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RESEARCH

Unpredictable Chronic Mild Stress Upregulates Dopamine Receptor Expression Independent of Fatty Acid-Binding Protein 7 Gene Deletion

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Abstract
Fatty acid-binding protein 7 (FABP7) assists in the intracellular trafficking of endogenous cannabinoids and polyunsaturated fatty acids (PUFAs) and has been implicated for various psychiatric diseases. Rising evidence demonstrates the crosstalk between the endocannabinoid and dopaminergic systems, particularly in response to stress. The present study seeks to examine the role of FABP7 expression under chronic stress conditions and its impact on the dopaminergic system, specifically dopamine D1 receptor (D1R) and dopamine D2 receptor (D2R) levels. Adult male FABP7$^{+/+}$ and FABP7$^{-/-}$ mice underwent 28-day treatment of unpredictable chronic mild stress (UCMS) procedure. After the stress paradigm, D1R and D2R levels were measured with in vitro autoradiography using [^{3}H] SCH23390 and [^{3}H] Spiperone, respectively. Stressed mice, regardless of genotype, exhibited an increase in D1R binding across the entire striatum (dorsal caudate putamen (CPu), dorsolateral CPu, dorsomedial CPu, ventral CPu, ventrolateral CPu, ventromedial CPu, nucleus accumbens core and shell), substantia nigra and olfactory tract. Additionally, an increase in D2R binding induced by UCMS was observed in the olfactory tract and certain regions of the striatum (dorsal CPu and ventral CPu). The UCMS paradigm upregulates D1R and D2R binding independent of FABP7 gene deletion, suggesting a compensatory role of other FABPs in the brain in maintaining dopaminergic homeostasis. This stress-induced shift in D1R: D2R ratio may underlie the pathogenesis of major depressive disorder and substance use disorder, as well as the high comorbidity among these conditions.

Keywords Fatty acid-binding protein 7 · Unpredictable chronic mild stress · Endocannabinoid · Dopamine · D1 receptors · D2 receptors

Introduction

The endocannabinoid system (ECS) has been documented for its extensive involvement in various physiological functions, including the stress response. The signaling pathway of ECS is predominantly mediated by the action of cannabinoid receptor type 1 (CB1R) and type 2 (CB2R), with CB1R being highly expressed in the brain, whereas CB2 is more involved in the immune cells [1]. The widely studied endogenous ligands, or endocannabinoids (eCBs), for ECS consist of 2-arachidonylglycerol (2-AG) and anandamide (AEA). While both ligands exert agonistic effects on

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both cannabinoid receptors, 2-AG acts as a full agonist for CB1R and exists at a higher concentration in the brain compared to AEA, a partial agonist for CB1R [2]. Degradation of AEA is primarily facilitated by fatty acid amide hydrolase (FAAH), whereas 2-AG is degraded by monoacylglycerol lipase (MAGL) [3]. Due to their lipid nature, AEA and 2-AG can readily diffuse across cellular membranes and require intracellular carrier proteins for transport to their respective catabolic enzymes. Fatty acid-binding proteins (FABPs) play a significant role in intracellular fatty acid shuttling, which include eCBs and long-chain polyunsaturated fatty acids (PUFAs) [4]. Distribution of different FABP isoforms vary throughout the body; FABP3, 5, and 7 are the primary lipid shuttlers in the brain [4]. FABP7 is localized in the astrocytes, neural stem cells, and radial glia-like cells in the spinal cord [5, 6]. Pharmacological inhibition of both FABP5/7 increases AEA levels in the brain and promotes analgesia [7]. FABP7 has also been noted for its influence on gene transcription through its transport of docosahexaenoic acid (DHA), which activates peroxisome proliferator-activated receptor (PPAR) [8]. Therefore, FABP7 represents as a promising pharmacological target for ECS modulation, with implications for various psychiatric disorders [9].

The dopaminergic (DAergic) system has been well-documented for its involvement in cognition, motivation, reward, learning, and mood [10]. The DAergic system is mediated by activating specific G-protein coupled receptors (GPCRs), which are categorized into two main families: D1-like family (D1R and D5R), which are Gαs-coupled proteins that promote an excitatory pathway, and the D2-like family (D2R, D3R, and D4R), which are Gαi/o-coupled protein that carry an inhibitory effect [11]. D1 receptor (D1R) can be found mostly on the post-synaptic terminal [12]. Pharmacological stimulation of D1R has been shown to exacerbate drug seeking behavior while antagonizing D1R suppress this behavior [13, 14]. In contrast, D2Rs are autoreceptors that are located on pre- and post-synaptic, which are responsible for modulating neuronal excitability and attenuating DA output [15]. Previous findings have shown that decreased D2R levels have been linked to increased impulsivity and addictive behavior [15–17].

Growing evidence supports the intricate relationship between the ECS and the dopaminergic system. CB1R, a Gαi/o-coupled protein, is co-located in similar brain regions that contain a high population of DA neurons, such as the striatum, NAc, prefrontal cortex (PFC), and ventral tegmental area (VTA) [18, 19]. Activation of CB1R on GABAergic and glutamatergic neurons, found at higher levels among GABAergic neurons [20], inhibits calcium channel activity, thereby decreasing the release of synaptic vesicles and synaptic transmission of these neurons [21–23]. Thus, activation of CB1R indirectly modulating DAergic release, influencing reward-seeking behavior and fear response [24–26]. There is also emerging evidence of hetero-dimeric formation of CB1R and dopamine D2R, which is a dynamic process that allows for the fine-tuning of the DAergic system through dual activation of both receptors [27–29]. Current research suggests the possibility that modifications to the ECS can lead to disturbances in the DAergic system, which can be implicated for various psychiatric diseases.

The ability to effectively manage stress is a significant factor in the development of certain psychiatric diseases such as major depressive disorder (MDD). Chronic stress has been documented to induce changes in both ECS and DAergic systems. While the ECS initially acts as a stress buffer by preventing hyperactivation of the hypothalamic–pituitary–adrenal (HPA) axis, chronic stress can impair this retrograde regulatory mechanism due to the desensitization of CB1R [30]. Therefore, this marks the ECS as a promising pharmacological target and etiological marker for MDD. Furthermore, chronic stress has also been recorded to induce complex changes to the DAergic system. Mild to moderate stressors have an activating effect on DA release, implicating it in addiction-like behaviors; however, chronic unpredictable stressors tend to have an inhibitory effect on DA release, implicating an anhedonia phenotype [31]. However, previous literature has yet to find a unanimous finding on the effect of stress on the expression of DA receptors. Therefore, the present study seeks to navigate the direction of change of stress on DA receptor expression using autoradiographic binding.

Deletion of FABP5 and FABP7 has been previously shown to reduce the anhedonia phenotype, a key feature for MDD [32]. Furthermore, deletion of FABP7 and FABP5 have shown to attenuate stress-induced reinstatement for cocaine place preference, while lowering stress-induced corticosterone levels [33]. Although the precise mechanisms remain unclear, previous findings demonstrated that genetic deletion of FABP7 leads to differential brain glucose utilization and a reduction in CB1R accompanied by an increase in N-methyl-d-aspartate (NMDA) receptors in the ventral striatum [34–37]. This suggests that FABPs play a critical role in the neurobiological mechanisms underlying both stress response and vulnerability to substance use disorders. Given these findings, the present study seeks to also examine the role of FABP7 under chronic stress and its impact on DAergic system, specifically D1R and D2R levels in the brain using in vitro autoradiography.

