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Effects of Capsanthin on the Dopamine System and Dopamine-Related Social Behavior

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Abstract Capsanthin, from paprika (*Capsicum annuum*), is a carotenoid with an orange-red pigment. It possesses pharmacological effects such as anti-obesity, antidiabetic, and anticancer activities. However, whether capsanthin affects the dopaminergic system remains unclear. Herein, we investigated its impact on the dopaminergic system and dopamine-associated social behaviors. Cerebral cortical neurons were cultured and treated with capsanthin (3, 30, and 300 μg/ml). Immunostaining was used to investigate dopamine-related protein expression. Healthy, wild-type ICR mice were used for animal experiments. Capsanthin (30 mg/kg) was orally administered via a gavage feeding tube from postnatal days 21 to 28. Behavioral tests, including motility, social-preference, and social-interaction tests, were conducted on juvenile mice from postnatal days 28 to 35 and on adult mice from postnatal day 56 onwards. Capsanthin treatment resulted in significantly reduced expression of dopamine receptors D3 and D5 in cerebral cortical neurons. Capsanthin administration induced a significant elevation in social preference during both the juvenile and adult periods, whereas enhancement of social interaction was observed only during the adult period. This study suggests that capsanthin enhanced social behavior via the dopaminergic system, especially through dopamine receptors D3 and D5. These findings propose capsanthin as a potential candidate for the amelioration of dopamine-associated psychiatric disorders, including schizophrenia and major depressive disorder.

Keywords: *Capsanthin, dopamine, dopamine receptor, locomotion, social preference, social interaction*

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1. Introduction

Dopamine (DA) is a crucial neurotransmitter that controls reward, motivation, and cognitive function. DA is synthesized in the synapse from tyrosine by tyrosine hydroxylase (TH) and is released extracellularly [1]. It subsequently propagates its signal by binding to postsynaptic DA receptors. Five types of DA receptors have been reported: DA receptor D1 (D1DR), D2DR, D3DR, D4DR, and D5DR [2,3]. Moreover, DA is taken up by the DA transporter (DAT), which modulates its extracellular concentration [4]. Dysregulation of DA-associated factors has been implicated in various psychiatric disorders. For example, patients with major depressive disorder often exhibit impaired social behavior characterized by unusual social-learning and abnormal social decision-making behavior, such as accepting unfair proposals [5,6]. These symptoms are associated with motivation and reward responses involving the DA system, characterized by decreased DA levels and a reduced affinity for DAT [7]. Autism spectrum disorders (ASD) are associated with alterations in reward circuits, exhibiting genetic variants and mutations in DAT, with the therapeutic potential observed via D1DR/D2DR inhibitors [8]. Additionally, treatment with the D1-like receptor antagonist SCH23390 induces social-learning impairment [9]. Social stimuli induce a release of DA in the prefrontal cortex, whereas an increase in DA levels in the nucleus accumbens has been associated with the alleviation of social defeat-induced social avoidance [10,11]. Furthermore, the DA system is implicated in social behavior associated with various conditions and psychiatric disorders. For instance, TH deficiency is associated with Parkinson's disease and encephalopathy [12]. In addition, the dysfunction of DA receptors and DAT is related to schizophrenia, Parkinson's disease,

attention-deficit/hyperactivity disorder (ADHD), and substance-related addiction [2,3,13,14]. Therefore, chlorpromazine and haloperidol (D2DR antagonists) and L-DOPA (a precursor of DA) are prescribed for schizophrenia and Parkinson's disease [3,15]. Disulfiram, an inhibitor of DA β-hydroxylase, is used for substance abuse disorder [16], whereas methylphenidate, an inhibitor of DAT, is prescribed for ADHD [13]. However, these antipsychotic stimulants have various lasting side effects, including extrapyramidal symptoms and tardive dyskinesia induced by chlorpromazine and haloperidol [17]; dyskinesia by L-DOPA [3]; headache, sleepiness, and halitosis by disulfiram [18]; and decreased appetite, insomnia, and headaches by methylphenidate [19]. Hence, exploring novel candidates for efficacious modulation of the DA system with fewer side effects is crucial.

