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Cannabinoids differentially modulate cortical information transmission through the sensorimotor or medial prefrontal basal ganglia circuits

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Background and Purpose: In the sensorimotor (SM) and medial prefrontal (mPF) basal ganglia (BG) circuits, the cortical information is transferred to the *substantia nigra pars reticulata* (SNr) through the hyperdirect trans-subthalamic pathway and through the direct and indirect trans-striatal pathways. The cannabinoid CB_1 receptor, which is highly expressed in both BG circuits, may participate in the regulation of motor and motivational behaviours. Here, we investigated the modulation of cortico-nigral information transmission through the BG circuits by cannabinoids.

Experimental Approach: We used single-unit recordings of SNr neurons along with simultaneous electrical stimulation of motor or mPF cortex in anaesthetized rats.

Key Results: Cortical stimulation elicited a triphasic response in the SNr neurons from both SM and mPF-BG circuits, which consisted of an early excitation (hyperdirect transmission pathway), an inhibition (direct transmission pathway), and a late excitation (indirect transmission pathway). In the SM circuit, after Δ^9-tetrahydrocannabinol or WIN 55,212-2 administration, the inhibition and the late excitation were decreased or completely lost, whereas the early excitation response remained unaltered. However, cannabinoid administration dramatically decreased all the responses in the mPF circuit. The CB_1 receptor antagonist AM251 (2 mg·kg^{-1}, i.v.) did not modify the triphasic response, but blocked the effects induced by cannabinoid agonists.

Conclusions and Implications: CB_1 receptor activation modulates the SM information transmission through the trans-striatal pathways and profoundly decreases the cortico-BG transmission through the mPF circuit. These results may be relevant for elucidating the involvement of the cannabinoid system in motor performance and in decision making or goal-directed behaviour.

Abbreviations: BG, basal ganglia; CV, coefficient of variation; mPF, medial prefrontal; SM, sensorimotor; SNr, *substantia nigra pars reticulata*; Δ^9-THC, Δ^9-tetrahydrocannabinol

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1 | INTRODUCTION

The basal ganglia (BG), which consist of the striatum, the external and internal *globus pallidus*, the subthalamic nucleus (STN), and the *substantia nigra pars reticulata* (SNr), are a highly organized network of subcortical nuclei that connects the cortex with the thalamus, creating the cortico-BG-thalamo-cortical loop circuits. In these complex circuits, cortical information is transferred to the output structures of the BG, SNr, and internal *globus pallidus* (equivalent to the entopeduncular nucleus in rodents) through three different pathways: (a) the hyperdirect trans-subthalamic pathway, (b) the direct trans-striatal pathway, and (c) the indirect trans-striatal pathway (Maurice, Deniau, Glowinski, & Thierry, 1999). Moreover, different anatomo-functional BG circuits can be distinguished according to the origin of cortical information they process. In rodents, the main distinction can be made between medial prefrontal (mPF) and sensorimotor (SM) BG circuits. While the SM circuits are important for appropriate motor functions, the mPF circuits play an important role in decision making, goal-directed behaviour, emotions, motivation, and cognition (G. E. Alexander, DeLong, & Strick, 1986; Haber, 2003; Parent & Hazrati, 1995). Abnormal functionality of these circuits has been described in motor and behavioural disorders and cognitive deficits (for review, see Tremblay, Worbe, Thobois, Sgambato-Faure, & Féger, 2015), and it has been related to the mechanism of action of some drugs, such as cannabinoids that also affect motor and cognitive functions. The use of cannabis is associated with deficits in working memory and decision making (related to mPF circuitry functionality; Grant, Gonzalez, Carey, Natarajan, & Wolfson, 2003; Schreiner & Dunn, 2012; Solowij & Battisti, 2008), as well as with alterations in sensory perception or impaired SM gating (related to dysfunctional processing in SM circuits; Broyd et al., 2013; Edwards, Skosnik, Steinmetz, O'Donnell, & Hetrick, 2009).

Cannabinoids regulate the strength of excitatory and inhibitory synaptic transmission in the mPF and SM-BG circuits via the activation of **CB_1** receptors, which are located pre-synaptically in the mPF and motor cortex (Freund, Katona, & Piomelli, 2003; Harkany, Mackie, & Doherty, 2008) and on glutamatergic corticostriatal projections (for review, see Morera-Herreras et al., 2016). The cortical expression of the CB_1 receptor is heterogenic, being higher in the mPF cortex than in the motor cortex (Heng, Beverley, Steiner, & Tseng, 2011). Similarly, striatal CB_1 receptor expression shows regional variations, displaying minimal levels in ventromedial areas and displaying the highest expression in dorso and ventrolateral territories (Julian et al., 2003; Mailleux & Vanderhaeghen, 1992; Van Waes, Beverley, Siman, Tseng, & Steiner, 2012). According to these observations, Van Waes et al. (2012) found an inverse relationship between cortical and striatal CB_1 receptor expression in the SM and the mPF circuits. In the SM circuits, there is a high striatal and low cortical CB_1 expression, and in contrast, in the mPF circuits, CB1 expression is low in striatum and high in the cortical region. CB_1 receptors have also been observed in striatal projections to the *globus pallidus* and the SNr and on subthalamonigral and subthalamopallidal terminals (for review, see Morera-Herreras et al., 2016). Therefore, the effect of cannabinoids may vary depending on the cortico-BG pathway they affect more. In addition, we have previously shown, by using in vivo recording techniques, that systemic cannabinoid agonist administration inhibits subthalamic neurons recorded in the area related to the motor circuits but stimulates neurons located in associative/limbic territories (Morera-Herreras, Ruiz-Ortega, Taupignon, et al., 2010; Morera-Herreras, Ruiz-Ortega, & Ugedo, 2010). In mice, the cannabinoid receptor agonist **WIN 55,212-2** induces long-term depression (a form of plasticity that is key to motor learning and habit formation; Jin & Costa, 2015) in the *nucleus accumbens* but does not induce long-term depression in the dorsolateral striatum (Zhang, Feng, & Chergui, 2015). Moreover, in healthy humans, **Δ^9-tetrahydrocannabinol** (Δ^9-THC) modulates dopamine transmission in the limbic striatum but not in other striatal subdivisions (Bossong et al., 2015). Nevertheless, at present, the specific cannabinoid regulation of cortico-BG transmission through cortical-BG circuits is unknown.

