Neuropharmacology 197 (2021) 108753

Contents lists available at ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

Decreased kynurenine pathway potentiate resilience to social defeat effect on cocaine reward

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ARTICLE INFO

Keywords:
Kynurenine
Tryptophan
Social defeat
Susceptibility
Resilience
Neuroinflammation
Cocaine

ABSTRACT

The kynurenine (KYN) pathway of tryptophan (TRP) degradation is activated by stress and inflammatory factors. It is now well established that social stress induces the activation of the immune system, with central inflammation and KYN metabolism being two of the main factors linking stress with depression.

The aim of the present study was to evaluate the long-lasting changes in the KYN pathway induced by social defeat (SD) associated with the resilience or susceptibility to an increase in the conditioned rewarding effects of cocaine. Mice were exposed to repeated SD and 3 weeks later, a conditioned place preference (CPP) induced by a subthreshold dose of cocaine (1.5 mg/kg) was developed. KYN levels in plasma, cerebellum, hippocampus, striatum and limbic forebrain were studied at the end of the CPP procedure. Changes in the KYN pathway after exposure to pharmacological (oxytocin and indomethacin) and environmental interventions (environmental enrichment) were also evaluated.

Our results showed that defeated susceptible (SD-S) mice had higher conditioning scores than resilient mice (SD-R). In addition, although KYN concentration was elevated in all defeated mice, SD-R mice showed smaller increases in KYN concentration in the cerebellum than SD-S mice. Oxytocin or Indomethacin treatment before SD normalized cocaine-induced CPP, although the increase in the KYN pathway was maintained. However, environmental enrichment before SD normalized cocaine-induced CPP and prevented the increase in the KYN pathway.

The present study highlights the role of the KYN pathway and anti-inflammatory drugs acting on TRP metabolism as pharmacological targets to potentiate resilience to social stress effects.

1. Introduction

Social stress has been implicated in the neural and behavioral alterations that contribute to the development of mental health disturbances, including drug addiction (Beutel et al., 2018). Stressful experiences can modify the reward system and influence the evolution from drug use to addiction, causing an increase in intake and drug-seeking behaviors (Koob and Schulkin, 2019; Miczek et al., 2008; Montagud-Romero et al., 2016a,b, 2018; Ruisoto and Contador, 2019).

Serotonin (5-HT) is one of the most important neurotransmitters implicated in the pathophysiology of psychiatric disorders such as depression and anxiety (Narayanan et al., 2011) and it is also involved in the regulation of stress (Harvey et al., 2004). Preclinical studies have reported an increase in 5-HT release, enhanced neuronal activity in the dorsal raphe nuclei, and increased 5-HT synthesis and turnover in response to stress (Chaouloff et al., 1999; Dunn, 1988). These stress-induced alterations in 5-HT activity occur in multiple brain regions, including the ventral striatum (Amato et al., 2007), the hippocampus (Keeney et al., 2006), PFC (Bruening et al., 2006; Smith et al.,

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https://doi.org/10.1016/j.neuropharm.2021.108753
Received 22 February 2021; Received in revised form 26 July 2021; Accepted 8 August 2021
Available online 11 August 2021

Abbreviations

5-HT	serotonin
COX	cyclooxygenase
CPP	conditioned place preference
EE	environmental enrichment
IDO1	indoleamine 2,3-dioxygenase
IL-1β	interleukin 1 beta
IL-6	interleukin 6
KYN	kynurenine
KYNA	kynurenic acid
LPS	lipopolysaccharide
NAc	nucleus accumbens
PFC	prefrontal cortex
PND	postnatal day
Post-C	postconditioning
Pre-C	preconditioning
QUIN	quinolinic acid
R	resilient mice
S	susceptible mice
SD	social defeat
SWR	social withdrawal ratio
TDO	tryptophan 2,3-dioxygenase
TRP	tryptophan
VTA	ventral tegmental area

2006). and the cerebellum (Azevedo et al., 2020).

Although tryptophan (TRP) can generate 5-HT, the KYN pathway is the main route of TRP metabolism and 95% of the amino acid is transformed into KYN (Schwarcz, 1993). Numerous studies have linked the KYN pathway to both inflammation and depression (Wang et al., 2018; Laumet et al., 2017). Increased formation of metabolites through the KYN pathway can lead to neural dysfunction by several mechanisms. KYN readily crosses the blood-brain barrier and is further metabolized along its two catabolic branches. 3-HydroxyKYN(3-HK) can generate free radicals and be further metabolized to quinolinic acid (QUIN), a glutamate receptor N-methyl-D-aspartate (NMDA) agonist (Chiarugi et al., 2001; Guillemin, 2012), which induces excitotoxicity. However, KYN also gives rise to a neuromodulatory metabolite, kynurenic acid (KYNA), which is a NMDA receptor antagonist (Perkins and Stone, 1982). Furthermore, KYNA can interact with several other receptors. It is an agonist at the aryl hydrocarbon receptor (DiNatale et al., 2010), acts at the astrocytic G-protein coupled receptor 35 (GPR35) (Wang et al., 2006) and, finally, acts inhibiting the presynaptic α7 nicotinic acetylcholine receptor (nAChR), blocking glutamate release (Hilmas et al., 2001). Therefore, increased activity of the KYN pathway modulates both serotonergic and glutamatergic neurotransmission (Müller and Schwarz, 2007; Miller, 2013).

The KYN pathway of TRP degradation is activated by stress and inflammatory factors (Gibney et al., 2013; Liu et al., 2013; Campbell et al., 2014). The stress-induced increase in KYN levels in the brain is reflected by an increase in the KYN/TRP ratio, indicating increased metabolism of TRP to KYN which is associated with an increase in the activity of indoleamine 2,3-dioxygenase (IDO1) (Larkin et al., 2016). This enzyme is expressed by immune cells and promotes TRP catabolism to KYN in the periphery and the brain (Dai and Zhu, 2010; Gibney et al., 2014; Robinson et al., 2003; Vécsei et al., 2013; Werner-Felmayer et al., 1989). Currently, there is growing evidence for hyperactivity of the KYN pathway in stress-related disorders (Bay-Richter et al., 2015; Kim et al., 2012; Maes et al., 2011; Réus et al., 2015; Savitz et al., 2015; Steiner et al., 2012; Sublette et al., 2011).

Animal models are useful tools for understanding the impact of stress on drug response and for studying its neurobiological mechanisms (Lynch et al., 2010). The social defeat (SD) paradigm is the most commonly used animal model for studying the consequences of stressful experiences (Hammels et al., 2015). In this model, the experimental subject is repeatedly confronted with an aggressive opponent mouse (Miczek et al., 2004). Using the conditioned place preference (CPP) paradigm, numerous studies have shown that SD induces both short- and long-lasting increases in the conditioned rewarding effects of cocaine, also increasing the time needed to extinguish drug-associated memories (Montagud-Romero et al., 2016a, 2016b, 2017; Rodríguez-Arias et al., 2017, 2018; Ferrer-Pérez et al., 2018). It is currently well established that social stress induces the activation of the immune system (Quan et al., 2001; Pfau et al., 2016; Ferrer-Pérez et al., 2018, 2019; Montagud-Romero et al., 2019; Rodríguez-Arias et al., 2018). In fact, central inflammation and KYN metabolism may be two of the factors linking stress with depression (Dantzer et al., 2008). Neuroinflammation upregulates the KYN pathway of TRP metabolism, mainly via enhancing the activity of IDO1, resulting in inflammation-induced depressive-like behaviors in mice (O'Connor et al., 2009; Walker et al., 2013). For example, Fuertig et al. (2016) reported that SD stress increased KYN levels in the brain and blood of mice. After a chronic SD procedure lasting 15 days, the levels of KYN in plasma and amygdala were increased in stressed animals 5 days after the last social encounter.

Although a number of preclinical studies have evaluated the role of the KYN pathway in the development of depressive-like behaviors after exposure to SD, there are no studies on the rewarding effects of cocaine. The aim of the present study was to evaluate the long-lasting changes in the KYN pathway induced by SD associated with the increase in the conditioned rewarding effects of cocaine. However, not all subjects exposed to stress will display unhealthy behaviors and develop addiction (Krishnan et al., 2007; Ródenas-González et al., 2020; Ballestín et al., 2021). Subjects susceptible to the effects of repeated SD exhibit depressive-like behaviors like social avoidance or decreased sucrose preference (Krishnan et al., 2007). In contrast, resilient counterparts successfully cope with stressful experiences and display an adjusted psychological functioning after stress (Brockhurst et al., 2015; Charney, 2004; Dantzer et al., 2018). Since KYN levels have been strongly correlated to depression (Claes et al., 2011; Müller and Schwarz, 2007), the role of the KYN pathway in resilience/susceptibility to social stress-induced effects warrants study. To evaluate if changes in the KYN pathway are related to resilience/susceptibility to SD effects, mice were exposed to repeated SD and 3 weeks later, a CPP induced by a subthreshold dose of cocaine (1.5 mg/kg) was developed. KYN levels in plasma, cerebellum, striatum, hippocampus and limbic forebrain were studied at the end of the CPP procedure. Changes in the KYN pathway after exposure to pharmacological (oxytocin and indomethacin) and environmental interventions (environmental enrichment) known to increase resilience to the effect SD were also evaluated.

2. Material and methods

2.1. Animals

A total number 107 adult male C57BL/6 mice (Charles River, France) were used in this study. Experimental mice were housed in groups of five in plastic cages (27 × 27 × 14 cm) during the entire experimental procedure. OF1 adult mice (Charles River, France) were used as aggressive opponents (N = 20) and were individually housed in plastic cages (21 × 32 × 20 cm) for at least a month prior to initiation of the experiments in order to heighten aggression (Rodríguez-Arias et al., 1998). All mice were housed in controlled laboratory conditions: constant temperature and humidity, and a reversed light schedule (lights off

at 08:00 and on at 20:00). Food and water were available ad libitum to all the mice used in this study, except during behavioral tests. All procedures were conducted in compliance with the guidelines of the European Council Directive 2010/63/UE regulating animal research and were approved by the local ethics committees of the University of Valencia.