Experimental Procedure

Animals

Male C57BL/6J (FABP7$^{+/+}$) (n = 9–10 for each treatment group; mean weight = 25.7 g) and FABP7$^{-/-}$ knockout mice (n = 10 for each treatment group; mean weight = 20.9 g) (graciously provided by Drs. Owada and Kagawa and generated as previously described [38]) were used for the experiment. All mice were single-housed in a standard plastic cage (19 × 29 × 12 cm) in a temperature-controlled environment (22 °C) on a reverse light cycle (10:00–22:00). The protocol was approved by the Institutional Animal Care and Use Committee at the State University of New York at Buffalo and the National Institutes of Health Guidelines for the Care and Use of Laboratory Animals.

Unpredictable Chronic Mild Stress Procedure and Timeframe

Mice were first habituated to the facility for 1 week prior to the experiment. The UCMS paradigm and related techniques were performed as previously described [34, 35]. FABP7$^{+/+}$ and FABP7$^{-/-}$ mice were randomly divided into two groups (n = 9–10/treatment group), with one group undergoing the UCMS procedure while the control group remained in their home cage. The stressed mice were exposed to a variety of stressors over 28 days (Fig. 1). All stress procedures (besides food deprivation, cage tilt, and moist bedding) were carried out in a designated room different from the holding room. After every stressor, mouse health was closely monitored for any abnormality (appearance, behavior, and activity). Following the UCMS procedure, all mice were euthanized using deep isoflurane anesthesia (3%), and brains were rapidly extracted and flash-frozen in 2-isopentane. Brains were then sectioned coronally at 14 µm thick using a Leica cryostat and stored at −80 °C until receptor bindings were performed.

D1 Receptor Autoradiography

D1 receptor expressions were determined using [^{3}H] SCH23390 autoradiography and were performed as previously described [39–43]. All sectioned tissues were preincubated for 60 min at room temperature in Tris-HCl buffer (50 nM Tris HCl, 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$,

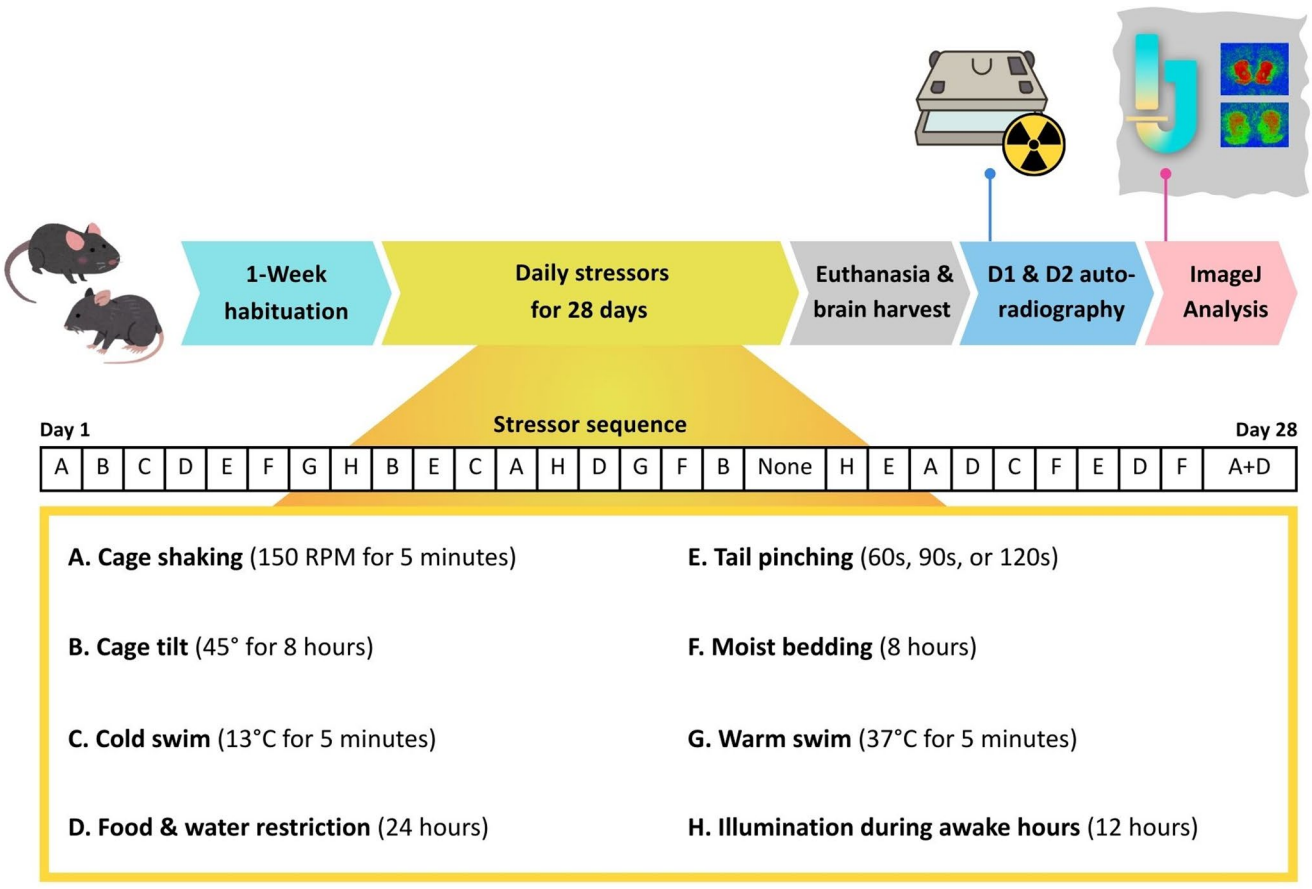


Fig. 1 A schematic diagram of experimental design. Different stressors were administered daily to FABP7$^{+/+}$ and FABP7$^{-/-}$ groups throughout the 28-days unpredictable chronic mild stress paradigm

1 mM $MgCl_2$; pH = 7.4). Slides were air-dried and incubated for 60 min at room temperature in Tris-HCl buffer containing 1.59 nM [^{3}H] SCH23390 (specific activity = 83.2 Ci/mmol, PerkinElmer, USA). Non-specific binding was determined using the adjacent sections and incubated in an identical radioactive buffer with the presence of 1 µM flupenthixol (F114, Sigma Aldrich). Following incubation, 2 × 5 min washes of 4 °C assay buffer solution were performed, and a rapid rinse was done in ice-cold distilled water.

D2 Receptor Autoradiography

D2 receptor expressions were determined using [^{3}H] Spiperone autoradiography and were performed as previously described [39–43]. All sectioned tissues were preincubated for 60 min at room temperature in Tris-HCl buffer (50 nM Tris HCl, 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$; pH = 7.4). Slides were air-dried and incubated for 60 min at room temperature in Tris-HCl preincubation buffer with 0.82 nM [^{3}H] Spiperone (specific activity = 16.2 Ci/mmol, PerkinElmer, USA) and 40 nM ketanserin (S006, Sigma Aldrich). Non-specific binding was determined using the adjacent sections and incubated in an identical radioactive buffer with the presence of 10 µM sulpiride (Cat. No. 0895, TOCRIS). Following incubation, 2 × 5 min washes of 4 °C assay buffer solution were performed, and a rapid rinse was done in ice-cold distilled water.

Regions of Interest Analysis

Bound slides were subsequently exposed to Biomax XAR film along with a tritium standard for 4 weeks or 8 weeks, retrospective to the ligands. The films were developed, scanned using Brother MFC-J6510DW at 1200 DPI, and images were analyzed using FIJI (ImageJ) software (National Institutes of Health). The regions of interest were taken from each hemisphere following the Franklin and Paxinos mouse brain atlas [44]. The caudate-putamen (CPu) was divided into subregions base on its function: dorsal lateral (DL CPu; habit formation [45]), dorsal medial (DM CPu; goal-directed behavior [46]), dorsal (D CPU; sensory processing and novelty detection [47]), ventral lateral (VL CPu; sensorimotor coordination [48]), ventral medial (VM CPu; motivational, and reward signals [49]), ventral caudal striatum (V CPu; sensory processing and aversive learning [47]); nucleus accumbens core (NAcC), nucleus accumbens shell (NAcS), olfactory tract (OT) and substantia nigra reticular (SNR) (Fig. 2.) Due to low basal level of expression of D2R in the SNR [50], receptor binding was only obtained for D1R.