The present study further investigated the modulatory role of the CB_1 receptor on cortical information transfer in both circuits. For this purpose, the effect of pharmacological agents targeting the CB_1 receptor on the transmission of SM and mPF cortical information to SNr neurons was studied by performing extracellular single-unit recordings in anaesthetized rats. Our results show that cannabinoids activating the CB_1 receptor hamper the SM information transfer through the trans-striatal pathways and dramatically reduce the cortico-BG transmission through the mPF circuit.

What is already known

- Different anatomo-functional basal ganglia (BG) circuits exist according to the cortical information they process.
- The cannabinoid CB_1 receptor is expressed and modulates BG nuclei activity.

What this study adds

- CB_1 receptors modulate cortical information transmission through the sensorimotor and medial prefrontal circuits of the BG.
- CB_1 receptors differentially modulate the cortical information transfer through both circuits.

What is the clinical significance

- The sensorimotor and medial prefrontal circuits are known to function abnormally in several disorders.
- Understanding the CB_1 receptor-mediated modulation of the BG may contribute to the development of therapies based on cannabinoids.

2 | METHODS

2.1 | Animals

Male Sprague–Dawley rats (250–325 g, RRID:RGD_70508) were housed in groups of four under standard laboratory conditions (22 ± 1°C, 55 ± 5% relative humidity, and 12:12 hr light/dark cycle) with food and water provided ad libitum. Every effort was made to minimize animal suffering and to use the minimum number of animals per group and experiment. Animal studies are reported in compliance with the ARRIVE guidelines (Kilkenny et al., 2010) and with the recommendations made by the *British Journal of Pharmacology*. The experimental protocols were reviewed and approved by the Local Ethical Committee for Animal Research of the University of the Basque Country (UPV/EHU, CEEA, Ref. ES48/054000/6069). All of the experiments were performed in accordance with the European Community Council Directive on "The Protection of Animals Used for Scientific Purposes" (2010/63/EU) and with Spanish Law (RD 53/2013) for the care and use of laboratory animals. A total of 177 animals were used in the present study for the characterization of the spontaneous and cortically-evoked activity of SNr neurons, 87 for recording in the SM circuits, and 90 for recording in the mPF circuits. For the pharmacological studies, cannabinoid drugs were administered to 32 of the 87 rats for recording in the SM, and in 57 of the 90 rats for recording in the mPF.

2.2 | Electrophysiological procedures

The electrophysiological procedures are schematically illustrated in Figure 1. The animals were anaesthetized with chloral hydrate (420 mg·kg^{-1} [i.p.] for induction, followed by continuous administration [i.p.] of chloral hydrate at a rate of 115.5 mg·kg^{-1}·hr^{-1} using a peristaltic pump to keep a steady level of anaesthesia). For additional drug administration, the right jugular vein was cannulated. The animal body temperature was maintained at ~37°C for the entire experiment with a heating pad connected to a rectal probe. The rat was placed in a stereotaxic frame with its head secured in a horizontal orientation. The skull was exposed, and two 3-mm burr holes were drilled over the right SNr and the ipsilateral motor or mPF cortex.

Single-unit extracellular recordings were made by an Omegadot single glass micropipette, pulled with an electrode puller (Narishige Scientific Instrument Lab., PE-2, Japan), broken back to a tip diameter of 1–2.5 μm under a light microscope and filled with 2% pontamine sky blue in 0.5% sodium acetate. This electrode was lowered into the SM (5.8 mm posterior to Bregma, 2.5 mm lateral to midline, and 7–8 mm ventral to the dura mater) or mPF region (5.4 mm posterior to Bregma, 1.8 mm lateral to midline, and 7–8 mm ventral to the dura mater) of the SNr. The signal from the electrode was amplified with a high-input impedance amplifier and then monitored on an oscilloscope and on an audio-monitor. SNr neurons were identified as non-dopaminergic by their classically defined electrophysiological characteristics: thin spikes (width, <2 ms) and ability to present relatively high-frequency discharges without a decrease in spike amplitude (as described in Aristieta, Ruiz-Ortega, Miguelez, Morera-Herreras, & Ugedo, 2016). Neuronal spikes were digitized using computer software (CED micro 1401 interface and Spike2 software [version 7], Cambridge Electronic Design, UK). The basal firing rate (FR) was recorded for 5 min. Although multiple neurons were recorded in each animal in order to characterize the spontaneous and cortically evoked activity in both SM and mPF territories, only one SNr cell was pharmacologically studied per animal.

Firing parameters such as FR and coefficient of variation (CV) of SNr neurons were analysed offline using Spike2 software (version 7). Burst-related parameters such as the number of bursts, mean duration of burst, number of spikes per burst, recurrence of bursts, and intraburst frequency were analysed during time epochs of 150 s applying a Spike2 script ("surprise.s2 s"), based on the Poisson surprise algorithm.

2.2.1 | Stimulation procedures

The motor cortex (3.5 mm anterior to Bregma, 3.2 mm lateral to midline, and 1.6 mm ventral to the dura mater) or the mPF cortex (2.9 mm anterior to Bregma, 0.6 mm lateral to midline, and 1.7 ventral to the dura mater) ipsilateral to the recording site was stimulated at 1 Hz (pulse width, 600 μs; intensity, 1 mA) using coaxial stainless-steel electrodes (diameter, 250 μm; tip diameter, 100 μm; tip-to-barrel distance, 300 μm; Cibertec S.A.).

As described previously (Maurice et al., 1999), cortical stimulation evokes characteristic triphasic responses in SNr cells consisting of a combination of an early excitation, inhibition, and/or late excitation. Peristimulus time histograms were generated from 180 stimulation trials using 1-ms bins. The criterion used to determine the existence of an excitatory response was set at an increase of twofold the SD, plus the mean of the number of spikes compared with the pre-stimulus frequency, for at least three consecutive bins. The amplitude of excitatory responses was quantified by calculating the difference between the mean number of spikes evoked within the time window of the excitation and the mean number of spikes occurring spontaneously before the stimulation. The duration of an inhibitory response corresponded to the time interval during which no spikes were observed, for at least three consecutive bins.