Capsanthin (CAP) is a carotenoid derived from paprika (*Capsicum annuum*), characterized by its orange-red pigment and lacking the spicy taste associated with capsaicin [20,21]. CAP has various pharmacological effects, including anti-obesity, antidiabetic, and anticancer activities [20]. Although CAP-induced memory improvement has been reported in the senescence-accelerated mouse model 8, its effect on social behavior based on the DA system has rarely been investigated [22]. Carotenoids, including CAP, are associated with improved cognitive function [23], and their proper intake is associated with a low incidence of Alzheimer's disease [24]. Moreover, carotenoids ameliorate neurodegenerative diseases, including Parkinson's disease, by protecting DA neurons via their antioxidant and anti-inflammatory effects [25]. However, the direct impact of carotenoids on the DA system and its association with behavior, including social functions, have seldom been reported. Accordingly, if the effect of CAP on the DA system is confirmed, CAP may be recommended as a novel therapy for various neurodevelopmental, neurodegenerative, and psychiatric disorders. In this study, we investigated whether CAP modulates the DA system in cerebral cortical neurons and what its effects on DA-associated social functions are *in vivo*.

2. Materials and Methods

2.1. Cellular Experiment

2.1.1. CAP Treatments

CAP, purchased from Tokyo Chemical Industry Co., Ltd. Japan (catalog # C0781), was administered at concentrations of 3, 30, and 300 μg/ml in the cell culture system.

2.1.2. Primary Cell Culture

Animal experiments were conducted in accordance with the Research Ethics Policy of the Korean Association of Laboratory Animal Science and approved by the Institutional Animal Care and Use Committee of Daegu Catholic University (IACUC-2022-041). Cerebral cortical neurons were obtained from ICR mice on embryonic day 14 (Young-Nam Bio, Inc., Daegu, Korea) and were cultured. Following sacrifice with pentobarbital sodium (200 mg/kg; Hanlim Pharm. Co., Ltd., Korea) and Zoletil 50 (30 mg/kg; Virbac, France), fetal brains were removed from the skull, and cortical neurons were dissected. Eight-well chamber slides were coated with 5.0 μg/ml poly-D-lysine (Sigma-Aldrich, St. Louis, MO, USA) for 24 h prior to cell harvesting. Cortical neurons (1.5×10^5 cells/well) were cultured on coated slides in a neurobasal medium (catalog # 21103049; Gibco, Rockville, MD, USA), supplemented with 12% horse serum (catalog # 26050070; Gibco), 0.6% glucose, and 2 mM L-glutamine. Cultures were maintained in a 37 °C incubator with 10% CO_2. One day after incubation, the medium was replaced with a fresh neurobasal medium supplemented with 2% B-27 (catalog # 17504044; Gibco). After 4 days, CAP at concentrations of 3, 30, and 300 μg/ml was administered to the medium, whereas the vehicle (VEH) was treated with an equivalent amount of corn oil (catalog # C8267; Sigma-Aldrich). After 24 h, all cells were treated with 0.4% paraformaldehyde for 2 h, followed by immunostaining.

2.1.3. Fluorescence Immunostaining

Mouse monoclonal anti-TH (catalog # ab129991; Abcam, Cambridge, UK), rabbit polyclonal anti-DAT (catalog # sc-14002; Santa Cruz, Dallas, TX, USA), rabbit polyclonal anti-DRD1 (catalog # sc-14001; Santa Cruz), mouse monoclonal anti-DRD2 (catalog # sc-5303; Santa Cruz), mouse monoclonal anti-DRD3 (catalog # sc-136170; Santa Cruz), mouse monoclonal anti-DRD4 (catalog # sc-136169; Santa Cruz), and rabbit polyclonal anti-DRD5 (catalog # MBS2516950; Mybiosource, San Diego, CA, USA) were used as primary antibodies.