2.2. Drugs

For CPP, a dose of 1.5 mg/kg of cocaine hydrochloride (Alcaliber laboratory, Spain) was employed and injected intraperitoneally (i.p.). This dose of cocaine was selected based on previous CPP studies showing that doses below 3 mg/kg are sub-threshold (Arenas et al., 2014; Montagud-Romero et al., 2017; Vidal-Infer et al., 2012). For pre-treatment, oxytocin (Sigma-Aldrich, Spain) was dissolved in physiological saline (NaCl 0.9%) and injected i.p. at a dose of 1 mg/kg 30 min before each SD episode. The anti-inflammatory indomethacin (Sigma-Aldrich, Spain) was dissolved in 5% DMSO (dimethyl sulfoxide) and injected i.p. at a dose of 10 mg/kg 30 min before each SD. All i.p. administrations were adjusted in a volume of 0.01 ml/g of body weight. Control groups were injected with physiological saline (NaCl 0.9%), which was also used to dissolve the drugs.

2.3. Experimental groups and experimental design

In this study, four different sets of mice were employed, all of which were exposed to the SD procedure or exploration from PND 54 to 63. 24 h after the last SD episode, all the animals performed the social withdrawal test to evaluate depressive-like behaviors.

In the first set of mice, after 3 weeks of being undisturbed in their home cages, mice underwent the CPP procedure (PND 83) with 1.5 mg/kg of cocaine. Animals were characterized as R or S depending on their social withdrawal ratios (SWR). Brain and blood samples were taken at the end of this procedure (PND 93).

The procedure was similar for the second and third sets of mice, except that animals received an i.p. injection of 1 mg/kg of oxytocin, or 10 mg/kg of indomethacin respectively, 30 min before each defeat procedure. Finally, in the fourth set, mice were housed in an enriched environment with PVC items from their arrival to the laboratory until the end of SD procedure. In these sets, half of the animals in each housing condition experienced a repeated social stress protocol, while the other half underwent a similar handling but without experiencing social stress (CTRL).

The experimental design is depicted in Table 1.

2.4. Apparatus and procedures

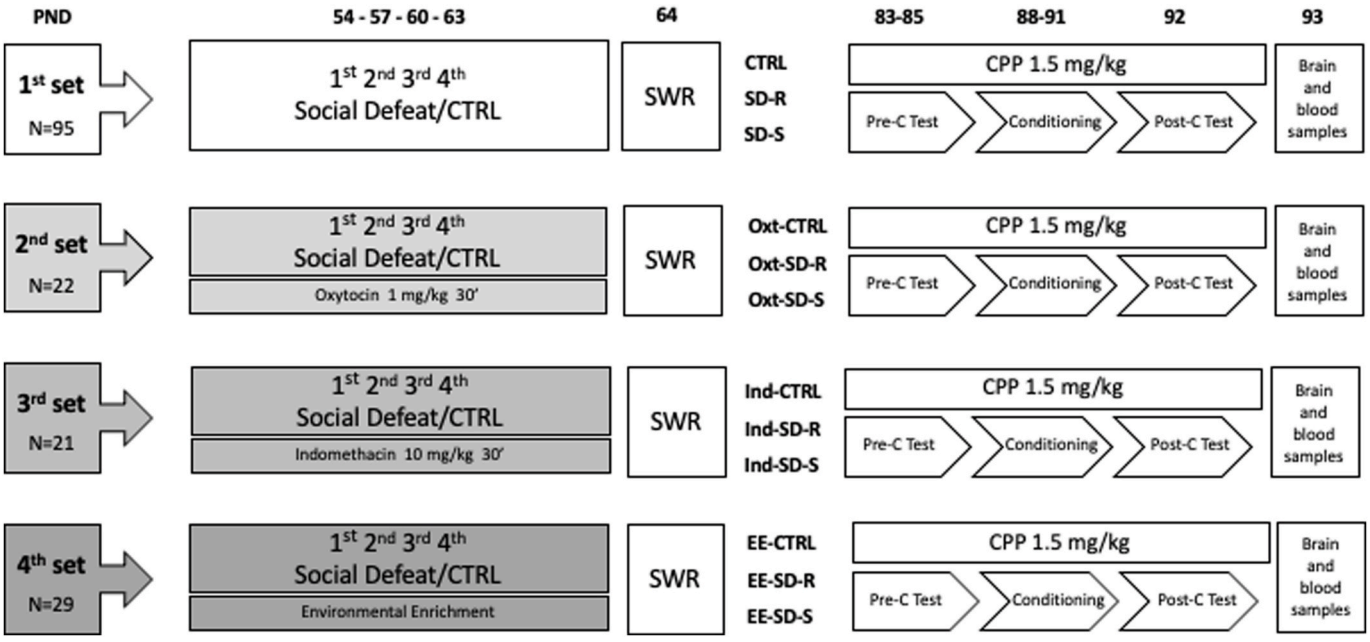
2.4.1. Housing conditions

The first, second and third sets of male mice were housed under regular housing conditions in groups of five in transparent plastic cages (27 × 27 × 14 cm) with no more enrichment other than standard bedding (wood flakes 1–3.35 mm), nesting material (paper strands) and two wooden gnaw sticks (5 × 1x1 cm) per cage. The male mice in the fourth set were housed in environmental enrichment (EE) conditions in groups of five in plastic cages (59 × 38 × 20 cm) with standard bedding and nesting material, two wooden gnaw sticks in addition to a PVC tunnel (13 × 5.5 cm) and a plastic mouse house (12.5 × 10.5 × 11 cm).

2.4.2. Procedure of social defeat (SD)

Animals in the stress/defeated groups were exposed to 4 episodes of SD during adulthood, each lasting 25 min and consisting of three phases. The initial phase began by introducing the "intruder" (the experimental animal) into the home cage of the "resident" (the aggressive opponent) for 10 min (Tornatzky and Miczek, 1993). During this initial phase, the intruder was protected from attack, but the wire mesh walls of the cage allowed for social interactions and species-typical threats from the male aggressive resident, thus facilitating instigation and provocation (Covington and Miczek, 2001) In the second phase, the wire mesh was removed from the cage to allow confrontation between the two animals over a 5-min period. Finally, the wire mesh was put back in the cage to separate the two animals once again for a further 10 min to allow for social threats by the resident. The non-stressed exploration groups underwent the same protocol, but without the presence of a "resident" mouse in the cage. Intruder mice were exposed to a different aggressor mouse during each SD episode. The criterion used to define an animal as defeated was the adoption of a specific posture signifying defeat,

Table 1
Experimental design.



characterized by an upright submissive position, limp forepaws, upwardly angled head, and retracted ears (Miczek et al., 1982; Rodríguez-Arias et al., 1998). All agonistic encounters of each SD protocol were videotaped to confirm social defeat of the intruder mice and to ethologically analyze the attack behaviors (duration and latency) of the resident mice. These behaviors were scored in resident mice and avoidance/flee and defensive/submissive behaviors were evaluated in intruder mice.

2.4.3. Social withdrawal ratio (SWR)

The social withdrawal ratio used was based on the social approach-avoidance test previously described by Berton et al. (2006). The test took place 24 h after the last SD during daylight and in a different environment from the confrontation sessions. First, animals were transferred to a quiet, dimly lit room 1 h before the test was initiated. After habituation, each animal was placed in the center of a square arena (white Plexiglas open field, 30 cm each side and 35 cm high) and its behavior was monitored by video (EthoVision XT 11, 50 fps; camera placed above the arena). Animals were allowed to explore the arena twice, for 600 s in each session, during two different experimental sessions. In the first session (object session), an empty perforated Plexiglas cage (10 × 6.5 × 35 cm) was placed in the middle of one wall of the arena. In the second session (social session), an unfamiliar C57BL/6 male mouse was introduced into the cage as a social stimulus. Although it can be argued that the probe mouse used in the SWR resembles the aggressor, and that this could foster social aversion, this is unlikely, since previous experiments demonstrate similar amounts of social investigation, irrespective of the strain used (i.e., C57BL/6; Berton et al., 2006). Before each session, the arena was cleaned with 5% alcohol solution to minimize odor cues. Between sessions, the experimental mouse was removed from the arena and returned to its home cage for 2 min.

Locomotion and arena occupancy during object and social sessions were determined using the animals' horizontal position, determined by commercial video tracking software (EthoVision XT 11, Noldus). Conventional measures of arena occupancy, such as time spent in the interaction zone and corners, were quantified. The former is commonly used as social preference-avoidance score and is calculated by measuring the time spent in a 6.5 cm wide corridor surrounding the restrain cage. Corners were defined as two squares of similar areas on the opposite wall of the arena. SWR is calculated by considering the time spent by an experimental mouse in the interaction zone when a social target is present divided by the time it spends in the interaction zone when the target is absent. A ratio equal to 1 means that equal time has been spent in the presence versus absence of a social target. Based on the regular behavior of control C57BL/6 mice, animals with a ratio under 1 are classified as S, while those with a ratio equal to or higher than 1 are classified as R (Golden et al., 2011).

2.4.4. Conditioned place preference (CPP)

For place conditioning, we employed eight identical Plexiglas boxes with two compartments of equal size (30.7 × 31.5 × 34.5 cm high) separated by a gray central area (13.8 × 31.5 × 34.5 cm high). The compartments had different colored walls (black vs white) and distinct floor textures (fine grid in the black compartment and wide grid in the white one). Four infrared light beams in each compartment of the box and six in the central area allowed the position of the animals and their crossings from one compartment to the other to be recorded. The equipment was controlled by three computers using MONPRE 2Z software (CIBERTEC, SA, Spain).