2.3 | Statistical analysis of data

The data and statistical analysis comply with the recommendations of the *British Journal of Pharmacology* on experimental design and analysis in pharmacology (Curtis et al., 2018). The experimental data, proceeding only from stimulation-responding neurons, was analysed using the computer program GraphPad Prism (v. 5.01, GraphPad Software, Inc; RRID:SCR_002798). As more than one neuron (one to three per rat) was recorded per animal in the characterization of the SM and mPF circuits, electrophysiological parameters such as FR, CV, burst-related parameters (i.e., number, duration, and spikes per burst, recurrence of burst, and intraburst frequency) and

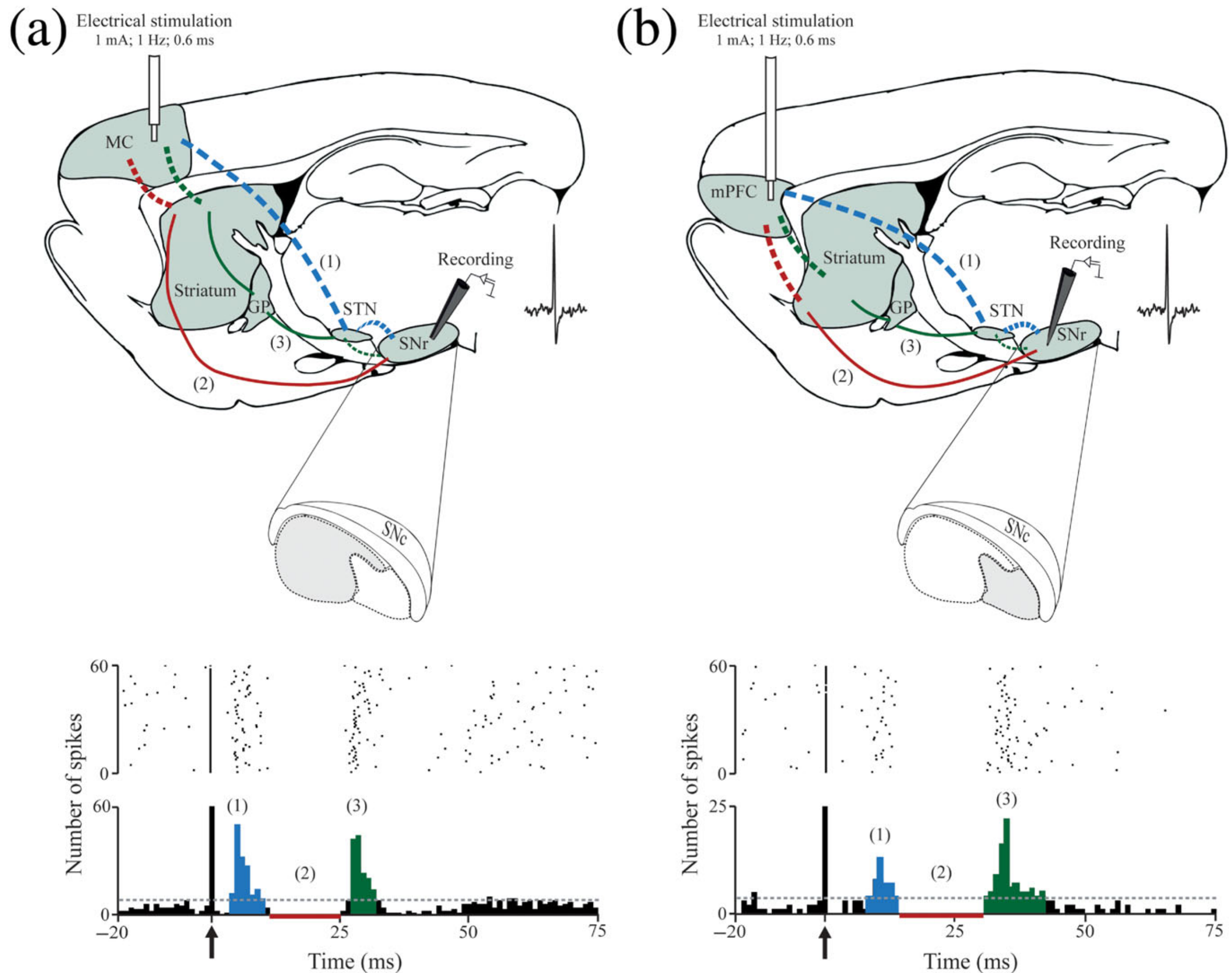

FIGURE 1 Illustration of the in vivo electrophysiological experiments in anaesthetized rats showing the SM and mPF circuits of the BG. (a) and (b) Top: schematic parasagittal sections of a rat brain showing the cortex and the BG nuclei (striatum, external *globus pallidus* [GP], STN and SNr. (a) Motor cortex (MC) or (b) mPF cortex (mPFC) was stimulated at 1 Hz (pulse width, 0.6 ms; intensity, 1 mA), and simultaneously, single-unit recordings were obtained in the corresponding anatomo-functional subdivisions of the SNr ([a] lateral part of the SNr [SM-SNr] or [b] medial part of the SNr [mPF-SNr]). Dashed lines represent glutamatergic projections and blunt line GABAergic projections. (a) and (b) Bottom: raster plot and peristimulus time histogram showing the characteristic cortically-evoked triphasic response in SNr neurons: (1)-blue: early excitation (activation of hyperdirect pathway [cortex-subthalamus-SNr]); (2)-red: inhibition (activation of direct pathway [cortex-striatum-SNr]), and (3)-green: late excitation (activation of indirect pathway [cortex-striatum-external GP-subthalamus-SNr]). Arrows indicate the time the stimulus was applied. SNc: *substantia nigra pars compacta*

parameters related to cortically-evoked responses (i.e., duration, latency, and amplitude of the responses) were averaged per animal, so that every animal had one value for each electrophysiological parameter. Averages from each rat FR, CV, and cortically-evoked related parameters were analysed by Student's two-tailed unpaired *t* test when looking for differences between SM and mPF circuits. To assess differences in the number of rats with burst firing neurons, Fisher's exact test was used. Parameters related to bursting activity were analysed using the Mann–Whitney rank sum test or, when necessary, Student's two-tailed unpaired *t* test. To assess the effects of the drugs (WIN 55,212-2 or Δ^9-THC), Student's two-tailed paired *t* test was used to compare the mean values of FR, CV, and parameters related to cortically-evoked responses, before and after drug application (one neuron per animal). To study the effect of cannabinoid drugs on burst activity, Fisher's exact test was used to assess differences in the number of rats with burst firing, before and after drug administration. To analyse the burst-related parameters before and after drug application, Wilcoxon matched-pairs signed rank test was used and, when necessary, Student's two-tailed paired *t* test.