Statistical Analysis and Graphing

A two-way ANOVA was conducted within each region of interest to determine the effect of stress (nonstress or UCMS) and genotype ($FABP7^{+/+}$ or $FABP7^{-/-}$) on D1R and D2R binding. The significance level was set at $\alpha = 0.05$ for each main effect, and post hoc analysis was conducted using Tukey's multiple comparison test for interaction effects observed. All statistical analyses were performed with Prism8 GraphPad software version 8.4.3.

Result

[^{3}H] SCH23390 D1 Receptor Binding

A two-way ANOVA showed a main Treatment effect (nonstress vs. UCMS) on [^{3}H] SCH23390 (D1R) binding levels in the DM CPu [$F(1,35) = 7.797$; $p = 0.0084$, Fig. 3A.], DL CPu [$F(1,35) = 8.214$; $p = 0.0070$, Fig. 3B.], D CPu [$F(1,35) = 5.698$; $p = 0.0225$, Fig. 3C.], NAcC [$F(1,35) = 0.0163$; $p = 0.0102$, Fig. 3D.], NAcS [$F(1,35) = 8.413$; $p = 0.0064$, Fig. 3E.], OT [$F(1,35) = 7.925$; $p = 0.0080$, Fig. 3F.], SNR [$F(1,35) = 4.670$; $p = 0.0367$, Fig. 3G.], VM CPu [$F(1,35) = 7.303$; $p = 0.0105$, Fig. 3H.], VL CPu [$F(1,35) = 8.215$; $p = 0.0070$, Fig. 3I.], and V CPu [$F(1,35) = 7.383$; $p = 0.0102$, Fig. 3J], such that mice who underwent UCMS exhibit an increase in D1R binding compared with the nonstress mice (Table 1.)

The main effects of Genotype ($FABP7^{+/+}$ vs. $FABP7^{-/-}$) and Genotype–Stress interaction were not found to have a significant effect on [^{3}H] SCH23390 binding across the brain regions examined ($p > 0.05$, Table 2 and S1.)

[^{3}H] Spiperone D2 Receptor Binding

A two-way ANOVA showed a main Treatment effect (nonstress vs. UCMS) on [^{3}H] Spiperone binding levels in the D CPu [$F(1,35) = 4.299$; $p = 0.0456$, Fig. 4C.], V CPu [$F(1,35) = 4.355$; $p = 0.0456$, Fig. 4F.], and OT [$F(1,35) = 7.925$; $p = 0.0080$, Fig. 4I.], such that mice who underwent UCMS exhibit an increase in D2R binding compared with nonstress mice.

The main effect of Genotype ($FABP7^{+/+}$ vs. $FABP7^{-/-}$) was not found to have a significant effect on [^{3}H] Spiperone binding across the brain regions examined ($p > 0.05$, Table 2.)

A significant Genotype–Stress interaction was observed in the NAcS [$F(1,35) = 4.194$; $p = 0.0481$.] However, post hoc analyses using Tukey's multiple comparison tests did

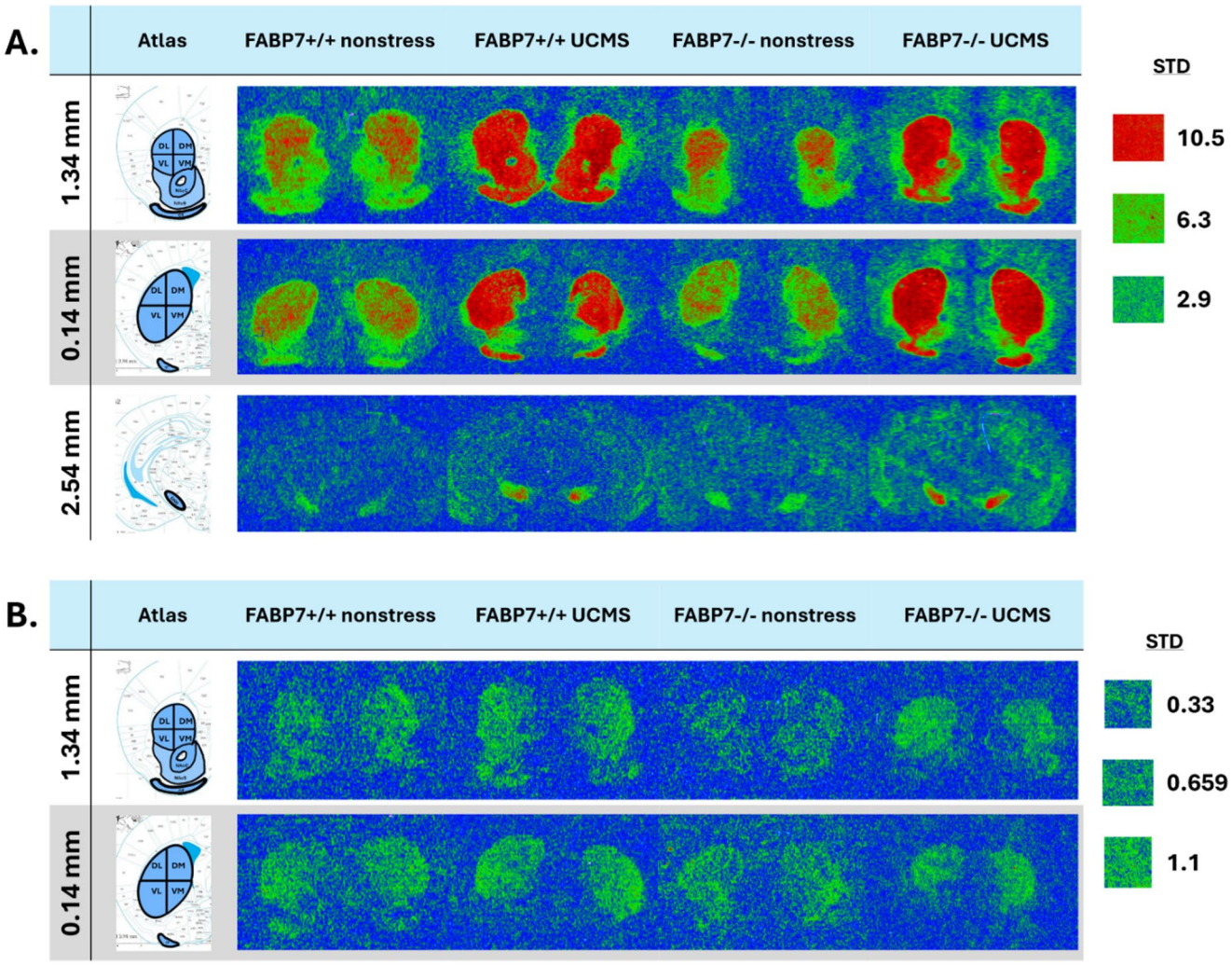


Fig. 2 Representative autoradiography images of dopamine receptor binding densities taken at three bregma points (mm). Colorized images from each group and outlined regions of interest are adopted from the Franklin and Paxinos Mouse Brain Atlas, 3rd edition [44]. **(A)** [^{3}H] SCH23390 binding; **(B)** [^{3}H] Spiperone

not show any significance across all groups ($p > 0.05$, Table S2.)

