40.03	270.80±27.99	281.50±12.50
$ZnCl_2$ (75 mg/kg/d)	20.17±4.04***	24.80±10.34***	22.67±3.80***	42.00±13.95***
$ZnCl_2$ + Q_1	122.20±17.00***###	157.00±30.77#	133.40±19.72**##	155.30±48.75#
$ZnCl_2$ + Q_2	164.10±18.05***###	181.30±55.46#	152.60±41.47**##	225.70±40.12##
$ZnCl_2$ + Q_3	130.20±10.88***###	133.20±32.59#	172.70±21.40*##	223.90±33.59##

Values are means±SEM of 8 mice per group.
*$P<0.05$, **$P<0.01$, and ***$P<0.001$ show a considerable difference from the control group and #$P<0.05$, ##$P<0.01$, and ###$P<0.001$ show a considerable difference from the $ZnCl_2$-treated group.
Q_1, Q_2, and Q_3: single, double, and triple doses of quercetin, respectively.

Table 2. Effects of resveratrol on $ZnCl_2$-induced passive avoidance memory retention alterations in step-through tasks

	24 h	48 h	96 h	168 h
Control	202.00±49.24	252.00±48.04	252.00±48.04	238.20±29.82
$ZnCl_2$ (75 mg/kg/d)	19.58±4.90**	26.86±12.41***	26.86±12.41**	22.24±7.14***
$ZnCl_2$ + RSV_1	74.00±17.49	109.40±23.80*	111.60±49.97	76.40±10.77***
$ZnCl_2$ + RSV_2	76.20±12.00	137.80±19.82*#	155.60±28.69	85.00±21.45***
$ZnCl_2$ + RSV_3	102.40±51.35	172.00±32.47#	216.60±43.70#	112.20±22.61***#

Values are means±SEM of 8 mice per group.
*P<0.05, **P<0.01, and ***P<0.001 show a considerable difference from the control group and #P<0.05, ##P<0.01, and ###P<0.001 show a considerable difference from the $ZnCl_2$-treated group.
RSV_1, RSV_2, and RSV_3: single, double, and triple doses of resveratrol, respectively.

Table 3. Effects of quercetin on sodium metavanadate (SMV)-induced passive avoidance memory retention alterations in step-through tasks

	24 h	48 h	96 h	168 h
Control	285.70±6.39	250.10±47.96	250.10±48.87	248.50±47.76
SMV (22.5 mg/kg/d)	28.12±1.75***	32.95±12.63***	39.73±16.24***	56.28±26.59***
SMV + Q_1	148.10±12.43***	214.90±29.15***##	179.00±27.07***##	193.40±30.48***##
SMV + Q_2	163.40±27.59***	165.70±22.89##	164.90±24.65##	213.30±39.19##
SMV + Q_3	142.80±38.00***	192.20±27.04##	189.40±29.49##	251.90±30.53##

Values are means±SEM of 8 mice per group.
***P<0.001 shows a considerable difference from the control group and #P<0.05 and ##P<0.01 show a considerable difference from the SMV-treated group.
Q_1, Q_2, and Q_3: single, double, and triple doses of quercetin, respectively.

Table 4. Effects of resveratrol on sodium metavanadate (SMV)-induced passive avoidance memory retention alterations in step-through tasks

	24 h	48 h	96 h	168 h
Control	295.80±2.57	298.00±2.00	280.00±20.00	276.20±19.40
SMV (22.5 mg/kg/d)	26.12±2.82***	20.14±2.42***	22.64±1.26***	26.72±4.46***
SMV + RSV_1	44.64±24.12***	79.88±35.52***	22.64±6.68***	42.00±13.19***
SMV + RSV_2	97.80±52.15**	83.80±40.86***	20.56±8.21***	37.40±14.13***
SMV + RSV_3	147.60±58.58**	196.00±38.29*##	89.00±10.05***##	74.00±20.15***

Values are means±SEM of 8 mice per group.
*P<0.05, **P<0.01, and ***P<0.001 show a considerable difference from the control group and ##P<0.01 shows a considerable difference from the SMV-treated group.
RSV_1, RSV_2, and RSV_3: single, double, and triple doses of resveratrol, respectively.

rotarod tasks (data not shown). Quercetin (single, double, and triple doses) significantly inhibited SMV-induced memory retention impairments (at 48, 96, and 168 h after training trials) in step-through avoidance tasks. However, there were no significant differences between single, double and triple doses of quercetin or resveratrol. For resveratrol-treated mice, those that received triple doses resveratrol (on days 10, 12, and 14 of SMV treatment) showed better responses at 48 and 96 h after the training trials.