To determine the role of the CB_1 receptor in the effect of cannabinoid drugs the mean values of FR, CV, and cortically-evoked responses before AM251, post-AM251 and post-AM251 + WIN 55,212-2 or Δ^9-THC were compared using a repeated-measures one-way ANOVA (one cell per animal). To determine if there was any difference in the number of rats with burst firing, chi-squared

test was used. To assess whether these drugs were altering the burst-related parameters of these neurons or not, the Friedman test was used and, when necessary, a repeated-measures one-way ANOVA. To determine whether the drugs were affecting the SM or mPF circuits cortically-evoked responses differently, a repeated-measures two-way ANOVA was performed. The level of statistical significance was set at $P < 0.05$. Data are presented as group means ± SEM of n rats.

2.4 | Drugs

Δ^9-THC (CAS no. 1972-08-3) was a generous gift from GW Pharmaceuticals Ltd. (Salisbury, UK). WIN 55,212-2 (CAS no. 131543-23-2) and chloral hydrate (CAS no. 302-17-0) were obtained from Sigma (Madrid, Spain). **AM251** (CAS no. 183232-66-8) was obtained from Tocris Bioscience (Spain). Δ^9-THC, WIN 55,212-2, and AM251 were diluted in 1:1:18 cremophor/ethanol/saline solution, and chloral hydrate was prepared in 0.9% saline. Drugs were freshly prepared immediately prior to use.

2.5 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Harding et al., 2018), and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18 (S. P. Alexander et al., 2017).

3 | RESULTS

3.1 | Firing properties and burst activity of SNr neurons

GABAergic neurons within the SNr display typical electrophysiological characteristics, that is, a narrow spike waveform and a relatively high firing rate with a regular pattern of discharge. To ensure the cells recorded cells belong to their corresponding nigral circuits (SM-SNr or mPF-SNr), only those responding to cortical stimulation were used in the analysis. Neurons meeting these criteria were recorded from a total of n = 177 animals, among which n = 87 were in the SM-SNr and n = 90 in the mPF-SNr. Their firing and burst activity properties are summarized in Table 1.

The firing pattern of the neurons from these two SNr territories was different. A larger percentage of mPF-SNr neurons exhibited bursting discharge in comparison to SM-SNr neurons. Consistently, the number and duration of bursts, as well as the recurrence of burst displayed by mPF-SNr neurons, was shown to be significantly higher than the number and duration of bursts, as well as the recurrence of burst, observed for the SM-SNr neurons.

TABLE 1 Firing properties of neurons from the SM and mPF subdivisions of the SNr

	SM-SNr (n = 87)	mPF-SNr (n = 90)
Firing rate (Hz)	25.2 ± 0.9	22.8 ± 0.9
Coefficient of variation (%)	47.0 ± 1.9	48.3 ± 2.2
Burst firing neurons/recorded neurons	39/87	74/90
Neurons exhibiting burst firing pattern (%)	44.8	82.2*
Number of bursts	12.4 ± 2.8	21.7 ± 3.0*
Duration of burst (ms)	0.6 ± 0.1	0.9 ± 0.1*
Number of spikes per burst	20.3 ± 3.5	23.2 ± 2.7
Recurrence of burst (number of burst·min^{-1})	4.1 ± 0.9	8.7 ± 1.2*
Intraburst frequency (spikes·s^{-1})	49.1 ± 2.8	45.5 ± 2.0

Note: Each value represents the mean ± SEM of n recorded rats.

*$P < 0.05$ versus SM-SNr (neurons exhibiting burst firing pattern: Fisher's exact test; burst parameters: Mann–Whitney rank sum test).

3.2 | Cortically-evoked responses of SNr neurons

According to previous publications (Aliane, Pérez, Nieoullon, Deniau, & Kemel, 2009; Kolomiets, Deniau, Glowinski, & Thierry, 2003; Maurice et al., 1999), cortical stimulation of the motor or mPF cortex evoked responses in the SNr neurons that consisted of an early excitation, followed by an inhibition and a late excitation, forming a characteristic triphasic response (bottom of Figure 1). The presence of the early excitation is attributable to the activation of the so-called “hyperdirect” cortico-subthalamo-nigral pathway. The activation of the “direct” cortico-striato-nigral pathway produces the observed inhibition, and the late excitation derives from the activation of the “indirect” cortico-striato-pallido-subthalamo-nigral pathway (Maurice et al., 1999). Different patterns of response were observed in both SNr territories, yielding triphasic, biphasic, and monophasic responses from the activation of the different pathways along the circuits. The percentage of occurrence of such patterns of responses in SM-SNr and mPF-SNr neurons is shown in Figure 2a.

Regarding the parameters analysed for each of the responses such as latency of appearance, duration of inhibition, and amplitude of the excitations, the major differences between the circuits were observed in the latency (Figure 2b). In the mPF circuit, the appearance of all three responses was significantly delayed in comparison to the SM circuit, as indicated by an increased latency (SM vs. mPF: 5.6 ± 0.4 vs. 8.5 ± 0.4 ms; 13.4 ± 0.3 vs. 21.2 ± 0.5 ms; 27.6 ± 0.7 vs. 34.5 ± 0.8 ms for early excitation, inhibition, and late excitation, respectively, $P < 0.05$, Student's two-tailed unpaired t test). Moreover, the duration of the inhibition was greater in the SM circuit than in the mPF circuit (SM vs. mPF; 15.0 ± 0.9 vs. 9.7 ± 0.6 ms, $P < 0.05$, Student's two-tailed unpaired t test).