Discussion

Chronic stress exposure has been shown to promote hyperactivity in the hypothalamic–pituitary–adrenal (HPA) axis and disrupt both the ECS and DAergic systems, contributing to anhedonia-like phenotypes and increased vulnerability to mood disorder [31, 51]. Patients diagnosed with MDD frequently present with persistent low mood, anhedonia, and recurrent suicidal ideations [52]. These symptoms are often accompanied by molecular alterations and dysregulation across key biological pathways. To model these depressive-like states in rodents, UCMS paradigms were used to provide insights into the neurobiological mechanisms underlying MDD. Given the intricate role of the FABP7 gene on the ECS [35], and the complexity of the crosstalk between the ECS and DAergic systems indicated above, the present study aims to elucidate the effect of the FABP7 gene deletion on the DAergic system under a chronic stress environment. Intriguingly, we observed that the UCMS paradigm modified the dopaminergic signaling independent of genetic deletion of FABP7. Specifically, UCMS up-regulated D1R binding across the striatum, with an increase ranging from 22.2% in the VL CPu and up to 48% in the SNR (Table 1). However, an increase in D2R binding exerted by UCMS treatment was only observed in selective regions of the striatum—the D CPu (33.9% increase), V CPu (37.9% increase), and OT (24.8% increase).

Previously, Hamilton and colleagues demonstrated that co-deletion of FABP7 and FABP5 increases sucrose consumption and decreases immobility under the forced

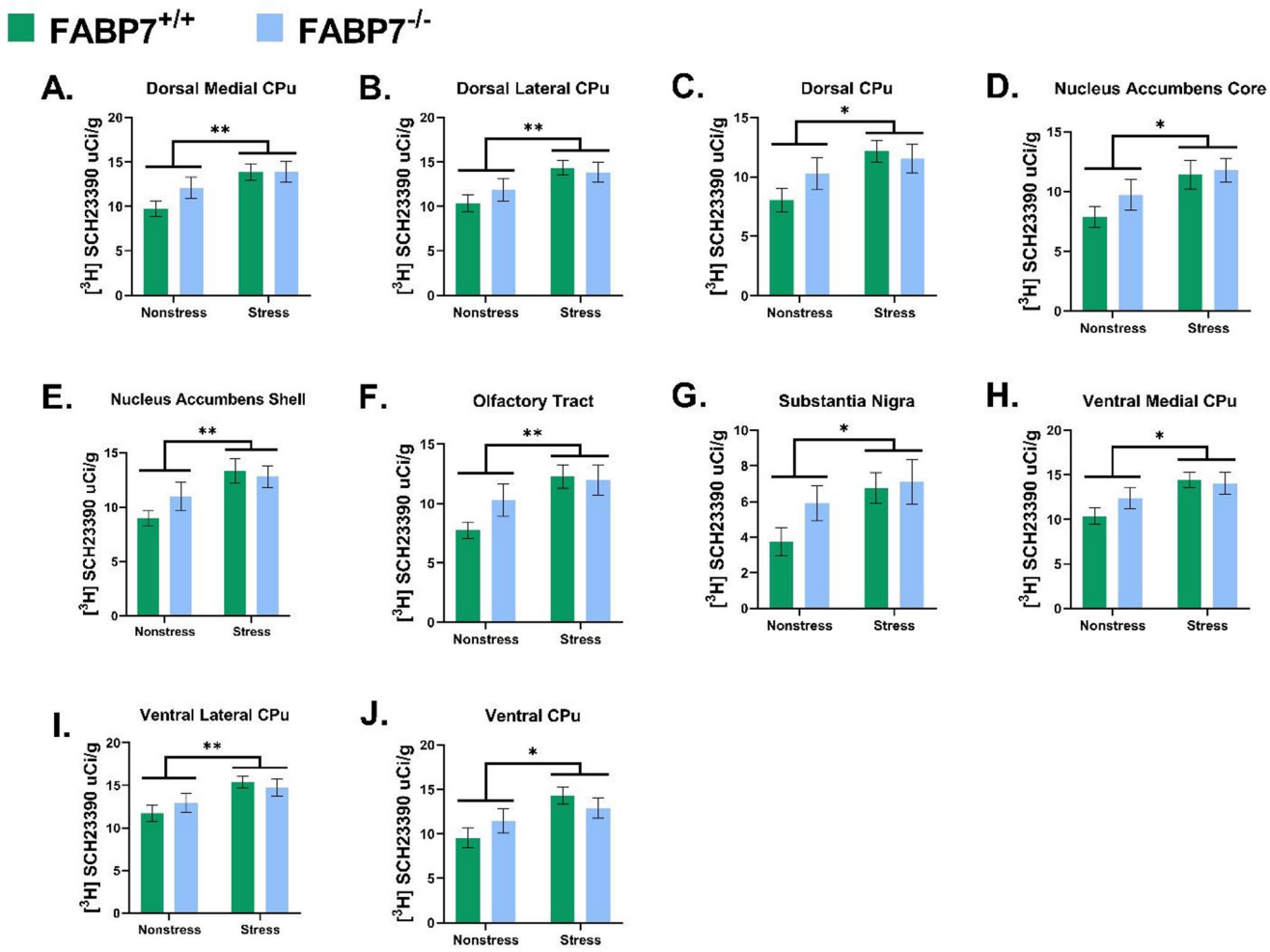


Fig. 3 [^{3}H] SCH23390 binding within each measured region in FABP7+/+ and FABP7-/- under control versus stress paradigm. **(A)** Dorsal medial caudate putamen (CPu); **(B)** Dorsal lateral CPu; **(C)** Dorsal CPu; **(D)** Nucleus accumbens core; **(E)** Nucleus accumbens shell; (**F**) Olfactory tract; (**G**) Substantia Nigra; **(H)** Ventral medial CPu; **(I)** Ventral lateral CPu; **(J)** Ventral CPu. Two-way ANOVA, $n = 9$–10/group, bar represent mean ± SEM, * indicates statistcally significant difference in an overall stress effect at $p < 0.05$, ** $p < 0.001$

Table 1 A summary of percent differences in average binding between Nonstress and UCMS mice

ROIs	Dopamine D2R Binding	Dopamine D1R Binding
Dorsal medial CPu	No change	↑ 27.1%
Dorsal lateral CPu	No change	↑ 27.0%
Dorsal CPu	↑ 33.9%	↑ 29.5%
Ventral medial CPu	No change	↑ 25.0%
Ventral lateral CPu	No change	↑ 22.2%
Ventral CPu	↑37.9%	↑ 29.9%
Nucleus accumbens core	No change	↑ 31.8%
Nucleus accumbens shell	No change	↑ 31.0%
Olfactory tract	↑24.8%	↑ 34.2%
Substantia nigra reticular	–	↑ 43.3%

swim test (FST) [32]. Shimamoto et al. also demonstrated that FABP7$^{-/-}$ alone can reduce immobility of FST, while accompanied by a decrease in time spent in the center area [53]; however, we did not observe any change in the mice's time spent in the center area based on our previous findings [37]. Additionally, FABP7$^{-/-}$ mice also exhibited anxiolytic-like effects on cognitive processing following traumatic stress [54]. Anti-depressive behaviors can be replicated by other means of CB1R activation. For instance, treatment with other CB1 agonists or AEA-raising compounds have also been shown to reduce immobility time in the FST [55]; whereas, chronic administration of the CB1 blocker rimonabant increases immobility time in the FST [30]. Furthermore, FAAH knockout mice displayed reduced immobility time which was normalized by a CB1 blocker [56].