DISCUSSION

The results of this study demonstrated 2-week oral administration of $ZnCl_2$ (75 mg/kg/d) and SMV (22.5 mg/kg/d) cause poor retrieval of learning behavior in passive avoidance tasks. In previous studies, elevated levels of Zn have been shown to be toxic for cognitive processes (Hamadani et al., 2002) and have been identified as a risk factor for AD (Cuajungco et al., 2000). However, an adequate amount of Zn consumed as part of a normal diet has an important role in memory processes, cognitive behavior, reducing oxidative stress (Ebuehi and Akande, 2008), and elevating cyclic nucleotide cyclic guanosine monophosphate, consequently activating protein kinase A (von Bülow et al., 2007; Hönscheid et al., 2012). However, studies have reported that Zn has detrimental effects on formation of neurotic plaques and deposition of cerebrovascular amyloid plaques in AD (Bitanihirwe and Cunningham, 2009). Indeed, Zn may induce oxidative stress and amyloid plaque formation, which causes memory loss (Bitanihirwe and Cunningham, 2009). Zn exhibits some regulatory roles through γ-amino butyric acid

and *N*-methyl-D-aspartate receptors in memory formation (Chowanadisai et al., 2005). For example, the inhibitory effects of Zn can cause spatial memory damage in rats and mice (Morris, 1989; Brun et al., 2001).

In previous studies, oral administration of SMV (25 mg /kg) before training has been suggested to impair spatial memory acquisition, as demonstrated in Morris water mazes, and reduce protein expression of cholinergic system markers [e.g., choline acetyltransferase (ChAT) and vesicular acetylcholine transporter] in the CA1 region of the hippocampus and medial septal area. In addition, SMV was shown to induce formation of reactive oxygen species and changes in oxidative state (Cuesta et al., 2011). Since oxidative damage has a major role in various disease such as cancer, aging, and some chronic disease, multiple studies have focused on the benefits of antioxidants for preventing and/or targeting these processes (Fahey and Talalay, 1999).

In the current study, treatment with resveratrol and quercetin significantly increased the latency time in retention trials, alleviating the retention latency induced by $ZnCl_2$ and SMV. Quercetin is a major flavonoid compounds found in many fruits and vegetables, and exhibits stronger antioxidative and anticarcinogenic activities than vitamin C (Takahama, 1988; Heo and Lee, 2004). Quercetin can pass through the BBB of *in situ* models (Youdim et al., 2004) and has demonstrated protective effect in an animal model of stroke (Cho et al., 2006). Quercetin is absorbed after oral consumption and passes through the BBB due to its lipophilicity and the action of efflux transporters such as P-glycoprotein (Lin and Yamazaki, 2003; Youdim et al., 2003).

A neuroprotective effect of quercetin against 6-hydroxydopamine-induced oxidative damage was previously demonstrated (Kim et al., 2004). Furthermore, animals administered quercetin exhibited acetylcholinesterase (AChE) activity in the homogenate of the hippocampus, indicative of improved cognitive performance due to enhanced acetylcholine at the synaptic terminals (Sriraksa et al., 2012). In addition, other studies have revealed that quercetin competitively inhibits AChE (Islam et al., 2013; Maciel et al., 2016; Suganthy et al., 2016).

Resveratrol has been well-documents to have anti-inflammatory effects (Švajger and Jeras, 2012) that can be protective against and decrease cognitive deficiency in normal aging via reducing levels of interleukin-1β and tumor necrosis factor-α (Gocmez et al., 2016). Furthermore, resveratrol can enhance cognitive function by neurogenesis and angiogenesis, thus acting to directly improve function of brain (Kodali et al., 2015). In addition, resveratrol can upregulate brain-derived neurotrophic factor (BDNF) levels in the hippocampus and amygdala of chronic mild unpredictable stress-exposed rats, which improves cognition (Yazir et al., 2015). Moreover, resveratrol has been shown to improve learning and memory function through the microRNA-cyclic adenosine monophosphate-response element binding protein-BDNF pathway in normal aged mice (Zhao et al., 2013), and to ameliorate the decreased learning and memory of AD model mice via decreasing AChE activity and increasing ChAT activity and acetylcholine content (Wang et al., 2017).

Quercetin acts to promote learning and memory performance through regulating acetylcholine esterase bioactivity, neurotrophic factors levels, oxidative status, anti-apoptotic gene expression, and Aβ fibril formation inhibition (Kumar et al., 2008; Bournival et al., 2009; Bhutada et al., 2010; Tongjaroenbuangam et al., 2011; Liu et al., 2013). Furthermore, quercetin increases proliferation, migration, and differentiation of rat neural stem cells (Kee et al., 2007; Clelland et al., 2009; Garthe et al., 2009) and increases expression of genes involved in neurogenesis (Spencer et al., 2003; Spencer, 2007).

In conclusion, this study demonstrated that administration of resveratrol and quercetin protects against cognitive impairments induced by $ZnCl_2$ and SMV in mice. Therefore, resveratrol and quercetin may represent new treatment opportunities for AD.

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AUTHOR DISCLOSURE STATEMENT

The authors declare no conflict of interest.

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