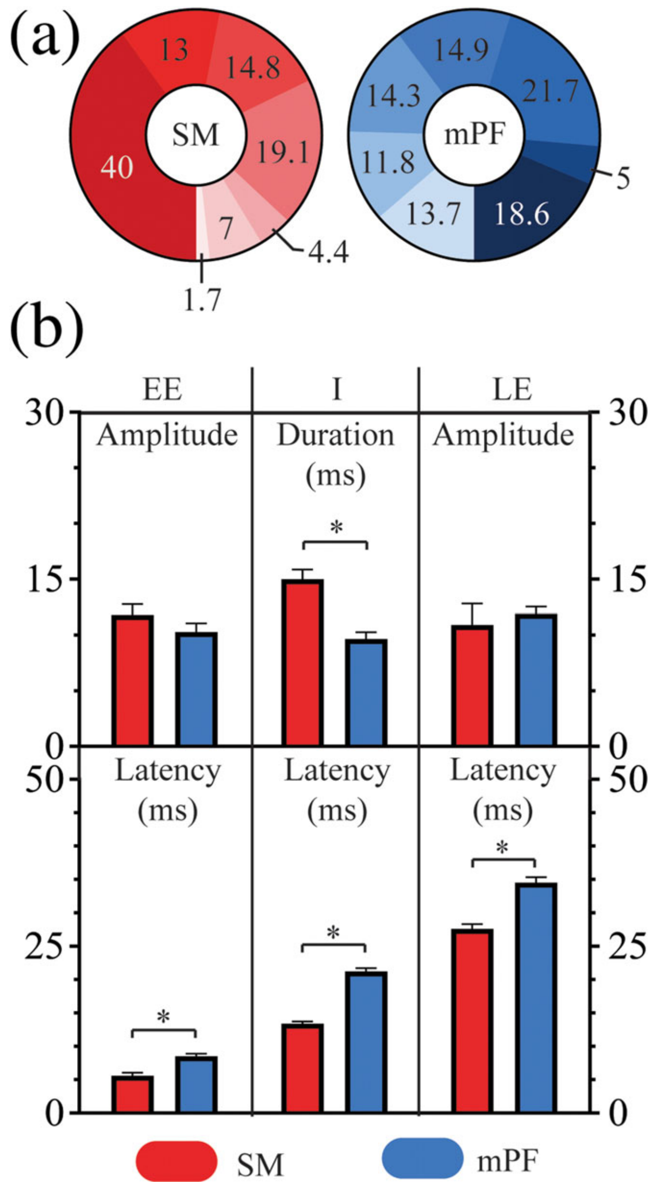

FIGURE 2 Patterns of responses evoked in the SNr neurons by cortical stimulation in SM- and mPF-BG circuits. (a) Percentage of occurrence of the different patterns of responses evoked in SNr cells by the cortical stimulation (EE: early excitation [SM: n = 70; mPF: n = 54]; I: inhibition [SM: n = 72; mPF: n = 67]; LE: late excitation [SM: n = 68; mPF: n = 77]). From darker to lighter colours: EE + I + LE; EE + I; I + LE; EE + LE; EE; I; LE. (b) Characteristics of the responses (latency, amplitude of excitations, and duration of the inhibition). Note that the duration of the inhibitions is shown to be shorter in the mPF circuit, whereas the appearance of all three responses is delayed when compared with the SM circuit, as a higher latency is observed. Each bar represents the mean ± SEM of n rats. *P < 0.05, Student's two-tailed unpaired t test

3.3 | Effects of cannabinoids on cortically-evoked activity in SNr neurons

We further explored the effect of the synthetic CB_1/CB_2-receptor full agonist, WIN 55,212-2, and the natural cannabinoid CB_1/CB_2-partial agonist, Δ^9-THC, on cortically-evoked responses of SNr cells identified as receiving input from the mPF or motor cortex. The doses of the cannabinoid agonists used in this study were carefully selected to minimize any effects on the firing activity of SNr neurons, which could make the analysis of the cortically-evoked responses difficult.

3.3.1 | Effect of WIN 55,212-2 on cortically-evoked activity in SNr neurons

Systemic administration of WIN 55,212-2 (125 μg·kg^{-1}, i.v., SM: n = 7; mPF: n = 17) modulated the transmission of cortical information through the hyperdirect pathway in the SM and mPF circuits differently (Figure 3). In the SM circuit, WIN 55,212-2 did not alter the early excitation (basal amplitude: 18.0 ± 5.6; after WIN 55,212-2: 12.0 ± 2.6; P > 0.05, Student's paired t test). However, in the mPF circuit, WIN 55,212-2 significantly reduced the amplitude of this response, in 80% (eight of 10) of rats (basal amplitude: 9.9 ± 2.6; after WIN 55,212-2: 3.6 ± 1.7; P < 0.05, paired Student's two-tailed t test). Transmission through the direct pathway was significantly diminished in both circuits, as shown by a reduction in the duration of the inhibitory component of the response (Figure 3). Thus, in the SM circuit, 100% of the rats tested showed a reduced transmission through the direct pathway (basal duration: 15.0 ± 1.5; after WIN 55,212-2: 4.4 ± 2.1; P < 0.05, Student's two-tailed paired t test). A similar reduction of transmission occurred in the mPF circuit, where 85% (11 of 13) of rats exhibited a significant reduction in the duration of its inhibitory component, after administration of this cannabinoid agonist (basal duration: 11.8 ± 2.3; after WIN 55,212-2: 2.4 ± 1.4; P < 0.05, Student's two-tailed paired t test). Transmission through the "indirect" cortico-striato-pallido-subthalamo-nigral pathway was also reduced in both circuits after WIN 55,212-2 injection (Figure 3). In the case of the SM circuit, 83% (five of six) of the rats tested experienced a reduction in the late excitatory component of the response (basal amplitude: 8.5 ± 1.7; after WIN 55,212-2: 2.9 ± 1.8; P < 0.05, Student's two-tailed paired t test). In the same way, 64% (seven of 11) of rats showed a reduction in the amplitude of this response in mPF-SNr neurons (basal amplitude: 10.7 ± 2.2; after WIN 55,212-2: 5.5 ± 2.1; P < 0.05, Student's two-tailed paired t test). At the dose administered, WIN 55,212-2 did not modify rats SNr neuronal firing rate in either of the two regions studied (SM-SNr: 18 ± 9% over baseline; mPF-SNr: 17 ± 11% over baseline, P > 0.05, Student's two-tailed paired t test, Table S1).