The complex psychiatric feature of anhedonia is partly attributed to hypodopaminergic tone, which co-aligns with

Table 2 Result of Two-way ANOVA analysis of [^{3}H] SCH23390 binding and [^{3}H] Spiperone with the factor of Genotype [FABP7$^{+/+}$, FABP7$^{-/-}$] and Treatment [Nonstress, UCMS] across different regions of interest. Numbers in parentheses indicate the degrees of freedom

Ligand	Regions of Interest	Genotype		Treatment		Interaction	
		F value	p value	F value	p value	F value	p value
[^{3}H] SCH23390	Dorsal medial CPu (1, 35)	1.258	0.2696	7.797	0.0084*	1.175	0.2858
	Dorsal lateral CPu (1, 35)	0.2178	0.6436	8.214	0.0070**	0.9014	0.3489
	Dorsal CPu (1, 35)	0.5177	0.4766	5.698	0.0225*	1.595	0.2149
	Ventral medial CPu (1, 35)	0.6384	0.4297	7.303	0.0105*	1.332	0.2563
	Ventral lateral CPu (1, 35)	0.0937	0.7613	8.215	0.0070*	0.9525	0.3358
	Ventral CPu (1, 35)	0.0530	0.8193	7.383	0.0102*	2.114	0.1548
	Nucleus accumbens core (1, 35)	1.042	0.3144	6.365	0.0163*	0.4338	0.5144
	Nucleus accumbens shell (1, 35)	0.5062	0.4815	8.413	0.0064**	1.402	0.2443
	Olfactory tract (1, 35)	1.03	0.3172	7.925	0.0080**	1.666	0.2053
	Substantia nigra reticular (1, 35)	1.667	0.2051	4.67	0.0376*	0.8467	0.3638
[^{3}H] Spiperone	Dorsal medial CPu (1, 35)	0.1622	0.6896	0.2731	0.6045	0.4240	0.5192
	Dorsal lateral CPu (1, 35)	0.6437	0.4228	1.931	0.1735	0.2433	0.6249
	Dorsal CPu (1, 35)	0.5234	0.4742	4.299	0.0456*	0.0021	0.9636
	Ventral medial CPu (1, 35)	0.1027	0.7505	0.1908	0.6649	0.2832	0.598
	Ventral lateral CPu (1, 35)	0.0051	0.9437	0.0559	0.8144	0.0183	0.8931
	Ventral CPu (1, 35)	0.1674	0.6849	4.355	0.0443*	0.0015	0.9696
	Nucleus accumbens core (1, 35)	0.0475	0.8287	1.323	0.2579	0.5593	0.4595
	Nucleus accumbens shell (1, 35)	0.6879	0.4125	0.0007	0.9782	4.194	0.0481*
	Olfactory tract (1, 35)	0.4058	0.5282	4.199	0.0480*	3.0861	0.0889

*$p<0.05$, **$p<0.001$

the function of the mesocorticolimbic DAergic system [52]. The system is well-established for controlling cognitive functions, motivated behavior, the central stress response, and the pleasure produced by reinforcers. Given the intricate crosstalk between the ECS and the DAergic systems, CB1 receptor agonists have been shown to enhance DA neuron firing in both the substantia nigra pars compacta and the VTA, as well as increase DA release in the NAc [57]. Specifically, retrograde signaling by the ECS at GABAergic and glutamatergic terminals result in depolarization-induced suppression of inhibitory and excitatory neurotransmission, respectively. While DA neurons in the mid brain region do not express CB1R, the membrane of DA neurons express biosynthetic enzymes for 2-AG at the presynaptic terminal, allowing a retrograde synaptic release of DA [58–60].

Deletion of both FABP5 and FABP7 genes has an anti-anhedonia effect and is presumably mediated by the alteration in the DAergic signaling via a regulatory mechanism described above. We have previously found that FABP5$^{-/-}$ mice display an elevation in D1R in the DM CPu, VM-CPu, and NAc Shell, further alluding to the involvement of FABPs in regulating the dopaminergic system [61]. In the present study, we did not record a significant change in DA receptor binding in FABP7$^{-/-}$ mice. This suggests that FABP5 may play a compensatory role in counteracting the remodeling of DAergic system. One potential factor contributing to the differences between FABP5 and FABP7 is their expression pattern. FABP5 is expressed in both neurons and glia, while FABP7 is most abundantly expressed in astrocytes and more involve in trafficking PUFAs [62]. Previous literature has shown that FABP5$^{-/-}$ mice have an increase in AEA levels in the striatum [63]. Fauzan et al. also demonstrated that FABP5 inhibited phasic 2-AG short-term synaptic plasticity without changing CB1R expression or function while also controlling tonic 2-AG and AEA signaling at striatal GABA synapses of MSN [63]. However, we could not eliminate the possibility of FABP3 playing a similar compensatory role as well. FABP3 is expressed exclusively in the neuron and more phylogenetically closely related to FABP7 compared with FABP5 [64, 65]. FABP3 was detected in D2R-expressing neurons within the rat striatum and was found to be able to bind specifically to the long isoform of D2R in yeast two-hybrid screening and co-immunoprecipitation assays [66]. Although a selective FABP7 inhibitor has not been developed (with SBF-26 currently functioning as a dual FABP5/FABP7 inhibitor), future studies should consider employing selective FABP inhibitors, such as MF1 for FABP3 and ART26.12 for FABP5 [67], to precisely define the role of each FABP subgroup in modulating DAergic system.

UCMS has been shown to exert heterogeneous changes on DAergic system in a region-dependent manner [31]. Our findings on the effects of UCMS on D1R have not previously been reported in previous literature. Prior studies observed selective regional increases in D1R binding [68–70] or no change under UCMS [71–73]. Additionally, the increase in D2R binding recorded in the present study supports Zhang et al.'s work [74], but contrasts with earlier reports that showed stress-induced reductions in the D2R protein and/or