Place conditioning, consisting of three phases, was carried out during the dark cycle following a procedure that is unbiased in terms of initial spontaneous preference (Manzanedo et al., 2001). During the first phase - or preconditioning (Pre-C) - mice were allowed access to both compartments of the apparatus for 900 s per day on 3 consecutive days. On day 3, the time spent in each compartment was recorded. Animals showing a strong unconditioned aversion (<33% of session time; i.e. 250 s) or preference (>67% of the session time; i.e. 650 s) for any compartment were discarded from the rest of the study. The ANOVA showed no significant differences between the time spent in the drug-paired and vehicle-paired compartments during the Pre-C phase. In the second phase (conditioning), which lasted 4 days, animals were conditioned with 1.5 mg/kg cocaine or saline. During this phase, half of the animals in each group received the drug or vehicle in one compartment, while the other half received it in the other compartment. An injection of physiological saline was administered before confining the mice to the vehicle-paired compartment for 30 min. After an interval of 4 h, the animals received cocaine immediately prior to confinement in the drug-paired compartment for a further 30 min. The central area was made inaccessible by guillotine doors during conditioning. The dose of cocaine used during the conditioning phase was a subthreshold dose (1.5 mg/kg, proven to be ineffective in controls) in order to evaluate increased sensitivity to the conditioned rewarding effects of cocaine. In the third phase - or postconditioning (Post-C) - which took place on day 8, the guillotine doors separating the two compartments were removed, and the time spent in each compartment by the untreated mice during a 900 s observation period was recorded. The difference in seconds between the time spent in the drug-paired compartment during the Post-C and Pre-C tests is a measure of the degree of conditioning induced by the drug (conditioning score). If this difference is positive, then the drug has induced a preference for the drug-paired compartment, while the opposite indicates an aversion.

2.4.5. Sample extraction

Sample extraction was carried out as previously described (Giménez-Gómez et al., 2018). Briefly, mice were killed by cervical dislocation, trunk blood was collected in tubes containing K2-EDTA (1:10) and immediately centrifuged twice at 1300×*g* at 4 °C for 10 min to obtain plasma. Plasma samples were collected and stored at −80 °C. Brains were removed and coronal slices were obtained using a mouse brain matrix (World Precision Instruments, USA) placed on an ice-cold Petri dish. After removal of the olfactory bulbs, brain tissue anterior to the optic chiasm was referred to as limbic forebrain (Wang et al., 2003). The cerebellum was dissected out from the remaining brain. We collected striatum and hippocampus samples from another batch of animals following the same protocol as in the 1st set of mice. Samples were stored at −80 °C.

2.4.6. KYN, TRP and 5-HT measurements in plasma, limbic forebrain, striatum, hippocampus and cerebellum

KYN, TRP and 5-HT concentrations were determined by HPLC following the method previously described (Giménez-Gómez et al., 2019). Briefly, brain areas were homogenized by sonication in 5 vol of deionized water (Labsonic, 2000U; B. Braun Melsungen, Melsungen, Germany). Samples were deproteinized by adding 25 μl of 6% perchloric acid per 100 μl of brain homogenate, or 12.5 μl of 6% perchloric acid and 187.5 μl of water to 50 μl plasma. After centrifugation, supernatants were frozen at −80 °C until analysis.

For KYN quantification, 60 μl of supernatant was applied to a reversed-phase column (80 mm × 4.6 mm, 3 μm; HR-80; Thermo Fisher Scientific, Waltham, MA, USA), and KYN was isocratically eluted using a mobile phase containing 0.1 M sodium acetate and 4% acetonitrile, pH 4.6, at a flow rate of 1 ml/min (Waters 510 pump). KYN was measured by UV detection (360 nm, 2487; Waters, Milford, MA, USA).

For 5-HT and TRP measurement, 20 μl of supernatant was applied to the same column. The mobile phase contained 0.5 M sodium acetate (adjusted to pH 6.2 with glacial acetic acid) and 5% acetonitrile delivered at 1 ml/min 5-HT and TRP were detected fluorometrically, using 290 and 337 nm for 5-HT and 270 and 360 nm for TRP as the excitation and emission wavelengths, respectively. The ratios of KYN or 5-HT to TRP were used as a measure of TRP degradation and of KYN and 5-HT formation, respectively.

2.5. Statistical analysis

Mice were previously classified into R and S groups based on their SWR. The data were analyzed by an ANOVA with a between-subjects variable - Stress, with three (Control, S and R), or two levels (Control and R). In all the studies, following the ANOVA, Bonferroni post-hoc tests were calculated whenever required. Statistical analyses were performed using SPSS Statistics v.26 for behavioral data and GraphPad Prism (v8; GraphPad Software Inc., CA, USA) for HPLC data. Data were expressed as mean ± SEM and a value of $p < 0.05$ was considered statistically significant.

3. Results

3.1. Effect of social defeat on SWR, conditioned rewarding effects of cocaine and brain KYN concentration

3.1.1. Susceptible mice had lower social withdrawal ratios (SWR) and higher conditioning scores than resilient mice

The ANOVA of the SWR performed after the last SD showed an effect of Stress [$F(2,35) = 8.146$; $p < 0.001$] (see Fig. 1A). The post-hoc comparison revealed lower social scores among SD-S mice in comparison with CTRL or SD-R animals ($p < 0.01$ in both cases).

The ANOVA of the Conditioning Score showed an effect of Stress [$F(2,35) = 9.960$; $p < 0.001$], with SD-S animals showing a significantly higher conditioning score than those in the CTRL ($p < 0.05$) or SD-R ($p < 0.001$) groups (see Fig. 1B).

3.1.2. Resilient mice showed lower increases in KYN concentration in cerebellum

In order to determine if SD can modify TRP metabolism we measured TRP, KYN and 5-HT concentrations and their ratios in various brain areas (the cerebellum, limbic forebrain, striatum and hippocampus) and in plasma. In the cerebellum we found a reduction in TRP concentration [$F(2,31) = 10.84$, $p < 0.001$] after SD in both the susceptible and resilient groups (Fig. 2A), while KYN concentration [$F(2,31) = 160.2$, $p < 0.001$] was elevated in the same groups, although the increase was markedly greater in the SD-S group compared with the SD-R group ($p < 0.001$) (Fig. 2B). There were no changes in 5-HT concentration [$F(2,26) = 0.23$, $p = 0.78$] (Fig. 2C). Finally, we found an increase in the KYN/TRP ratio [$F(2,30) = 95.69$, $p < 0.001$] for both groups of socially defeated mice, and again the increase was markedly greater in the SD-S group compared with the SD-R group ($p < 0.001$) (Fig. 2D). The 5-HT/TRP ratio remained unchanged [$F(2,25) = 2.93$, $p = 0.071$] (Fig. 2E). No changes were found in the limbic forebrain (Supplementary Fig. 1), hippocampus (Supplementary Fig. 3), striatum (Supplementary Fig. 4), or plasma (Supplementary Fig. 2).

3.2. Effect of oxytocin treatment on socially defeated mice

3.2.1. Oxytocin treatment before social defeat normalized SWR and cocaine-induced CPP

The ANOVA of the SWR performed after the last SD in the group of mice treated with oxytocin showed an effect of Stress [$F(2,22) = 4.110$; $p < 0.033$] (see Fig. 3A). 13 defeated mice were classified as resilient (SWR higher than 1) and only 2 as susceptible. The post-hoc comparison failed to reveal statistically significant differences probably due to the small number of SD-S animals. For this reason, in the rest of the statistical analyses of oxytocin treated animals, only control and SD-R groups will be analyzed.

The ANOVA of the Conditioning Score did not show any effect of Stress [$F(1,19) = 0.168$; $p < 0.679$], meaning that there was no conditioning to cocaine in control or SD-R mice.

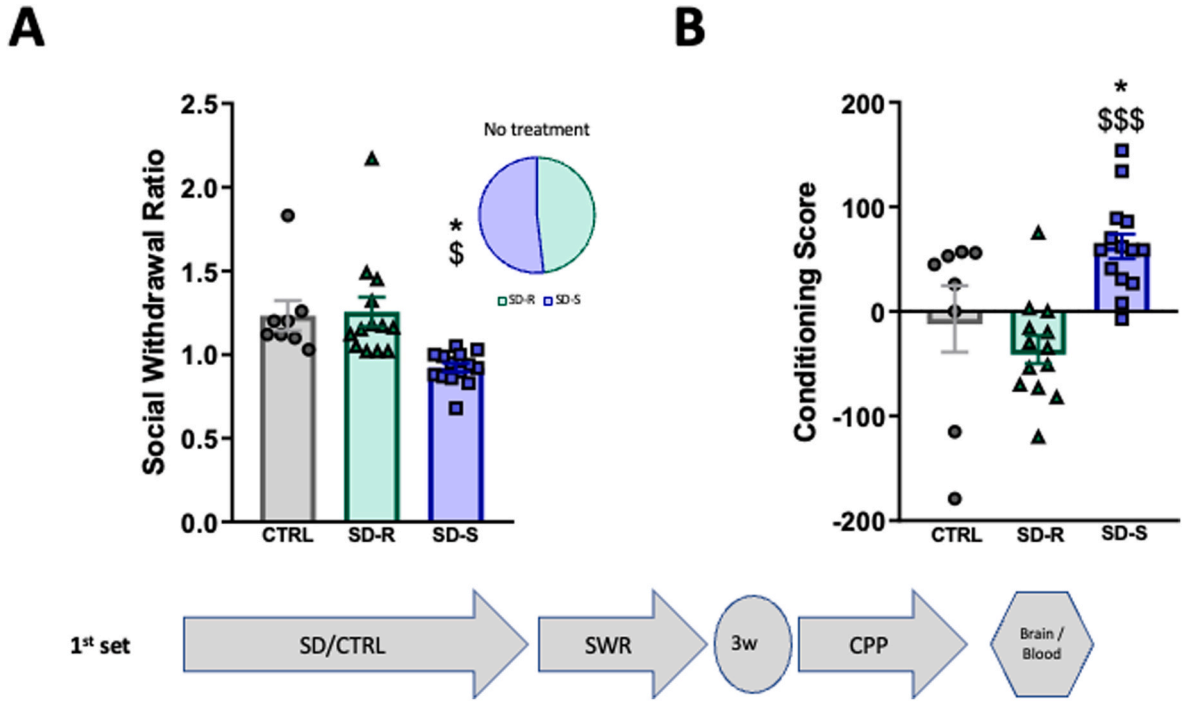


Fig. 1. Effect of repeated SD on SWR and Conditioning Score in C57BL/6 male mice. A) The bars represent the time spent in the social/object session in the interaction zone. Values > 1 indicate preference for social interaction and <1 indicate social avoidance (Golden et al., 2011). The p ie chart represents the percentage of resilient vs susceptible mice. B) The b ars represent the difference in time (s) spent in the compartment associated with the drug before and after conditioning sessions (Conditioning Score). Results are shown as mean ± S.E.M (n = 8–14). Bonferroni post-hoc test * $p < 0.05$, significant difference compared to CTRL group; $ $p < 0.05$, $$$ $p < 0.001$, significant difference compared to SD-R. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