In all of the rats tested, the effects induced by WIN 55,212-2 on the cortico-nigral transmission through these two BG circuits were effectively blocked by pretreatment with the selective CB_1 receptor antagonist AM251 (2 mg·kg^{-1}, i.v., SM: n = 9; mPF: n = 11; Figure 4). Moreover, AM251 did not modify the cortico-nigral information transfer by itself (P > 0.05, repeated-measures one-way ANOVA for early excitation, inhibition, and late excitation in both circuits; Figure 4). Additionally, no changes in the spontaneous activity of SNr cells were found after administration of AM251 in the rats tested (Table S2).

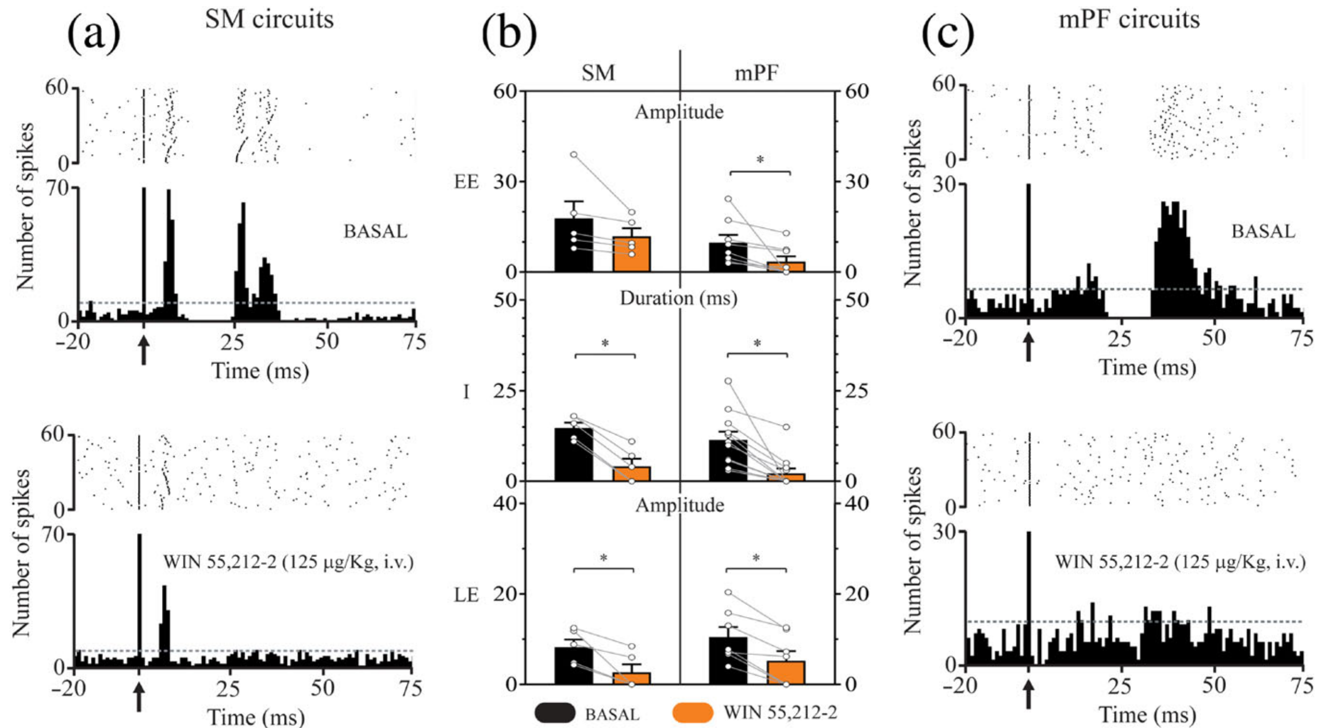

FIGURE 3 Effect of systemic administration of WIN 55,212-2 (125 μg·kg^{-1}, i.v.) on cortico-nigral information transmission in SM and mPF BG circuits. (a) Top: raster plot and peristimulus time histogram showing a representative example of a triphasic response evoked in a SNr neuron by stimulation of the motor cortex in basal condition. Bottom: after WIN 55,212-2 injection, the inhibitory and late excitatory components disappeared, with the early excitation remaining unaltered. Arrows indicate a stimulation artefact. (c) Top: raster plot and peristimulus time histogram showing a representative example of a triphasic response evoked in a SNr neuron by stimulation of the mPF cortex under basal conditions. Bottom: in this circuit, WIN 55,212-2 injection was able to dramatically reduce transmission through all three pathways. Arrows indicate a stimulation artefact. (b) Bar graphs showing the mean effect of WIN 55,212-2 (125 μg·kg^{-1}, i.v.) on cortically-evoked responses in SNr neurons (amplitude of early [EE; SM: n = 5; mPF: n = 8] and late [LE; SM: n = 5; mPF: n = 7] excitations and duration of inhibition (I; SM: n = 5; mPF: n = 11]) in SM and mPF circuits. Each bar represents the mean ± SEM of n rats. Each dot represents the value from one neuron before and after drug administration. *P < 0.05, Student's two-tailed paired t test

3.3.2 | Effect of Δ^9-THC on cortically-evoked activity in SNr neurons

I.v. administration of Δ^9-THC (0.5 mg·kg^{-1}) profoundly affected the cortically-evoked activity of SNr neurons (Figure 5, SM: n = 11; mPF: n = 15). The transmission through the hyperdirect pathway appeared to be significantly reduced in both circuits after Δ^9-THC administration. In the case of the SM circuit, a reduction in the amplitude of the early excitation was observed in 70% (seven of 10) of the rats tested (basal amplitude: 9.9 ± 2.2; after Δ^9-THC: 6.3 ± 1.9; P < 0.05, Student's two-tailed paired t test), whereas the early excitation was completely abolished in 63% (five of eight) of the rats for the mPF circuit (basal amplitude: 7.7 ± 1.8; after Δ^9-THC: 0 ± 0; P < 0.05, Student's two-tailed paired t test). The Δ^9-THC effect on the information transmission through the hyperdirect pathway resulted in a significant difference between circuits, with changes caused in the early excitation being larger in the mPF circuit than in the SM circuit (P < 0.05, repeated-measures two-way ANOVA).