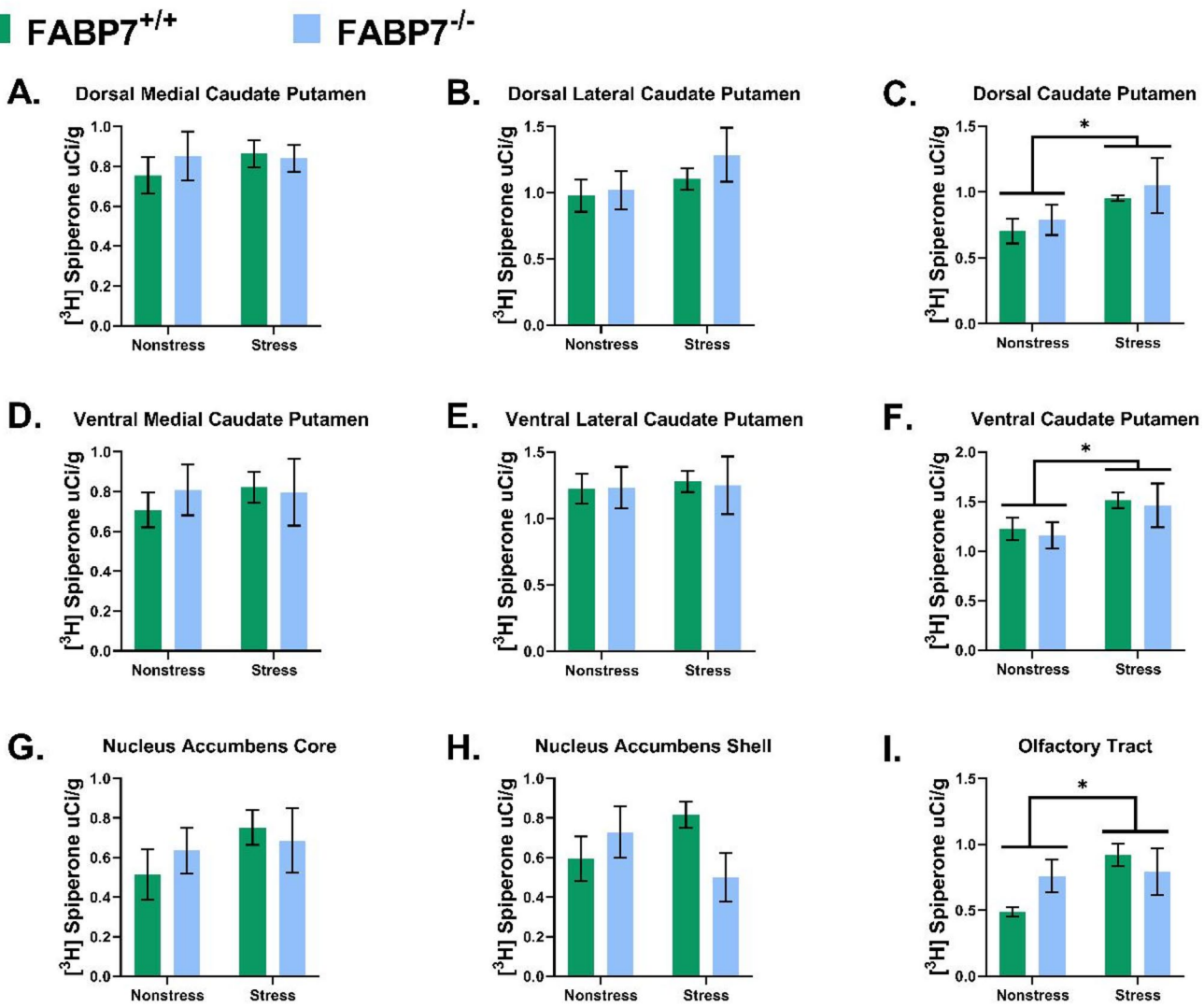


Fig. 4 [^{3}H] Spiperone binding within each measured region in FABP7$^{+/+}$ and FABP7$^{-/-}$ under control versus stress paradigm. **(A)** dorsal medial caudate putamen (CPu); **(B)** dorsal lateral CPu; **(C)** dorsal CPu; **(D)** ventral medial CPu; **(E)** ventral lateral CPu; **(F)** ventral CPu; **(G)** Nucleus accumbens (NAc) core; **(H)** NAc shell; **(I)** Olfactory tract. Two-way ANOVA, $n = 9$–10/group, bar represent mean ± SEM, * indicates statically significant difference in an overall stress effect at $p < 0.05$

transcriptional activity [70, 71, 75]. It is also worth noting that the present study also confounds with our previous findings where UCMS did not affect D1R or D2R binding [73]. A plausible mechanism for this variation could be due to the different types of stressors employed in UCMS paradigms. In the previous study, Delis et al. included paired housing and white noise as part of the UCMS paradigm while excluding food/water deprivation, cold/warm swim, and tail pinching, which were part of the present study [73, 76]. The aim of UCMS is to promote hyperactivity of HPA axis and reduced inhibitory feedback, both of which are key markers for MDD pathophysiology. The modified stressors utilized in the present study (food/water deprivation, cold/warm swim, and tail pinching) have been documented to elicit a heightened HPA response compared to paired housing and white noise [77], suggesting a closer-fitting model for pathophysiology of MDD; however, more investigation is needed to confirm this.

The co-morbidity between MDD and substance use disorders (SUDs) persists at a rate that suggests strong association between the two conditions [78]. In a recent review, De Filippis et al. described the challenges faced in clinical practice establishing the driver in patients with MDD-SUDs (whether MDD leads to more substance consumption or substance consumptions leads to progression in MDD), as well as the inadequate care in patient with MDD-SUDs [79]. Although the etiology of MDD-SUDs remains elusive, the most prevalent hypothesis surrounding the potential predictor behind the disease would be characterized by Reward Deficiency Syndrome (RDS), a work previously

coined by Blum's research team, suggests a hypodopaminergic state and reduction of D2R as the common root of behavioral manifestations [80]. Previous works have shown that chronic stress can lead to a reduction in dopamine in the VTA [31, 81]. Intriguingly, in the present study we also demonstrated that chronic stress leads to imbalance in the D1R: D2R ratio, where there are more D1Rs compared with D2Rs. As depicted in the RDS, a deficiency in D2R also has been recognized as a hallmark for increased drug consumption and implicated for SUDs due to reduction in inhibitory counterbalance signal, the "No-go Pathways" [14, 17, 76, 82]. Contrarily, D1R has been documented to be the driver for drug seeking behavior and reinforcement, stimulating the "Go Pathway" [83–85]. Volkow et al. noted in a review that repeated drug exposure would favor overexpression of the low-affinity D1R and tonic DA response while downregulating high-affinity D2R and phasic DA [14]. Therefore, we speculate that increase in D1R across the striatum in the present study could be implicated in a risk for SUD and sparingly increased in D2R is likely a compensatory response to the increase in D1R across the striatum. More research is needed to test this speculation. These findings, combined with the support of the RDS hypothesis, propose a potential underlying relationship between MDD-SUDs.

The OT has been previously documented for its role in odor-reward and odor-danger associative learning. As part of the ventral striatum, the OT receives significant dopaminergic input from the VTA and is involved in motivated behaviors [86]. D1R expression in the OT has been shown to encode odor valence (whether an odor means reward or punishment) and motivated or avoidance behaviors, depending on the specific OT subdivision [87, 88]; therefore, a stress-induced increase in D1R would be expected to have a similar effect. In contrast, D2R is more selective for odor identity [88], and its activation in the anteromedial OT has been shown to initiate aversive and avoidance behaviors in mice [89]. Our results show that UCMS increases D2R in the OT, suggesting an enhancement in avoidance behavior as typically seen in anhedonic subjects.

Limitations

The present study acknowledges the existence of limitations. We acknowledge that while the UCMS procedure has been used to promote stress markers (behaviors and cortisol level), we did not evaluate any of the biomarkers. In our prior research, we observed distinct results from genetic deletion of FABPs and pharmacological inhibition of FABPs [32]. It is plausible that FABP7$^{-/-}$ mice differ from wild-type mice in terms of their neural connections, which could make it difficult to characterize the condition. Another limitation of our present study is lack of female data, which restricts our understanding of sex-based differences. Future research should also use pharmacological inhibitors of FABPs to further elucidate the disease's underlying pathogenesis and conduct additional investigations in female subjects.

Conclusions

In conclusion, the present study demonstrates that UCMS upregulates D1R and D2R expression in the striatum, regardless of FABP7 gene deletion. D1R expression increased across all analyzed regions (DL CPu, DM CPu, D CPu, VL CPu, VM CPu, V CPu, NAcC, NAcS, OT, and SNR), while D2R upregulation was restricted to select regions (D CPu, V CPu, and OT). Given that UCMS is an established model for depression, these findings suggest that chronic stress may be a key factor in the etiology of MDD-SUDs. Furthermore, the lack of effect of FABP7 deletion on dopamine receptor binding suggests a potential compensatory role by other FABPs, such as FABP3 and FABP5.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