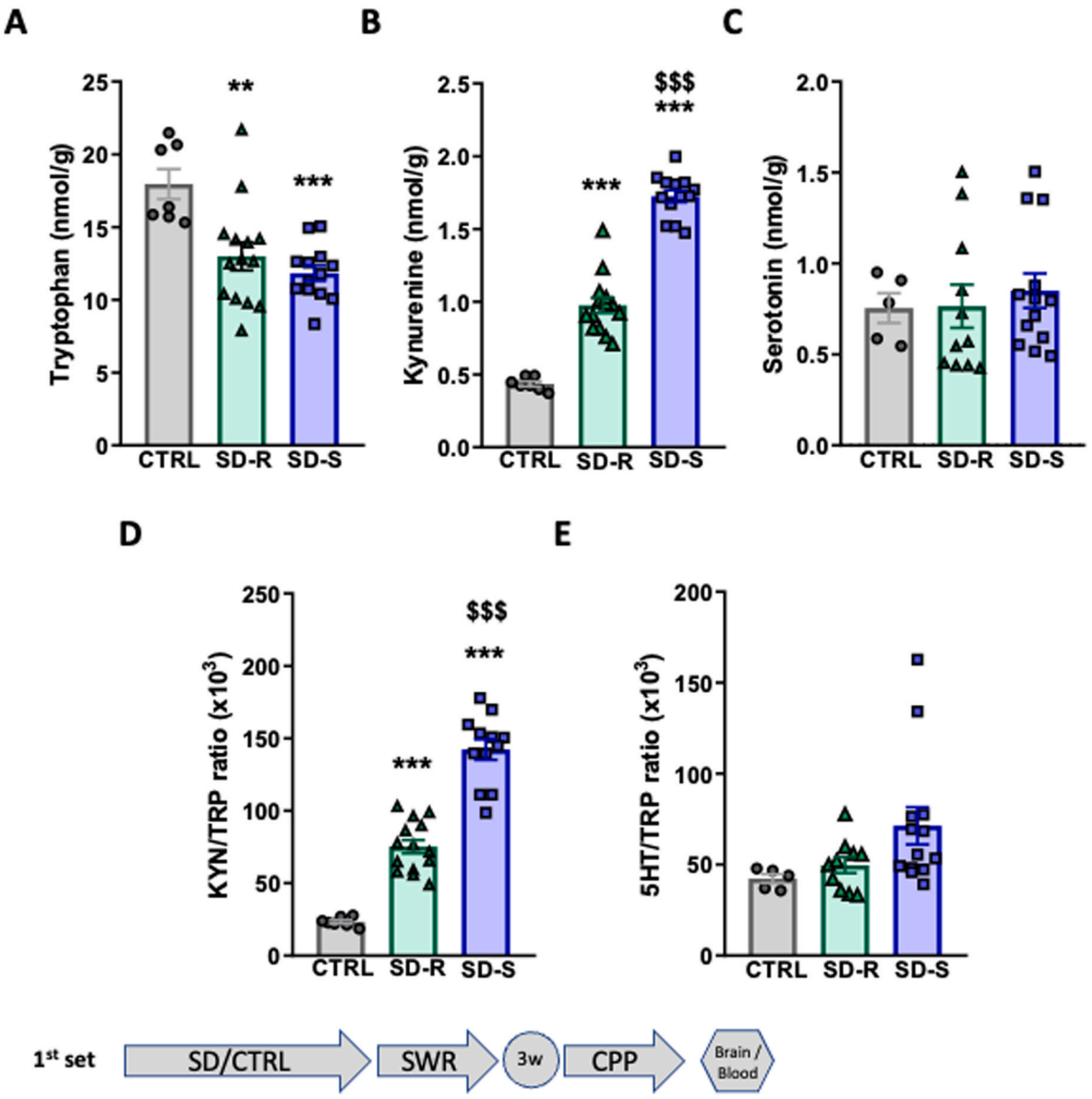


Fig. 2. Alterations in TRP metabolism in the cerebellum of mice after social defeat exposure. Graphs represent TRP (A), KYN (B) and serotonin (C) concentrations and KYN/TRP (D) and 5-HT/TRP (E) ratios. Results are shown as mean ± S.E.M (n = 8–12). Bonferroni post-hoc **p < 0.01, ***p < 0.001 different from CTRL; $$$p < 0.001, different from SD-S.

3.2.2. Effect of oxytocin treatment on TRP metabolism in cerebellum of socially defeated mice

In defeated animals treated with oxytocin, there were no changes in TRP concentration in the cerebellum (Fig. 4A; t(18) = 0.83, p = 0.412). However, Oxt-SD-R mice treated with oxytocin showed an increase in KYN concentration (Fig. 3B; t(17) = 5.865, p < 0.001). Regarding 5-HT, no changes were observed (Fig. 4C; t(17) = 1.101, p = 0.286). SD increased the KYN/TRP ratio (Fig. 4D; t(18) = 5.336, p < 0.001) in resilient mice (Oxt-SD-R). Finally, there were no changes in the 5-HT/TRP ratio following oxytocin administration (Fig. 4E; t(18) = 0.76, p = 0.45). In the limbic forebrain, SD increased 5-HT levels following oxytocin treatment (Supplementary Fig. 1B; t(18) = 2.247, p = 0.03). No changes were observed in the plasma (Supplementary Fig. 2).

3.3. Effect of indomethacin treatment on socially defeated mice

3.3.1. Indomethacin treatment before social defeat normalized cocaine-induced CPP

The ANOVA of the SWR performed after the last SD in the group of mice treated with indomethacin showed an effect of Stress [F(2,21) = 4.008; p < 0.036] (see Fig. 5A). 11 defeated mice were classified as SD-R (SWR higher than 1) and only 2 as SD-S. The post-hoc comparison revealed lower social scores among susceptible mice in comparison with CTRL or resilient animals (p < 0.05 in both cases). Due to the reduced number of susceptible animals, in the rest of the statistical analyses of indomethacin treated animals, only control and resilient groups will be analyzed.

The ANOVA of the Conditioning Score did not show any effect of Stress [F(1,19) = 2.783; p < 0.114], meaning that there was no conditioning to cocaine in control or resilient mice (see Fig. 5B).

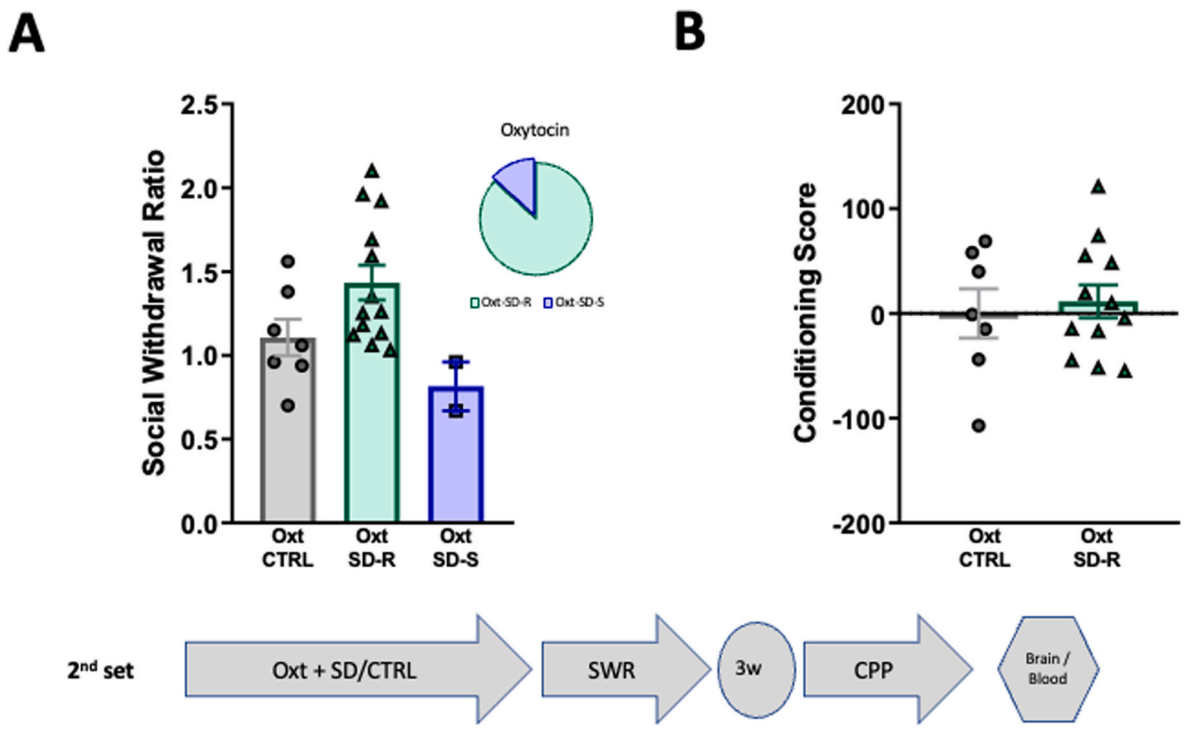


Fig. 3. Effect of oxytocin before each SD on SWR and Conditioning Score in C57BL/6 male mice. A) The bars represent the time spent in the social/object session in the interaction zone. Values > 1 indicate preference for social interaction and <1 indicate social avoidance (Golden et al., 2011). The p ie chart represents the percentage of resilient vs susceptible mice. B) The b ars represent the difference in time (s) spent in the compartment associated with the drug before and after conditioning sessions (Conditioning Score). Results are shown as mean ± S.E.M (n = 7–13). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