Moreover, i.v. administration of Δ^9-THC was shown to significantly reduce transmission through the direct pathway in both circuits since a reduction in the duration of the inhibitory response was found (Figure 5). In the SM circuit, a reduction in the inhibitory response was observed in 83% (five of six) of rats (basal duration: 12.5 ± 1.3; after Δ^9-THC: 1.8 ± 1.8; P < 0.05, Student's two-tailed paired t test). The same pattern of response was seen in the mPF circuit, with 63% (five of eight) of rats displaying a reduction in the duration of the inhibitory component of the response (basal duration: 11.7 ± 2.9; after Δ^9-THC: 2.8 ± 2.8; P < 0.05, Student's two-tailed paired t test). A disruption in information transmission was also observed through the indirect pathway in both circuits, as seen by a reduction in the amplitude of the late excitation after Δ^9-THC administration (Figure 5). For the SM circuit, this reduction in the late excitation was observed in 67% (six of nine) of the rats tested (basal amplitude: 15.8 ± 3.0; after Δ^9-THC: 5.4 ± 2.3; P < 0.05, Student's two-tailed paired t test). Similarly, in the mPF circuit, 82% (nine of 11) of rats showed a reduction in the late excitatory response (basal amplitude: 15.2 ± 3.0; after Δ^9-THC: 2.6 ± 1.5; P < 0.05, Student's two-tailed paired t test). The dose of Δ^9-THC used in this study was not able to change the spontaneous firing rate in either the SM-SNr or the mPF-SNr neurons of the rats tested (SM: 3 ± 12% over baseline; mPF: 0.3 ± 11% over baseline, P > 0.05, Student's two-tailed paired t test, Table S1).

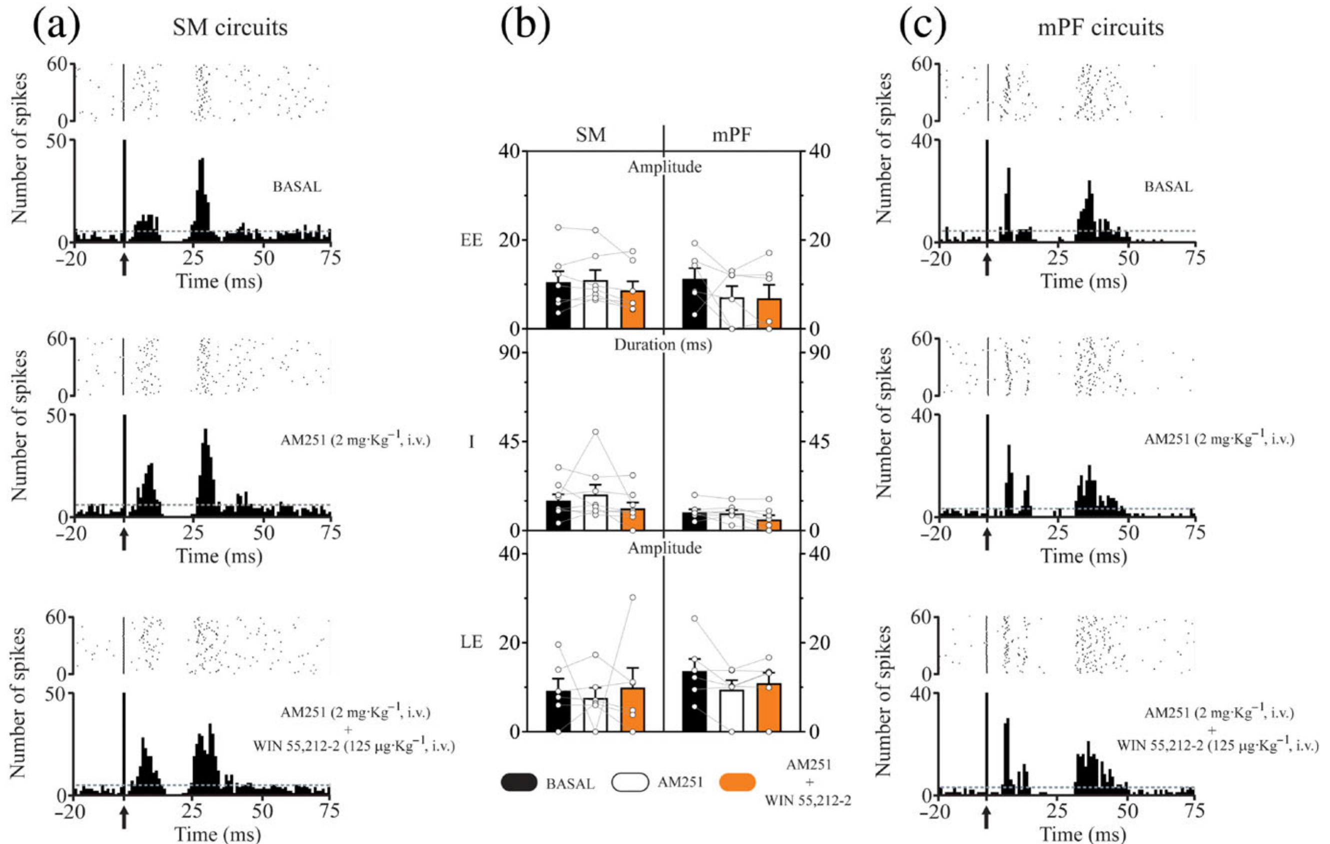

FIGURE 4 Blockade of WIN 55,212-2-induced effects on cortico-nigral information transmission in SM and mPF BG circuits by pretreatment with the selective CB_1 antagonist AM251 (2 mg·kg^{-1}, i.v.). (a) Top: raster plot and peristimulus time histogram showing a representative example of a triphasic response evoked in a SNr neuron by stimulation of the motor cortex under basal conditions. AM251 administration did not modify the characteristics of the three components of the cortically-evoked response (middle) but blocked the effects induced by WIN 55,212-2 (bottom). Arrows indicate a stimulation artefact. (c) Top: raster plot and peristimulus time histogram showing a representative example of a triphasic response evoked in a SNr neuron by stimulation of the mPF cortex under basal conditions. As in an SM circuit, AM251 administration did not modify the characteristics of the cortically-evoked triphasic response (middle) but blocked the effects mediated by WIN 55,212-2 (bottom). Arrows indicate a stimulation artefact. (b) Bar graphs showing the mean effect of AM251 (2 mg·kg^{-1}, i.v.) and WIN 55,212-2 (125 μg·kg^{-1}, i.v.) on cortically-evoked responses in SNr neurons (amplitude of early [EE; SM: n = 7; mPF: n = 6] and late [LE; SM: n = 6; mPF: n = 6] excitations and duration of inhibition [I; SM: n = 8; mPF: n = 7]) in SM and mPF circuits. Each bar represents the mean ± SEM of n rats. Each dot represents the value from one neuron before and after drug administration