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References

1. 1. Rezende, B., et al., *Endocannabinoid System: Chemical Characteristics and Biological Activity.* Pharmaceuticals (Basel), 2023. **16**(2).
2. Stella N, Schweitzer P, Piomelli D (1997) A second endogenous cannabinoid that modulates long-term potentiation. Nature 388(6644):773–8
3. Hill MN et al (2023) The endocannabinoid system as a putative target for the development of novel drugs for the treatment of psychiatric illnesses. Psychol Med 53(15):7006–7024
4. 4. Liu, R.Z., et al., *Fatty acid binding proteins in brain development and disease.* Int J Dev Biol, 2010. **54**(8–9): p. 1229-39.
5. Sharifi K et al (2011) FABP7 expression in normal and stab-injured brain cortex and its role in astrocyte proliferation. Histochem Cell Biol 136(5):501–13
6. 6. Hamilton, H.L., et al., *FABP7 drives an inflammatory response in human astrocytes and is upregulated in Alzheimer's disease.* Geroscience, 2024. **46**(2): p. 1607–1625.
7. Kaczocha M et al (2014) Inhibition of fatty acid binding proteins elevates brain anandamide levels and produces analgesia. PLoS One 9(4):e94200
8. 8. Mita, R., et al., *Brain fatty acid-binding protein and omega-3/omega-6 fatty acids: mechanistic insight into malignant glioma cell migration.* J Biol Chem, 2010. **285**(47): p. 37005-15.
9. Powell A et al (2025) The role of fatty acid binding proteins in neuropsychiatric diseases: a narrative review. Front Biosci (Landmark Ed) 30(6):26812
10. 10. Febo, M., et al., *Dopamine homeostasis: brain functional connectivity in reward deficiency syndrome.* Front Biosci (Landmark Ed), 2017. **22**(4): p. 669–691.
11. Beaulieu JM, Gainetdinov RR (2011) The physiology, signaling, and pharmacology of dopamine receptors. Pharmacol Rev 63(1):182–217
12. Mishra A, Singh S, Shukla S (2018) Physiological and functional basis of dopamine receptors and their role in neurogenesis: possible implication for Parkinson's disease. J Exp Neurosci 12:1179069518779829
13. Gu SM et al (2020) Dopamine D1 receptor antagonist reduces stimulant-induced conditioned place preferences and dopamine receptor supersensitivity. Naunyn Schmiedebergs Arch Pharmacol 393(1):131–138
14. Volkow ND, Michaelides M, Baler R (2019) The neuroscience of drug reward and addiction. Physiol Rev 99(4):2115–2140
15. Thanos PK et al (2016) Dopamine D2 gene expression interacts with environmental enrichment to impact lifespan and behavior. Oncotarget 7(15):19111–23
16. Thanos PK et al (2001) Overexpression of dopamine D2 receptors reduces alcohol self-administration. J Neurochem 78(5):1094–103
17. Thanos PK et al (2008) D2R DNA transfer into the nucleus accumbens attenuates cocaine self-administration in rats. Synapse 62(7):481–6
18. Herkenham M et al (1991) Neuronal localization of cannabinoid receptors in the basal ganglia of the rat. Brain Res 547(2):267–74
19. Luo SX, Huang EJ (2016) Dopaminergic neurons and brain reward pathways: from neurogenesis to circuit assembly. Am J Pathol 186(3):478–88
20. Marsicano G, Lutz B (1999) Expression of the cannabinoid receptor CB1 in distinct neuronal subpopulations in the adult mouse forebrain. Eur J Neurosci 11(12):4213–25
21. Garcia C et al (2016) Cannabinoid-dopamine interactions in the physiology and physiopathology of the basal ganglia. Br J Pharmacol 173(13):2069–79
22. Twitchell W, Brown S, Mackie K (1997) Cannabinoids inhibit N- and P/Q-type calcium channels in cultured rat hippocampal neurons. J Neurophysiol 78(1):43–50
23. Melis M et al (2004) Endocannabinoids mediate presynaptic inhibition of glutamatergic transmission in rat ventral tegmental area dopamine neurons through activation of CB1 receptors. J Neurosci 24(1):53–62
24. Wang H et al (2015) Cocaine-induced endocannabinoid mobilization in the ventral tegmental area. Cell Rep 12(12):1997–2008
25. 25. Wenzel, J.M., et al., *Phasic Dopamine Signals in the Nucleus Accumbens that Cause Active Avoidance Require Endocannabinoid Mobilization in the Midbrain.* Curr Biol, 2018. **28**(9): p. 1392–1404 e5.
26. Oleson EB et al (2012) Endocannabinoids shape accumbal encoding of cue-motivated behavior via CB1 receptor activation in the ventral tegmentum. Neuron 73(2):360–73
27. Kearn CS et al (2005) Concurrent stimulation of cannabinoid CB1 and dopamine D2 receptors enhances heterodimer formation: a mechanism for receptor cross-talk? Mol Pharmacol 67(5):1697–704
28. Przybyla JA, Watts VJ (2010) Ligand-induced regulation and localization of cannabinoid CB1 and dopamine D2L receptor heterodimers. J Pharmacol Exp Ther 332(3):710–9
29. Khan SS, Lee FJ (2014) Delineation of domains within the cannabinoid CB1 and dopamine D2 receptors that mediate the formation of the heterodimer complex. J Mol Neurosci 53(1):10–21
30. Hillard CJ, Liu QS (2014) Endocannabinoid signaling in the etiology and treatment of major depressive illness. Curr Pharm Des 20(23):3795–811
31. Baik JH (2020) Stress and the dopaminergic reward system. Exp Mol Med 52(12):1879–1890
32. Hamilton J et al (2018) Fatty acid-binding proteins 5 and 7 gene deletion increases sucrose consumption and diminishes forced swim immobility time. Behav Pharmacol 29(6):503–508
33. Hamilton J et al (2018) Fatty acid binding protein deletion prevents stress-induced preference for cocaine and dampens stress-induced corticosterone levels. Synapse 72(6):e22031
34. Hamilton J et al (2022) Unpredictable chronic mild stress differentially impacts resting brain glucose metabolism in fatty acid-binding protein 7 deficient mice. Psychiatry Res Neuroimaging 323:111486
35. Lu H et al (2025) Fatty acid-binding protein 7 gene deletion promotes decreases in brain cannabinoid type 1 receptor binding. Neurosci Lett 844:138040
36. Kaczocha M et al (2015) Fatty acid binding protein deletion suppresses inflammatory pain through endocannabinoid/N-acylethanolamine-dependent mechanisms. Mol Pain 11:52
37. Khan A et al (2024) The role of fatty acid-binding protein 5 and 7 on locomotor, anxiety and social behavior: interaction with NMDA signaling. Neurosci Lett 836:137862
38. Owada Y et al (2006) Altered emotional behavioral responses in mice lacking brain-type fatty acid-binding protein gene. Eur J Neurosci 24(1):175–87
39. Bobick M et al (2025) Exercise leads to brain glucose metabolism activation, increased dopamine D1 receptor levels and is negatively correlated with social behavior. J Integr Neurosci 24(6):36646
40. Lagamjis G et al (2025) Combined chronic oral methylphenidate and fluoxetine decreases D2R levels in the caudate putamen and nucleus accumbens. Neurochem Res 50(4):230
41. Tyler J et al (2023) High intensity interval training exercise increases dopamine D2 levels and modulates brain dopamine signaling. Front Public Health. https://doi.org/10.3389/fpubh.2023.1257629