3.3.2. Effect of indomethacin treatment on TRP metabolism in the cerebellum of socially defeated mice

In the cerebellum, we found that in indomethacin-treated animals, SD produces a decrease in TRP concentration (Fig. 6A; $t(14) = 2.98$, $p < 0.01$) in the Ind-SD-R group and an increase in KYN concentration (Fig. 6B; $F(17) = 2.501$, $p < 0.02$) in the same group. Regarding 5-HT concentration no changes were observed (Fig. 6C; $t(14) = 1.711$, $p = 0.109$). A similar effect was observed in the KYN/TRP ratio as found in KYN concentration. SD increased the ratio in the resilient group (Ind-SD-R) (Fig. 6D; $t(15) = 2.56$, $p < 0.02$). In addition, the 5-HT/TRP ratio was elevated in the SD resilient group (Fig. 6E; $t(14) = 2.46$, $p < 0.02$). Regarding the limbic forebrain, we found an elevation in the KYN/TRP ratio in the Ind-SD-R group (Supplementary Fig. 1C; $t(18) = 2.169$, $p = 0.04$. Finally, we found no changes in the plasma (Supplementary Fig. 2).

3.4. Effect of environmental enrichment on socially defeated mice

3.4.1. Environmental enrichment before social defeat normalized cocaine-induced CPP

The ANOVA of the SWR performed after the last SD in the group of mice exposed to environmental enrichment showed an effect of Stress [$F(2,29) = 4.628$; $p < 0.019$] (see Fig. 7A). 12 defeated mice were classified as SD-R (SWR higher than 1) and 7 as SD-S. The post-hoc comparison revealed lower social scores among susceptible mice in comparison with CTRL or resilient animals ($p < 0.05$ in both cases).

The ANOVA of the Conditioning Score did not show any effect of Stress [$F(1,29) = 0.953$; $p < 0.339$] meaning that there was no conditioning to cocaine in control or resilient mice (see Fig. 7B).

3.4.2. Effect of environmental enrichment treatment on TRP metabolism in the cerebellum of socially defeated mice

In the cerebellum, we found that environmental enrichment in defeated mice did not induce changes in TRP concentration [$F(2,24) = 2.76$, $p = 0.08$] (Fig. 8A), with a slight reduction in KYN concentration [$F(2,23) = 5.96$, $p = 0.008$] in both socially defeated groups (EE-SD-R and EE-SD-S) in comparison with the CTRL group. This reduction is greater in the EE-SD-S ($p < 0.01$) group than EE-SD-R group ($p < 0.05$) (Fig. 8B). There were no changes in 5-HT concentration [$F(2,26) = 0.33$, $p = 0.71$] (Fig. 8C), the KYN/TRP ratio [$F(2,26) = 0.13$, $p = 0.87$] (Fig. 8D) or the 5-HT/TRP ratio [$F(2,24) = 2.23$, $p = 0.12$] (Fig. 8E). Finally, there were no changes in the limbic forebrain (Supplementary Fig. 1) or in the plasma (Supplementary Fig. 2) when mice were exposed to environmental enrichment.

4. Discussion

Our main results showed that resilience and susceptibility to SD are related to the KYN pathway in the cerebellum. Although SD increases KYN synthesis and the KYN/5-HT ratio in mice classified as resilient according to their depressive-like behavior and their lower response to cocaine-induced CPP, this increase is significantly lower than in susceptible mice, indicating that there is a link between the increased activity of the KYN pathway and the effects of SD. Both pharmacological interventions, oxytocin and indomethacin administration before SD, effectively augmented resilience to depressive-like behaviors and the increased conditioned cocaine reward, with practically all animals being classified as resilient. Accordingly, their KYN profile is consistent with that of the untreated resilient animals. Environmental enrichment before and during SD blocks the increased conditioned rewarding effects of cocaine, but surprisingly, only half of the animals were classified as resilient according to their SWR. Moreover, the SD-S and SD-R mice housed in EE conditions did not show any alteration of the KYN pathway, with KYN concentrations being similar to those in the CTRL group.

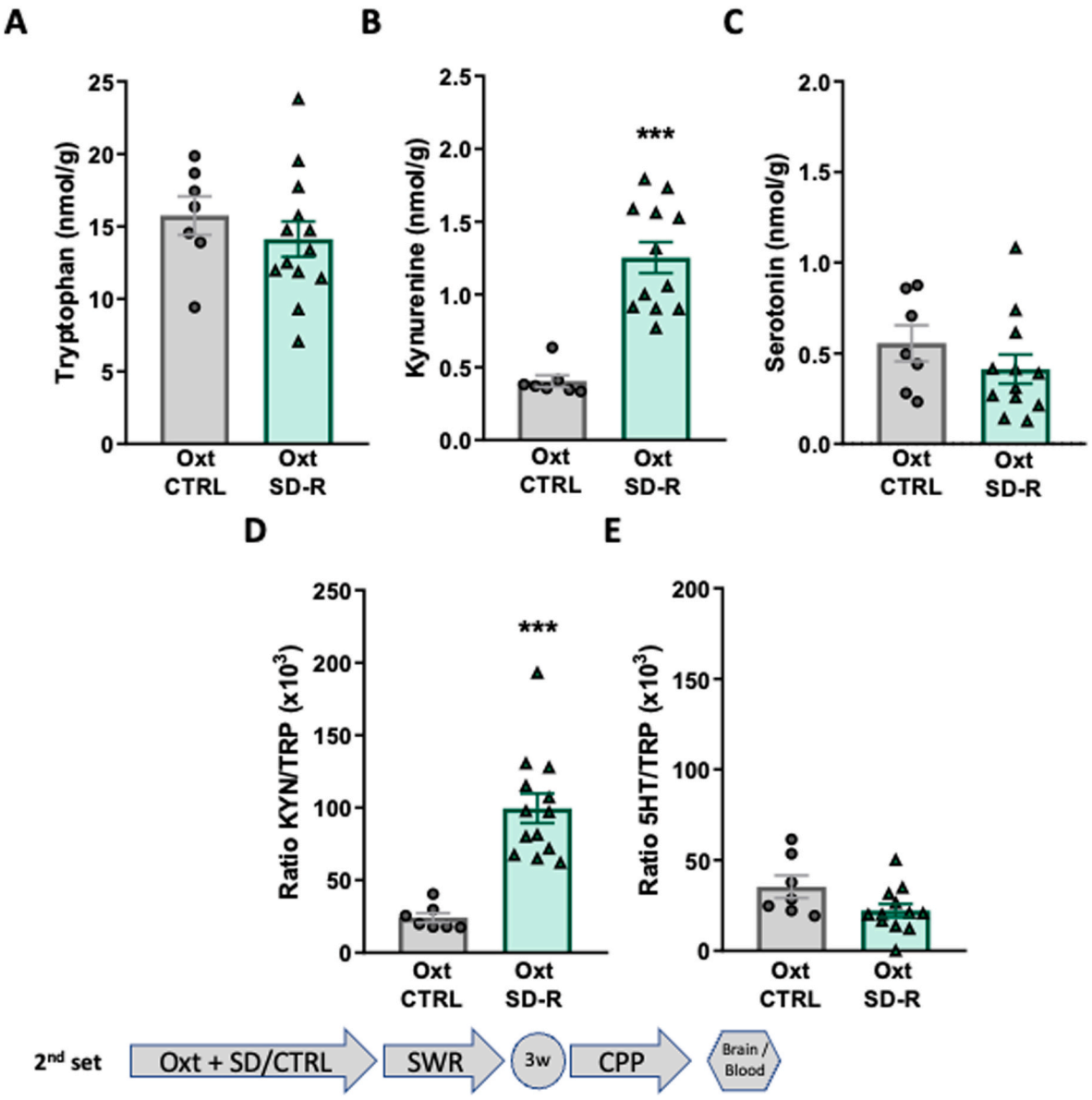


Fig. 4. Alterations in TRP metabolism in the cerebellum of mice after social defeat exposure and oxytocin treatment. Graphs represent TRP (A), KYN (B) and serotonin (C) concentrations and KYN/TRP (D) and 5-HT/TRP (E) ratios. Results are shown as mean ± S.E.M, (n = 7–13). Different from CTRL: ***p < 0.001.

4.1. Resilience to the increased conditioned rewarding effects of cocaine induced by SD

As we expected, SD induced an increase in the conditioned rewarding effects of cocaine only in those animals characterized as susceptible depending on the SWR (Ballestín et al., 2021). Numerous studies have shown that exposure to social stress induces a depressive-like phenotype characterized by, among other behaviors, social avoidance (Berton et al., 2006; Kudryavtseva et al., 1991; Rygula et al., 2005) The SWR when performed 24 h after the last SD is widely used as a reliable test to characterize resilience or susceptibility to stress-induced depressive-like behavior (Golden et al., 2011). In the present study, we confirmed that susceptible mice with an increased response to cocaine also have greater depressive-like behaviors, meaning that the susceptible or resilient response develops in several behavioral domains.