Twenty-four hours after CAP treatment, cells were fixed with 4% paraformaldehyde for 2 h. Thereafter, cells were washed thrice with phosphate-buffered saline (PBS) and incubated with primary antibodies for 24 h at 4 °C. After treatment, secondary Alexa Fluor 488 goat anti-mouse immunoglobulin G (catalog # A-11001; Life Technologies, Waltham, MA, USA) and Alexa Fluor 594 goat anti-rabbit antibodies (catalog # A-11012; Life Technologies) were added and incubated for 2 h at 24 ℃. Subsequently, 1 μg/ml of 4′,6-diamidino-2-phenylindole (DAPI; catalog # 1023627001; Sigma-Aldrich) was used to counterstain nuclei for 10 min. After washing thrice with PBS, cells were mounted with aqua-poly mount (Polysciences, Inc., Warrington, PA, USA). Images of stained cells were captured using a fluorescence microscope (Leica DM2500; Leica Microsystems, Wetzlar, Germany). Images were captured at random culture sites under each treatment condition, and quantification of fluorescent signals in the images was performed offline using ImageJ software [26]. Fluorescence intensity was calculated by dividing the number of cells with fluorescent signals by the total number of cells with DAPI staining in each image. This value was subsequently expressed as a percentage of the VEH ratio.

2.2. In Vivo Experiment

2.2.1. Animal Experiments

Animal experiments were conducted in accordance with the Research Ethics Policy of the Korean Association of Laboratory Animal Science and were approved by the Institutional Animal Care and Use Committee of Daegu

Catholic University (IACUC-2022-044). Pregnant ICR mice on gestational day 14 were purchased from Young-Nam Bio. Mice were individually housed in cages and acclimatized before delivery. The dams and pups were separated on postnatal day (PND) 21. Male pups were randomly assigned to cages to ensure a similar average weight per group, with three to four mice per cage. VEH (corn oil, n = 29) or CAP (30 mg/kg, n = 10) was administered once daily for 7 days by using an oral gavage-feeding tube (from PND21 to PND28). Behavioral tests were conducted from PND28 to PND35 during the juvenile period and from PND56 to PND63 during the adult period. The housing environment was maintained at 22 ± 1°C with a relative humidity of 50%–60%. Lighting was maintained on a 12-h light-dark cycle, and standard rodent chow and water were provided *ad libitum*. Cage bedding was changed once a week. Environmental enrichment, such as nesting material and hiding places, was provided to ensure the well-being of the mice.

2.2.2. Open Field Test

Experimental mice were placed in an open field chamber (40 × 40 × 40 cm) and allowed to explore freely; their behavioral patterns were recorded for 90 min by using Bandicam software (V4.6.5.1757; Bandicam Company Corp., Seoul, Korea). The distance traveled was analyzed using Ethovision XT software (version 11.5; Noldus, Wageningen, The Netherlands) and expressed as the total distance traveled and locomotor activity at 10-min intervals (in cm).

2.2.3. Social Preference Test

Mice were placed in an open field chamber (40 × 40 × 40 cm). On one side, a strange mouse that had never been exposed to the experimental mice before was placed in a wire-mesh box, whereas on the opposite side in the same box, a novel object that the mice had never encountered before was placed. Exploratory behavior towards each side was recorded for 10 min by using the Bandicam software. Behavioral analysis was conducted using BORIS software [27], focusing on the time (s) that the animal spent on each side of the box to explore the strange mouse or novel object. Social preference was expressed as the percentage of social behavior (time spent towards the strange mouse) or non-social behavior (time spent towards the novel object) to the total exploratory behavior.

2.2.4. Social Interaction Test

A strange mouse that had never been exposed to the experimental mice before was placed in an open field chamber (40 × 40 × 40 cm). A VEH- or CAP-treated mice were introduced into the same open field chamber. Their social behaviors were recorded for 10 min by using the Bandicam software. Behavioral analysis was performed, using the BORIS software [27], to measure the duration (s) of social contact, including nose-to-nose contact, oral-oral contact, genital sniffing, and anal sniffing.