42. Hamilton J et al (2018) Roux-en-Y gastric bypass surgery normalizes dopamine D1, D2, and DAT levels. Synapse. https://doi.org/10.1002/syn.22058
43. Robison LS et al (2017) Chronic oral methylphenidate treatment reversibly increases striatal dopamine transporter and dopamine type 1 receptor binding in rats. J Neural Transm 124(5):655–667
44. Franklin KBJ, Paxinos G (2008) The mouse brain in stereotaxic coordinates, 3rd ed. Academic Press, New York
45. Yin HH, Knowlton BJ, Balleine BW (2006) Inactivation of dorsolateral striatum enhances sensitivity to changes in the action-outcome contingency in instrumental conditioning. Behav Brain Res 166(2):189–96
46. Robison CL et al (2021) Inactivation of posterior but not anterior dorsomedial caudate-putamen impedes learning with self-administered nicotine stimulus in male rats. Behav Brain Res 413:113438
47. Lee K et al (2023) Anatomical and functional comparison of the caudate tail in primates and the tail of the striatum in rodents: implications for sensory information processing and habitual behavior. Mol Cells 46(8):461–469
48. dos Santos LM et al (2012) The role of the ventrolateral caudoputamen in predatory hunting. Physiol Behav 105(3):893–8
49. Liu S et al (2017) CRFR1 in the ventromedial caudate putamen modulates acute stress-enhanced expression of cocaine locomotor sensitization. Neuropharmacology 121:60–68
50. Nagatomo K et al (2017) Dopamine D1 receptor immunoreactivity on fine processes of GFAP-positive astrocytes in the substantia nigra pars reticulata of adult mouse. Front Neuroanat 11:3
51. Hill MN et al (2010) Endogenous cannabinoid signaling is essential for stress adaptation. Proc Natl Acad Sci U S A 107(20):9406–11
52. Belujon P, Grace AA (2017) Dopamine system dysregulation in major depressive disorders. Int J Neuropsychopharmacol 20(12):1036–1046
53. Shimamoto C et al (2014) Functional characterization of FABP3, 5 and 7 gene variants identified in schizophrenia and autism spectrum disorder and mouse behavioral studies. Hum Mol Genet 23(24):6495–511
54. Vanderheyden WM et al (2022) Fabp7 is required for normal sleep suppression and anxiety-associated phenotype following single-prolonged stress in mice. Neuroglia 3(2):73–83
55. Umathe SN, Manna SS, Jain NS (2011) Involvement of endocannabinoids in antidepressant and anti-compulsive effect of fluoxetine in mice. Behav Brain Res 223(1):125–34
56. Bambico FR et al (2010) Genetic deletion of fatty acid amide hydrolase alters emotional behavior and serotonergic transmission in the dorsal raphe, prefrontal cortex, and hippocampus. Neuropsychopharmacology 35(10):2083–100
57. Laksmidewi A, Soejitno A (2021) Endocannabinoid and dopaminergic system: the pas de deux underlying human motivation and behaviors. J Neural Transm (Vienna) 128(5):615–630
58. Kreitzer AC, Malenka RC (2005) Dopamine modulation of state-dependent endocannabinoid release and long-term depression in the striatum. J Neurosci 25(45):10537–45
59. Julian MD et al (2003) Neuroanatomical relationship between type 1 cannabinoid receptors and dopaminergic systems in the rat basal ganglia. Neuroscience 119(1):309–18
60. Uchigashima M et al (2007) Subcellular arrangement of molecules for 2-arachidonoyl-glycerol-mediated retrograde signaling and its physiological contribution to synaptic modulation in the striatum. J Neurosci 27(14):3663–76
61. Richardson BJ et al (2023) Fatty acid-binding protein 5 differentially impacts dopamine signaling independent of sex and environment. Addict Neurosci. https://doi.org/10.1016/j.addicn.2023.100118
62. Owada Y (2008) Fatty acid binding protein: localization and functional significance in the brain. Tohoku J Exp Med 214(3):213–20
63. Fauzan M et al (2022) Fatty acid-binding protein 5 modulates brain endocannabinoid tone and retrograde signaling in the striatum. Front Cell Neurosci 16:936939
64. 64. Smathers, R.L. and D.R. Petersen, *The human fatty acid-binding protein family: evolutionary divergences and functions.* Hum Genomics, 2011. **5**(3): p. 170 − 91.
65. 65. Glaser, S.T., et al., *Fatty acid binding proteins are novel modulators of synaptic epoxyeicosatrienoic acid signaling in the brain.* Sci Rep, 2023. **13**(1): p. 15234.
66. 66. Takeuchi, Y. and K. Fukunaga, *Differential subcellular localization of two dopamine D2 receptor isoforms in transfected NG108-15 cells.* J Neurochem, 2003. **85**(4): p. 1064-74.
67. Warren WG et al (2024) Potential safety implications of fatty acid-binding protein inhibition. Toxicol Appl Pharmacol 491:117079
68. 68. Ossowska, G., et al., *Brain monoamine receptors in a chronic unpredictable stress model in rats.* J Neural Transm (Vienna), 2001. **108**(3): p. 311-9.
69. 69. Nanni, G., et al., *Acquisition of an appetitive behavior prevents development of stress-induced neurochemical modifications in rat nucleus accumbens.* J Neurosci Res, 2003. **73**(4): p. 573 − 80.
70. 70. Papp, M., V. Klimek, and P. Willner, *Parallel changes in dopamine D2 receptor binding in limbic forebrain associated with chronic mild stress-induced anhedonia and its reversal by imipramine.* Psychopharmacology (Berl), 1994. **115**(4): p. 441-6.
71. 71. Dziedzicka-Wasylewska, M., P. Willner, and M. Papp, *Changes in dopamine receptor mRNA expression following chronic mild stress and chronic antidepressant treatment.* Behav Pharmacol, 1997. **8**(6–7): p. 607 − 18.
72. 72. Wu, C., et al., *Adolescent chronic unpredictable stress causes a bias in goal-directed behavior and distinctively changes the expression of NMDA and dopamine receptors in the dorsomedial and dorsolateral striatum in male rats.* Dev Psychobiol, 2022. **64**(2): p. e22235.
73. Delis F et al (2015) Regulation of ethanol intake under chronic mild stress: roles of dopamine receptors and transporters. Front Behav Neurosci 9:118
74. Zhang Y et al (2015) Dopamine receptor D2 and associated microRNAs are involved in stress susceptibility and resistance to escitalopram treatment. Int J Neuropsychopharmacol. https://doi.org/10.1093/ijnp/pyv025
75. Willner P et al (1991) Changes in mesolimbic dopamine may explain stress-induced anhedonia. Psychobiology 19(1):79–84
76. Delis F et al (2013) Chronic mild stress increases alcohol intake in mice with low dopamine D2 receptor levels. Behav Neurosci 127(1):95–105
77. Markov DD, Novosadova EV (2022) Chronic unpredictable mild stress model of depression: possible sources of poor reproducibility and latent variables. Biology. https://doi.org/10.3390/biology11111621
78. Hunt GE et al (2020) Prevalence of comorbid substance use in major depressive disorder in community and clinical settings, 1990–2019: systematic review and meta-analysis. J Affect Disord 266:288–304
79. De Filippis S et al (2025) Major depression in comorbidity with substance use disorders: patients' features and clinical-neurobiological rationale of antidepressant treatments. Curr Neuropharmacol 23(3):256–275
80. Blum K et al (2022) Reward deficiency syndrome (RDS) surprisingly is evolutionary and found everywhere: is it "blowin' in the wind"? J Pers Med. https://doi.org/10.3390/jpm12020321
81. 81. Douma, E.H. and E.R. de Kloet, *Stress-induced plasticity and functioning of ventral tegmental dopamine neurons.* Neurosci Biobehav Rev, 2020. **108**: p. 48–77.

82. Blum K et al (2024) Identification of stress-induced epigenetic methylation onto dopamine D2 gene and neurological and behavioral consequences. Gene & Protein in Disease. https://doi.org/10.36922/gpd.1966
83. Lowen SB et al (2015) Cocaine-conditioned odor cues without chronic exposure: implications for the development of addiction vulnerability. Neuroimage Clin 8:652–9
84. Graham DL et al (2007) Differential ability of D1 and D2 dopamine receptor agonists to induce and modulate expression and reinstatement of cocaine place preference in rats. Psychopharmacology Berl 191(3):719–30
85. Calipari ES et al (2016) In vivo imaging identifies temporal signature of D1 and D2 medium spiny neurons in cocaine reward. Proc Natl Acad Sci U S A 113(10):2726–31
86. Yamaguchi M (2024) Connectivity of the olfactory tubercle: inputs, outputs, and their plasticity. Front Neural Circuits 18:1423505
87. Ikemoto S (2003) Involvement of the olfactory tubercle in cocaine reward: intracranial self-administration studies. J Neurosci 23(28):9305–11
88. Martiros N et al (2022) Distinct representation of cue-outcome association by D1 and D2 neurons in the ventral striatum's olfactory tubercle. Elife. https://doi.org/10.7554/eLife.75463
89. Murata K et al (2019) Opposing roles of dopamine receptor D1- and D2-expressing neurons in the anteromedial olfactory tubercle in acquisition of place preference in mice. Front Behav Neurosci 13:50

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