Many psychosocial factors can induce a successful response to stress, potentiating resilient responses and diminishing the appearance of psychiatric illnesses such as depressive disorder or substance use disorders. We are only starting to identify the neurobiological mechanisms underlying these protective factors. It is well known that facing your fears and presenting an active coping of stress is a positive strategy associated with a resilient response. Therefore, resilient mice showed active coping during social defeats with less time in defensive and submissive behavior than those susceptible (Ródenas-González et al., 2020; Ballestín et al., 2021). Social competence and social support effectively promote resilience (Masten and Coatsworth, 1998; Southwick et al., 2005) and, in line with this, oxytocin increases the value of social reward and reduces fear responses. In accordance with previous reports, oxytocin administered before each SD was capable of blocking the SD-induced increase in the conditioned cocaine reward, thereby potentiating resilience (Ferrer-Pérez et al., 2018; Reguilón et al., 2020). Moreover, in the present study, oxytocin resilient mice to cocaine reward also showed resilience to depressive-like behaviors (Oxt-SD-R, measured by SWR), since only 13% of the defeated mice were characterized as susceptible (Oxt-SD-S, n = 2) according to their SWR. Therefore, oxytocin administration prior to SD potentiates resilience to depressive-like behaviors and the increase of the rewarding effects of

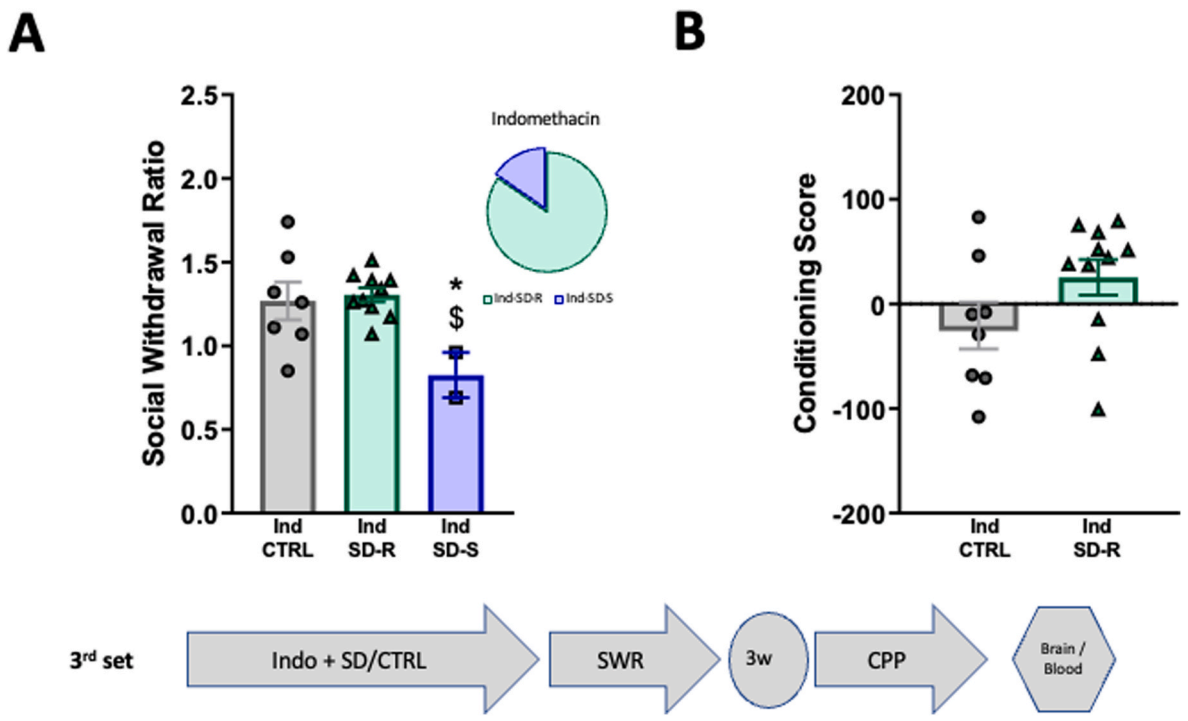


Fig. 5. Effect of indomethacin before each SD on SWR and Conditioning Score in C57BL/6 male mice. A) The bars represent the time spent in the social/object session in the interaction zone. Values > 1 indicate preference for social interaction and <1 indicate social avoidance (Golden et al., 2011). The p ie chart represents the percentage of resilient vs susceptible mice. B) The b ars represent the difference in time (s) spent in the compartment associated with the drug before and after conditioning sessions (Conditioning Score). Results are shown as mean ± S.E.M (n = 7–11). Bonferroni post-hoc test * $p < 0.05$, significant difference compared to CTRL group; $ $p < 0.05$, significant difference compared to SD-R. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

cocaine. Based on these and other results found in the literature, oxytocin can be considered a promising target to buffer the effects of social stress due to its anti-stress potential. Several studies have explored the use of exogenous oxytocin to treat depressive or anxiogenic symptoms derived from exposure to social stress, although they revealed important discrepancies and gender differences (Dodhia et al., 2014; Luo et al., 2017; Schwaiger et al., 2019; Ferrer-Pérez et al., 2021).

Comparable results were obtained with the anti-inflammatory drug indomethacin. Numerous studies indicated that social stress induces activation of the immune system, modulating peripheral and central cytokine and chemokine levels, and inducing microglial activation, among other inflammatory responses (Hodes et al., 2014; Pfau and Russo, 2016; Montagud-Romero et al., 2018). We already know that treatment with indomethacin before each stress episode reversed the increase in the rewarding effects of cocaine in defeated mice and prevented the enhancement of plasmatic and striatal levels of IL-6 (Ferrer-Pérez et al., 2018). Here, in addition to confirming this protective role of indomethacin, we showed a similar effect on the development of depressive-like behaviors induced by SD. Only 2 defeated mice were classified as susceptible (Ind-SD-S, 15%) according to SWR. Hence, as with oxytocin, indomethacin administration prior to SD also potentiates resilience to depressive-like behaviors and the increase of the rewarding effects of cocaine. Indomethacin is a non-steroidal anti-inflammatory drug frequently used in many inflammatory conditions (Lucas, 2016). Our results point to a new application of this drug.

Environmental conditions are powerful determinants of animal behavior and well-being. (McQuaid et al., 2018). In laboratory facilities, mice used to be housed under standardized conditions that contributed to more homogenous interlaboratory subject environments (Toth et al., 2011). EE usually consists of social housing in larger cages with increased environmental complexity that promotes physical activity through interaction with items and materials that can be manipulated and used for species typical behaviors, such as hiding and nesting (McQuaid et al., 2018). These environments have been traditionally related to an enhanced psychological and physiological well-being, increased cognitive functioning (He et al., 2017; Li et al., 2017) and improved brain recovery (McDonald et al., 2018). EE has also been reported to enhance stress resilience (Aujnarain et al., 2018; Camarini et al., 2018), being effective in protecting against the physiological and behavioral maladaptive effects of chronic and acute stress (Bahi, 2017). For example, mice rehoused in EE conditions after physical stress (restraint) or social stress (chronic subordinate colony) were protected against the anxiolytic effects of these stress experiences (Ashokan et al., 2016; Bahi, 2017). Moreover, EE also reduced drug seeking and stress-induced reinstatement of cocaine self-administration (Chauvet et al., 2009), modulating the increase of ethanol intake and ethanol-induced CPP (Bahi, 2017). In our study, we showed that exposure to EE before and during SD was capable of blocking the increase in cocaine conditioned reward, although it did not affect SD-induced depressive-like behaviors. In contrast to defeated mice pretreated with oxytocin or indomethacin, among those exposed to EE, 7 mice were characterized as susceptible according to SWR (EE-SD-S, 37%), close to the 52% of susceptible mice observed under standard housing conditions (SD-S). However, regardless of being resilient or susceptible according to their SWR, none of the defeated mice exposed to EE developed preference for cocaine, meaning that EE effectively blocked the increased conditioned reward of cocaine. Therefore, EE housing potentiated resilience to the increase of the rewarding effects of cocaine but it did not affect depressive-like behaviors induced by SD. The available literature indicates the clear benefits of enriched environments in buffering stress. In line with preclinical studies showing that housing under EE prevents epigenetic changes induced by SD (Seo et al., 2021), a supportive family environment during childhood also prevents cellular and epigenetic changes due to stressful experiences (Brody et al., 2016; Merrill et al., 2019).