2.3. Data Analyses

All results are expressed as the mean ± standard error. Data were analyzed using OriginPro (version 2024; OriginLab Corporation, Northampton, MA, USA) and Statistica (Version 14.0.1.25; TIBCO Software, Santa Clara, CA, USA). Social-preference and social-interaction test results were analyzed using an independent t-test; however, fluorescence-immunostaining results and the total distance traveled during the open field test were analyzed using one-way analysis of variance (ANOVA) with Tukey's post-hoc tests. Additionally, the distance traveled in 10-min intervals during the open field test was analyzed using a repeated two-way ANOVA with Bonferroni's post-hoc test. Statistical significance was set at $p < 0.05$.

3. Results

CAP treatment did not significantly alter the expression of TH, DAT, D1DR, or D2DR (Figure 1). However, D3DR ($f_{[3,51]} = 7.489$, $p < 0.001$; Tukey's post-hoc test, $p = 0.010$ at 3 μg/ml, $p < 0.001$ at 30 μg/ml, and $p = 0.002$ at 300 μg/ml) and D5DR ($f_{[3,114]} = 5.851$, $p < 0.001$; Tukey's post-hoc test, $p = 0.014$ at 3 μg/ml, $p = 0.004$ at 30 μg/ml, and $p = 0.003$ at 300 μg/ml) expression, but not D4DR expression, was reduced upon CAP treatment compared with that upon VEH treatment (Figure 2).

During the juvenile and adult periods, no significant differences in distance traveled in 10-min intervals were noted with CAP treatment compared to that with VEH treatment (Figure 3). Moreover, the total distance traveled was not significantly different between VEH- and CAP-treated mice during both the juvenile and adult periods.

Social preference was also measured during the juvenile and adult periods (Figure 4). In the juvenile period, social and non-social behaviors were heightened upon CAP treatment compared with those upon VEH treatment ($p = 0.005$ for social behavior, $p = 0.005$ for non-social behavior). Moreover, these effects were similar during the adult period ($p < 0.001$ for social behavior, $p = 0.004$ for non-social behavior).

In the social interaction test, CAP treatment did not result in significant differences compared to VEH treatment during the juvenile period ($p = 0.067$), whereas CAP administration induced a significant enhancement in familiar behavior compared to VEH treatment ($p = 0.049$; Figure 4) during the adult period.

We likewise measured changes in body weight following CAP and VEH treatment; however, no significant difference in body weight was noted between the CAP and VEH groups (Online Resource 1).