To sum up, we confirmed that SD induced resilience/susceptibility to

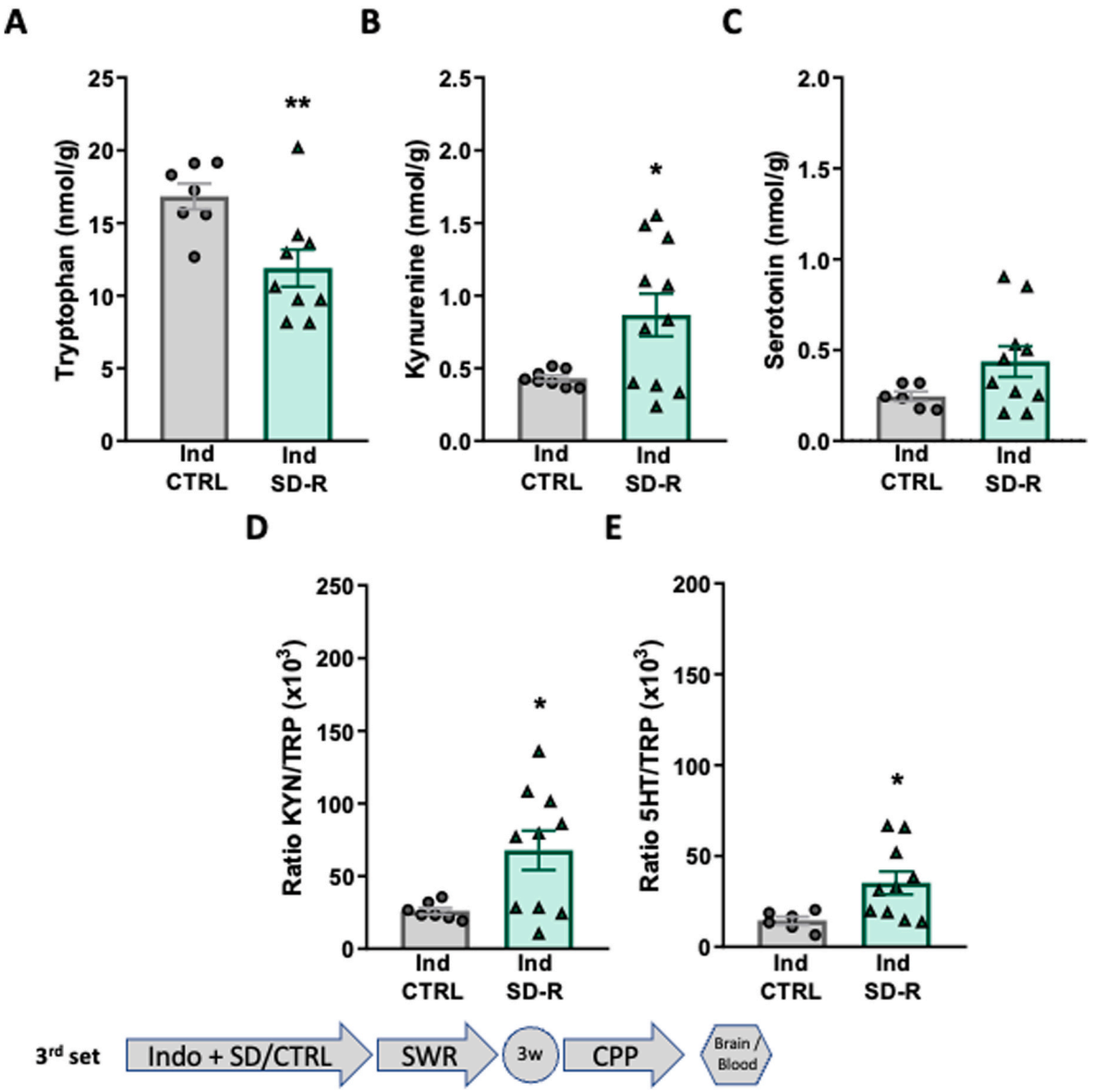


Fig. 6. Alterations in TRP metabolism in the cerebellum after social defeat exposure and indomethacin treatment. Graphs represent TRP (A), KYN (B) and serotonin (C) concentrations and KYN/TRP (D) and 5-HT/TRP (E) ratios. Results are shown as mean ± S.E.M, n = 7–10. Different from CTRL: *p < 0.05, **p < 0.01.

cocaine reward and depressive-like behaviors, with resilience being potentiated by oxytocin or indomethacin administration prior to each SD. Housing in an EE prior to and during SD also potentiated resilience to the increased cocaine reward while no effects were observed on depressive-like behaviors.

4.2. *KYN pathway modulates resilience to social defeat stress effects*

SD has been previously described as inducing a long-lasting increase in the central and peripheral KYN pathways (Fuertig et al., 2016). These increases have also been associated with inflammation-induced depressive-like behaviors in mice (O'Connor et al., 2009; Walker et al., 2013). Our results confirmed that SD increases the activity of the KYN pathway in the cerebellum, without changes in that of the limbic forebrain, hippocampus, striatum or plasma. In addition to employing an intermittent SD procedure, our study was designed to evaluate the long-lasting changes in the KYN pathway induced by SD after cocaine exposure. This design can explain the lack of changes observed in plasmas and most of the brain structures in comparison with the results obtained in other studies employing a more intense protocol of SD and measuring KYN signaling shortly after the last stress experience.

SD in the cerebellum decreased TRP, and increased KYN levels, consequently increasing the KYN/TRP ratio. However, although these results appeared in all defeated mice, those classified as resilient (SD-R; Oxt-SD-R; Ind-SD-R and EE-SD-R) presented a significantly smaller increase in KYN levels and KYN/TRP ratio than susceptible animals. We have shown for the first time that animals resilient to depressive-like behaviors and resistant to cocaine increased reward show a less intense affectation of the KYN pathway, linking KYN production to susceptibility to SD effects. A limitation of this study is the lack of quantification of other KYN pathway metabolites. This fact makes it unclear if SD regulates downstream metabolites such as kynurenic acid or quinolinic acid and the extent of the contribution that these metabolites can exert in the effects of SD in the brain. Further research is needed to answer these questions and to elucidate the effect of SD over other metabolites of this metabolic pathway.

Moreover, the pharmacological and environmental interventions effective at blocking the SD effects also confirmed the link between KYN and resilience/susceptibility. Although resilient mice treated with oxytocin or indomethacin presented a significant increase in KYN levels

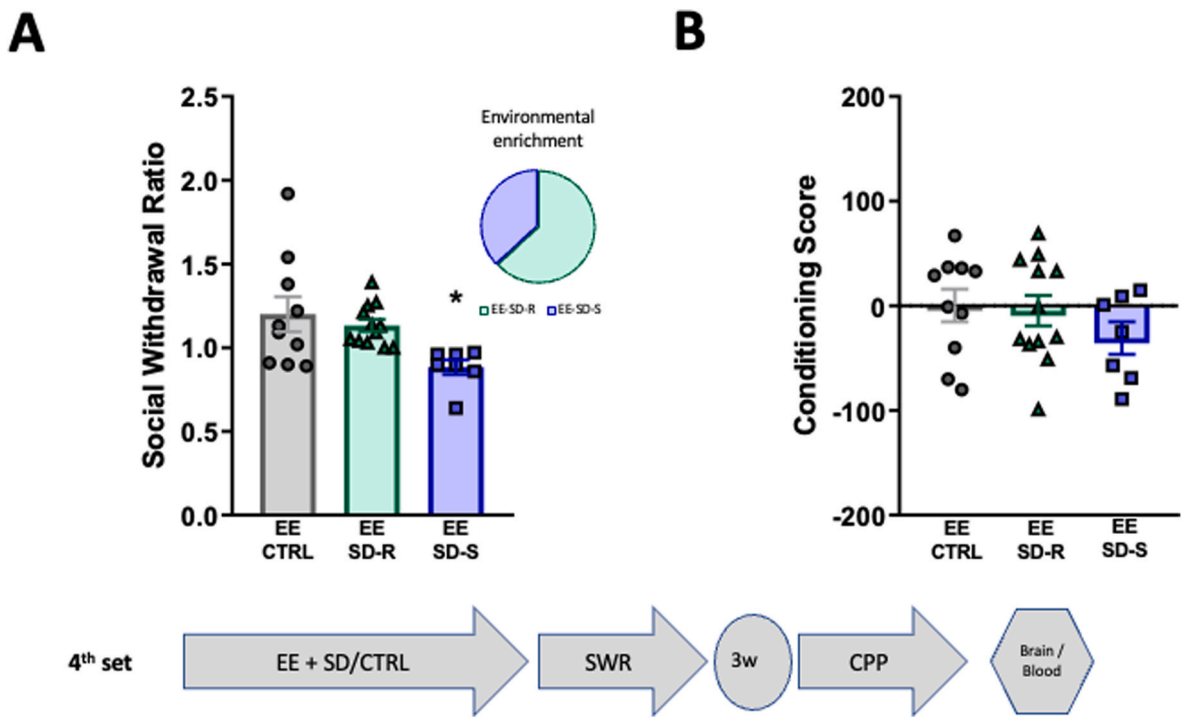


Fig. 7. Effect of environmental enrichment before SD on SWR and Conditioning Score in C57BL/6 male mice. A) The bars represent the time spent in the social/object session in the interaction zone. Values > 1 indicate preference for social interaction and values < 1 indicate social avoidance (Golden et al., 2011). The p ie chart represents the percentage of resilient vs susceptible mice. B) The b ars represent the difference in time (s) spent in the compartment associated with the drug before and after conditioning sessions (Conditioning Score). Results are shown as mean ± S.E.M (n = 7–12). Bonferroni post-hoc test * $p < 0.05$, significant difference compared to CTRL group. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

or their KYN/TRP ratio (Oxt-SD-R; Ind-SD-R), this increment was lower than that observed in susceptible mice (SD-S). Furthermore, environmental enrichment is capable of blocking all the changes in the KYN pathway, even decreasing KYN levels (EE-SD-R). Due to the well-known potentiating effect of neuroinflammation on KYN production through IDO1 activation (O'Connor et al., 2009; Walker et al., 2013), we propose that the decreased neuroinflammatory response described in resilient mice could be responsible for the lesser activation of the KYN pathway.

The question remains as to why all the differences in the KYN pathway have been observed only in the cerebellum. The relationship between KYN levels in the blood and brain is well established in the literature and, in general, changes that occur in the periphery are also seen in the brain (Schwarcz et al., 2012). Despite this, our data suggest that under certain conditions it is possible to find differences in the KYN pathway between the brain and the serum, an interesting idea since it opens the door to the possibility of region-specific regulation of the KYN pathway as shown in the present work. Evidence in this direction has been previously observed. For example, it is well established that KYN concentration or the KYN/TRP ratio can change in the brain but not in the plasma 24 h after an LPS injection (Larsson et al., 2016). Moreover, there is evidence that peripheral LPS administration induces brain region-dependent changes in the balance of KYN metabolites (Parrott et al., 2016).