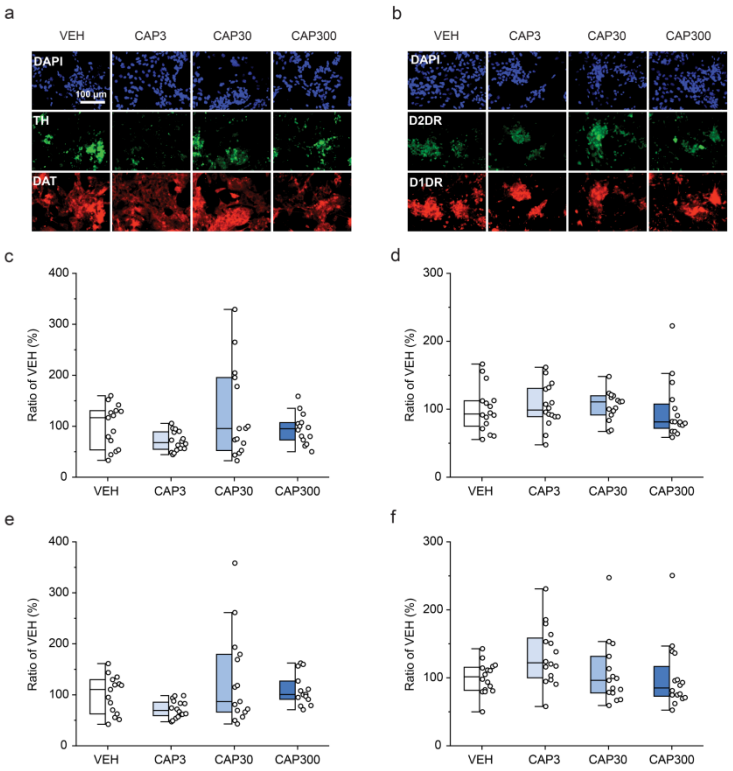

Figure 1. (Color online) Effects of capsanthin on tyrosine hydroxylase, dopamine transporter, dopamine receptor D1, and dopamine receptor D2 expression. **a** DAPI (blue), TH (green), and DAT (red) expression in the cerebral cortical neuron. **b** DAPI (blue), D2DR (green), and D1DR (red) expression in the cerebral cortical neuron. **c** The bar graph indicates the percentage of VEH in TH expression induced by CAP treatment. **d–f** These bar graphs are similar to graph (c); however, they indicate D2DR (d), DAT (e), and D1DR (f) expression. Protein expression was analyzed using one-way ANOVAs with Tukey's post-hoc test. Statistical significance was set at $p < 0.05$.

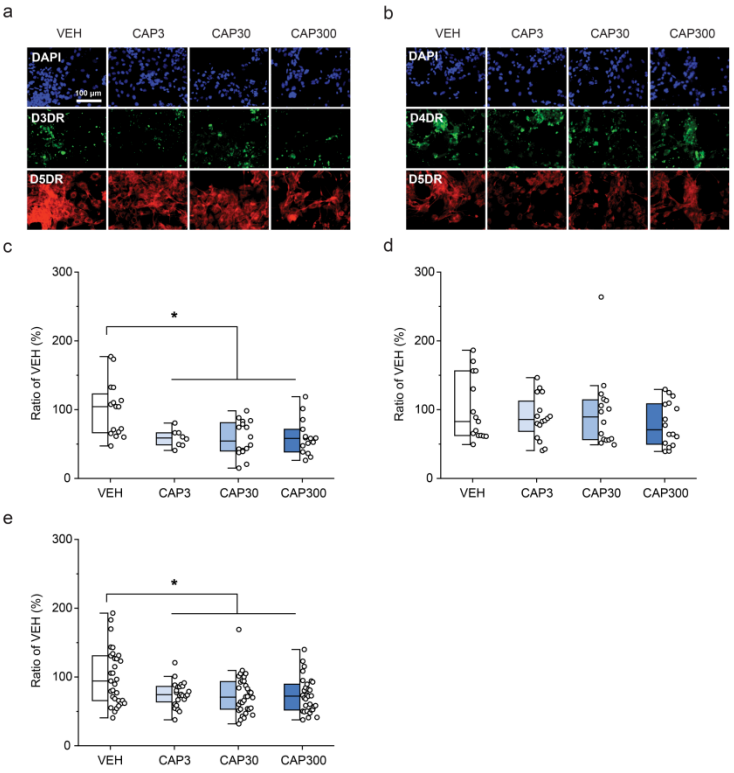

Figure 2. (Color online) Effects of capsanthin on dopamine receptors D3, D4, and D2 expression. a DAPI (blue), D3DR (green), and D5DR (red) expression in the cerebral cortical neuron. b DAPI (blue), D4DR (green), and D5DR (red) expression in the cerebral cortical neuron. c The bar graph indicates the percentage of VEH in D3DR expression induced by CAP treatment. d, e These bar graphs are similar to graph (c); however, they indicate the expression of D4DR (d) and D5DR (e). Protein expression was analyzed using one-way ANOVAs with Tukey's post-hoc test. Statistical significance was set at $p<0.05$.

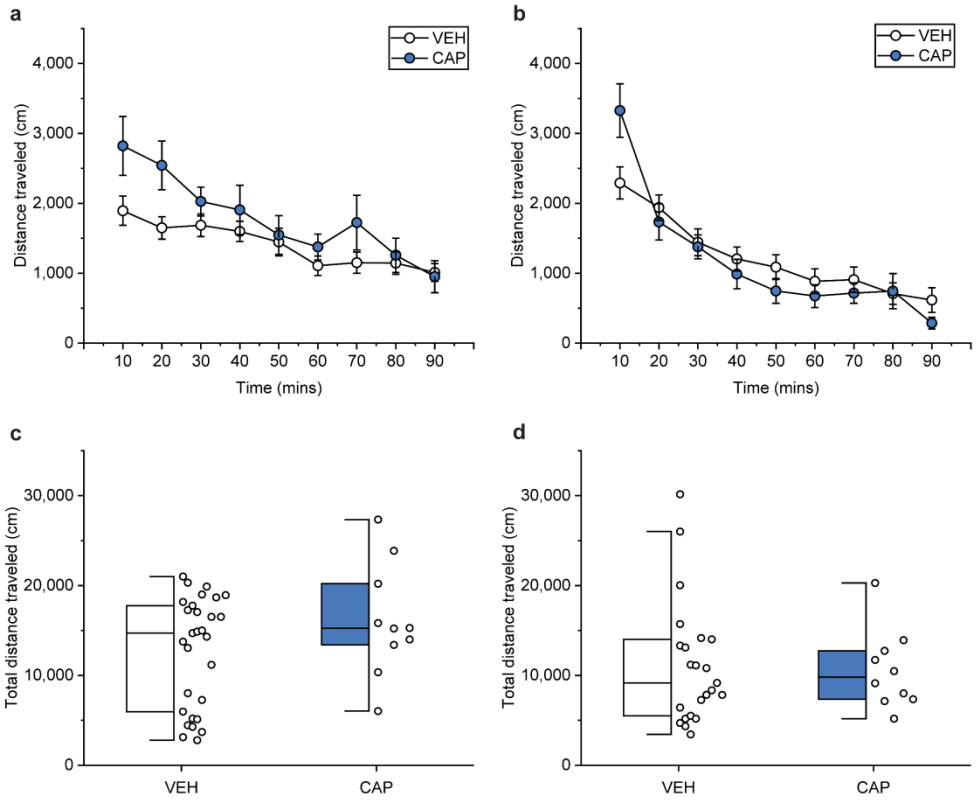

Figure 3. (Color online) Effects of capsanthin in the open field test. **a** Distance traveled in 10-min intervals induced by vehicle (VEH; corn oil) and capsanthin (CAP; 30 mg/kg body weight) treatments in the juvenile period. **b** This graph exhibits similar trends but pertains to the adult period. **c** Total distance traveled induced by VEH and CAP treatments during the juvenile period. **d** This bar graph is similar to graph (c) but indicates the adult period. Distance traveled in 10-min intervals was analyzed using a two-way ANOVA with Bonferroni's post-hoc test. Statistical significance was set at $p<0.05$. The total distance traveled was analyzed using one-way ANOVA with Tukey's post-hoc test. Statistical significance was set at $p<0.05$.