Although classically the cerebellum is a brain structure associated with control of motor function, numerous reports associate this structure with the control of language, spatial and emotional processing, reward, working memory, or executive functions (Watson et al., 2014; Wagner et al., 2017; Carta et al., 2019). The cerebellum exerts a direct control over the VTA (Watabe-Uchida et al., 2012; Carta et al., 2019), suggesting it modulates brain functions that might be altered in drug addiction (Miquel et al., 2016). In agreement with results showing cerebellar activation after the presentation of drug-related cues in drug addicts (Grant et al., 1996), only the mice that developed cocaine-induced CPP exhibited an increased activity at the apical region of the cerebellar vermis (Carbo-Gas et al., 2014, 2017). Gil-Miravet and co-workers proposed that the cerebellum exerts a tonic inhibitory control over the VTA, which, upon inhibition, promotes drug conditioning (Gil-Miravet et al., 2021). How KYN pathway metabolites can alter the tonic inhibitory control that the cerebellum exerts over the VTA remains unclear but there is evidence that GABA release by GABAergic interneurons in the cerebellum reduces the activity of the cerebellum (Rossi et al., 2003). The presence of NMDA receptors and α7 nicotinic receptors on these GABAergic neurons (Buhler and Dunwiddie, 2002; Nugent et al., 2007) suggests the possible involvement of KYN pathway metabolites, such as KYNA, in altering GABAergic transmission. Thus, we can hypothesize that KYN acts by inhibiting glutamatergic projections from the cerebellum to the VTA and NAc, disrupting cocaine-induced CPP via a GABA-dependent mechanism in the cerebellum.

Oxytocin and indomethacin both alter the KYN pathway possibly by decreasing inflammatory markers that stimulate IDO1. Thus, oxytocin is known to suppress LPS-induced inflammation and reduces cytokines such as IL-1β (Inoue et al., 2019; Yuan et al., 2016), which induces IDO1 (Hu et al., 1995). Similarly, indomethacin inhibits COX, reducing the levels of prostaglandin E2, which stimulates IDO1 (Nalamachu and Wortmann, 2014).

EE is the most efficient intervention regulating the KYN pathway, with a reduction in KYN after this housing condition. Other interventions such as exercise also reduce KYN levels (Zimmer et al., 2019). EE produces a decrease in several pro-inflammatory cytokines and an increase in anti-inflammatory cytokines (Jurgens and Johnson, 2012; McQuaid et al., 2013). IDO1 is tightly regulated by both pro- and anti-inflammatory cytokines and it is reasonable that EE produces its effects via a decrease in IDO1 activity. Furthermore, EE reduces stress (De Almeida et al., 2018) and TDO is regulated by glucocorticoids (Keaton et al., 2019; Venancio et al., 2019). Thus, it is possible that the

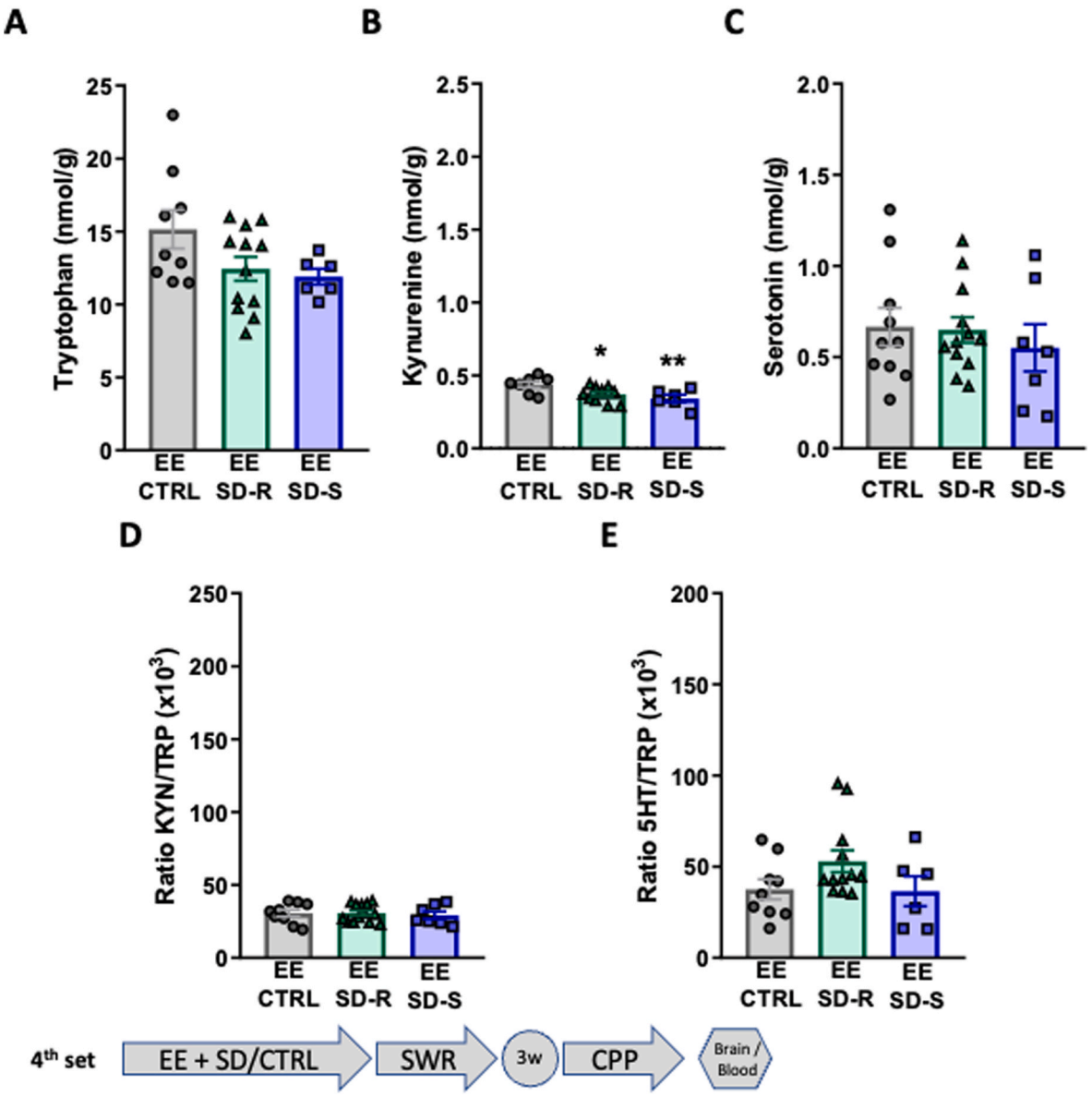


Fig. 8. Alterations in TRP metabolism in the cerebellum after social defeat exposure and environmental enrichment. Graphs represent TRP (A), KYN (B) and serotonin (C) concentrations and KYN/TRP (D) and 5-HT/TRP (E) ratios. Results are shown as mean ± S.E.M (n = 6–12). Different from CTRL: *p < 0.05, **p < 0.01.

effect of EE over the KYN pathway involves both IDO1 and TDO. In addition, EE has been linked to stimulating functional changes and promoting neuroplastic processes that include increased levels of brain-derived neurotrophic factor (BDNF), neurogenesis and synaptogenesis (Dandi et al., 2018; Gong et al., 2018; Monteiro et al., 2014).

5. Conclusions

The study of the mechanisms explaining the development of depression and vulnerability to drug addiction after exposure to social stress is a very attractive field that opens up a wide range of real innovations. Research in this field provides valuable targets for the development of new drugs, although the effects of SD in females still remain poorly studied. As with the studies showing that neuroinflammation is a key factor in the development of depression or SUDs after social stress, the present study highlights the role of the KYN pathway and anti-inflammatory drugs acting on TRP metabolism as pharmacological targets to potentiate resilience to social stress effects.

Funding sources

This work was supported by the Ministerio de Economía y Competitividad, Dirección General de Investigación, (PSI, 2017-83023-R); Ministerio de Ciencia e Innovación (SAF2016-78864-R and PID2019-105847RB-I00), Ministerio de Sanidad, Consumo y Bienestar Social [PNSD 2017I017 and 2019I025], and Universidad Complutense de Madrid (910258). Instituto de Salud Carlos III, Red de Trastornos Adictivos (RTA; RETICS RD16/0017/0007; RD16/0017/0021) and Unión Europea, Fondos FEDER "A way to build Europe".

CRediT authorship contribution statement

Pablo Giménez-Gómez: Software, Formal analysis, Investigation, Data curation, Writing – original draft, Visualization. **Raúl Ballestín:** Methodology, Software, Formal analysis, Investigation, Data curation, Writing – original draft, Visualization. **Leticia Gil de Biedma-Elduayen:** Methodology, Investigation. **Rebeca Vidal:** Methodology, Formal analysis. **Carmen Ferrer-Pérez:** Formal analysis, Investigation,

Visualization. **Marina D. Reguilón:** Formal analysis, Investigation, Writing – original draft. **Esther O'Shea:** Formal analysis, Investigation. **José Miñarro:** Conceptualization, Resources, Writing – review & editing, Supervision, Project administration, Funding acquisition. **María Isabel Colado:** Conceptualization, Resources, Writing – original draft, Writing – review & editing, Supervision, Project administration, Funding acquisition. **Marta Rodríguez-Arias:** Conceptualization, Methodology, Resources, Writing – original draft, Writing – review & editing, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

This work has not been published previously and is not under consideration for publication elsewhere. The authors have no possible conflict of interest in the carrying out and reporting of this research.

Acknowledgements

We wish to thank Guillem Chuliá for his English language editing.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuropharm.2021.108753.

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