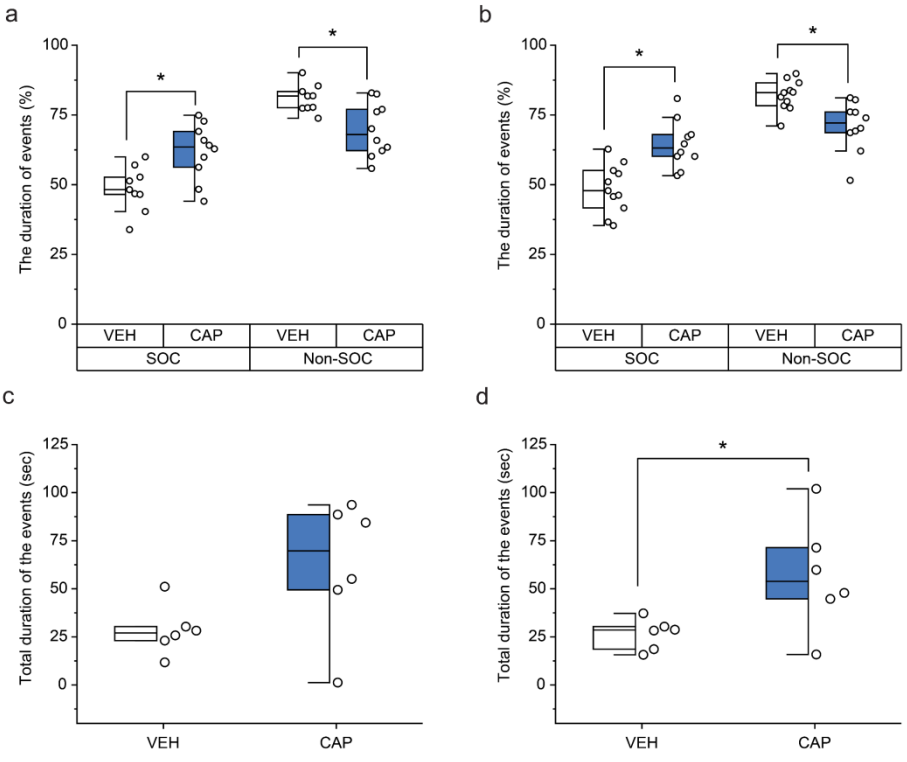

Figure 4. (Color online) Effects of capsanthin on social preference and social interaction. **a** This bar graph compares VEH and CAP administration to show the percentage of duration in social (SOC) and non-social (Non-SOC) behavior relative to the total duration of behavior during the juvenile period. **b** This graph is similar to graph (a) but pertains to the adult period. **c** This bar graph shows the total duration of familiar behavior in social interaction during the juvenile period upon VEH and CAP administration. **d** This graph is similar to graph (c) but pertains to the adult period. Social behavior was analyzed using an independent t-test. Statistical significance was set at $p<0.05$.

4. Discussion

Although CAP reportedly has various pharmacological effects, its effect on the DA system and DA-associated social behaviors has rarely been investigated. In this study, we discovered that CAP elevated D3DR and D5DR expression. Additionally, CAP administration during the weaning period led to an augmentation in social preference during both the juvenile and adult periods; however, it enhanced social interaction only during the adult period. These results suggest that CAP affects social behavior in association with D3DR and D5DR.

DA receptors are composed of five subtypes, D1DR to D5DR, characterized into D1-like (D1/D5) and D2-like (D2/D3/D4) receptors [2,3]. DA receptors play a crucial role in behavior modulation. D3DR agonists ameliorate social deficits in a valproic acid-induced zebrafish autism model, whereas treatment with the D3DR-selective antagonist NGB 2904 has been associated with susceptibility to depression-like effects in mice [28,29]. Conversely, D5DR is associated with cognitive function, as D5DR knockout mice exhibit impairments in object location, object recognition, and spatial learning [30]. Moreover, social stress-induced impairments in object and spatial memory with decreased social function suggest that social behavior is partly related to the object and spatial memory circuits through D5DR modulation [31]. These results imply that modulation of the DA system is necessary to control social behaviors. In the present study, CAP treatment induced reductions in D3DR and D5DR expression among the five types of DA receptors without alterations in TH and DAT expression. This suggests that CAP influences brain function via D3DR and D5DR rather than via DA synthesis and reuptake.

To elucidate the effect of CAP on the complex neural system, we investigated whether CAP administration during neurodevelopment affected brain function, including social behavior. DA affects the entire neurodevelopmental process, and the DA system shows projections to various areas of the brain, including the ventral tegmental area, substantia nigra compacta, prefrontal cortex, striatum, nucleus accumbens, and amygdala. Consequently, DA is strongly associated with neurodevelopmental disorders, including schizophrenia, ADHD, and ASD [9,32]. Furthermore, the administration of *Astragalus membranaceus* and *Ecklonia stolonifera* extracts as natural products during the juvenile period reduces ADHD-like behavior; in contrast, this effect disappears when the mice reach adulthood [33,34]. These findings indicate that neural stimuli during neurodevelopment induce changes in brain function and that these neural changes may be readapted during neurodevelopment. As such, CAP exhibits neural effects that depend on neurodevelopmental processes.

Herein, social-preference and social-interaction tests were conducted to investigate social behaviors associated with the DA system. CAP administration resulted in enhanced social preference during both the juvenile and adult periods. In contrast, social interactions were heightened only in the adult period following CAP administration. Social stimuli increase the activity of DA neurons in the ventral tegmental area and enhance the release of DA in the nucleus accumbens [35]. In addition, the inhibition of neural activity in the ventral tegmental area induces a decrease in social preference, and treatment with DAT inhibitors mitigates social deficits caused by neonatal ethanol exposure [36,37]. This suggests that the DA system plays a role in social behavior, including social preference and social interaction. Therefore, changes in social behavior caused by CAP are associated with the DA system. Notably, CAP administration revealed differences between social preferences (under indirect contact) and social interactions (under direct contact). Social preference involves the use of social recognition or social memory to discriminate social targets [38]. Conversely, social interaction, although similar to social preference, can be divided into two phases: the initiation and maintenance of a social encounter to develop social relations [39]. These findings imply that CAP administered during the juvenile period affects the neurodevelopmental processes associated with social behavior, enhancing social cognition rather than sociability.

This study had several limitations. First, the effects of CAP administration were investigated only in healthy, wild-type mice. Further research is needed to elucidate whether CAP enhances social behavior in animal models of social deficits. Moreover, CAP was administered only during the weaning period. Thus, further studies are required to determine the effects of CAP administration during other developmental periods.

5. Conclusions

In this study, CAP enhanced social behavior based on the DA system, particularly via D3DR and D5DR. This suggests that CAP is a potential candidate for the treatment of DA-associated psychiatric disorders.

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Competing Interests

The authors have no competing interests to declare that are relevant to the content of this article.

Ethics Approval

Animal experiments were conducted in accordance with the Research Ethics Policy of the Korean Association of Laboratory Animal Science and approved by the Institutional Animal Care and Use Committee of Daegu Catholic University (IACUC-2022-041 and IACUC-2022-044).

Consent

Not applicable.

Data availability

The data that support the findings of this study are available from the corresponding author, YA Lee, upon reasonable request.

Authors' contributions

Jae-Won Jung: Investigation, Methodology, Validation, Formal analysis, Data curation, Visualization; **Na-Hyun Kim:** Investigation, Methodology, Validation, Formal analysis, Data curation, Visualization; **Yong Heo**: Conceptualization, Funding acquisition; **Jong-Sik Jin:** Conceptualization, Resources; **Young-A Lee:** Conceptualization, Methodology, Software, Validation, Formal analysis, Resources, Data curation, Writing - Original Draft, Writing - Review & Editing, Visualization, Supervision, Project administration, Funding acquisition.

Abbreviations

ADHD, Attention-deficit/hyperactivity disorder; ANOVA, analysis of variance; ASD, Autism spectrum disorders; CAP, Capsanthin; D1DR, Dopamine receptor D1; D2DR, Dopamine receptor D2; D3DR, Dopamine receptor D3; D4DR, Dopamine receptor D4; D5DR, Dopamine receptor D5; DA, Dopamine; DAPI, 4′,6-diamidino-2-phenylindole; DAT, Dopamine transporter; PBS, phosphate-buffered saline; PND, Postnatal day; TH, Tyrosine hydroxylase; VHE, Vehicle.

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