According to the results obtained with WIN 55,212-2, in all of the rats tested, the effects of Δ^9-THC administration on the cortico-nigral transmission through the SM- and mPF-BG circuits were blocked by pretreatment with AM251 (2 mg·kg^{-1}, i.v., SM: n = 5; mPF: n = 14; Figure 6). As we have previously demonstated, in these experiments, AM251 also did not alter the cortically-evoked responses (P > 0.05, repeated-measures one-way ANOVA for early excitation, inhibition, and late excitation in both circuits; Figure 6). Furthermore, AM251 did not change the spontaneous activity of the SNr neurons recorded (Table S2).

4 | DISCUSSION

In the present study, we analysed the role of the CB_1 receptor in cortico-nigral information transmission through the SM and mPF circuits of the BG. The results show that the activation of CB_1 receptors by the administration of the agonists, WIN 55,212-2 or Δ^9-THC, modulates them differently. While the cortico-nigral information transmission was almost completely abolished via direct and indirect trans-striatal pathways in both circuits, transmission via the trans-subthalamic pathway was only impaired in the mPF circuit, whereas that in the SM circuit was unaltered.

4.1 | Spontaneous activity and cortically-evoked responses of SNr neurons from SM and mPF territories

The present results show that the neurons recorded in mPF-SNr region had a more irregular firing pattern than those recorded in the SM-SNr region, displaying a greater number of cells exhibiting a burst firing pattern. These differences may be due to the different glutamatergic input that these two regions receive. It is important to note that SNr neuronal burst activity is mediated mainly by stimulation of

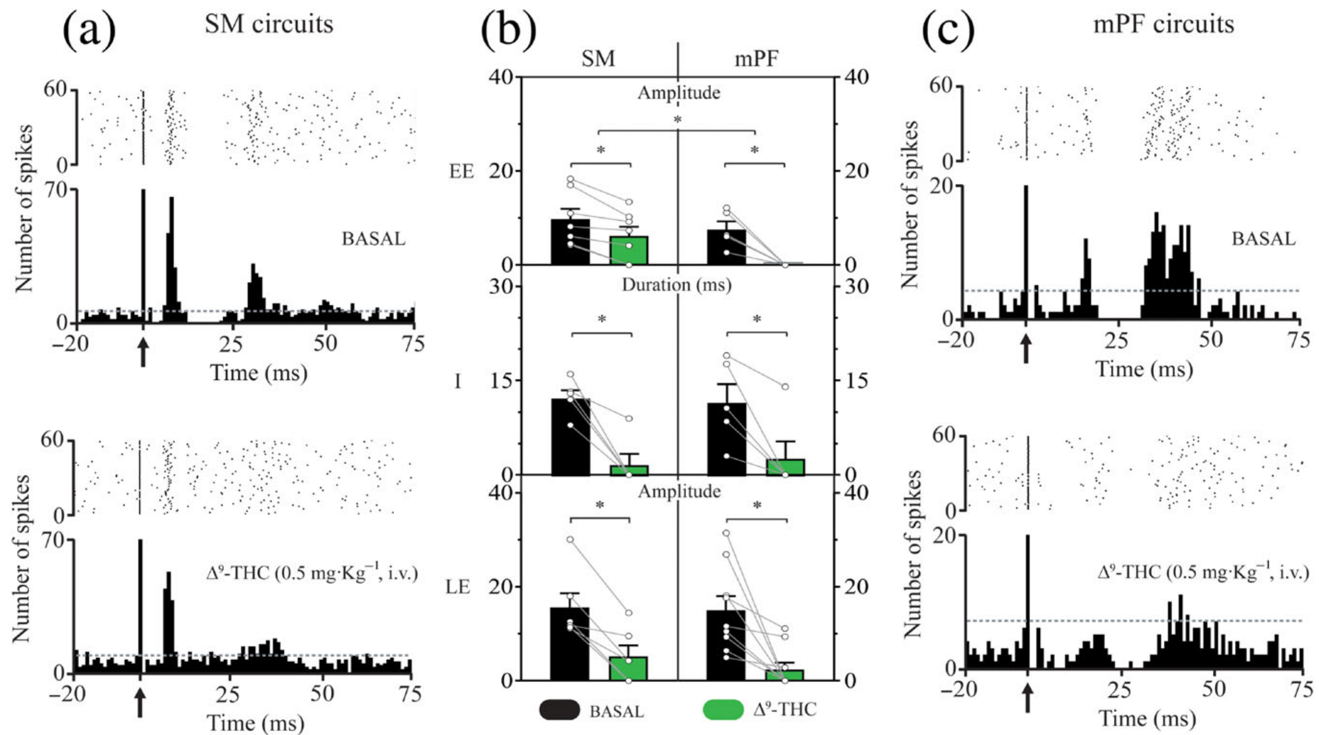

FIGURE 5 Effect of systemic administration of Δ^9-THC (0.5 mg·kg^{-1}, i.v.) on cortico-nigral information transmission in SM and mPF BG circuits. (a) Top: raster plot and peristimulus time histogram showing a representative example of a triphasic response evoked in a SNr neuron by stimulation of the motor cortex under basal conditions. Bottom: after Δ^9-THC injection, the inhibitory and late excitatory components disappeared, with the early excitation remaining slightly diminished. Arrows indicate a stimulation artefact. (c) Top: raster plot and peristimulus time histogram showing a representative example of a triphasic response evoked in a SNr neuron by stimulation of the mPF cortex under basal conditions. Bottom: in this circuit, Δ^9-THC injection was able to reduce transmission through all three pathways. Arrows indicate a stimulation artefact. (b) Bar graphs showing the mean effect of Δ^9-THC (0.5 mg·kg^{-1}, i.v.) on cortically-evoked responses in SNr neurons (amplitude of early [EE; SM: n = 7; mPF: n = 5] and late [LE; SM: n = 6; mPF: n = 9] excitations and duration of inhibition [I; SM: n = 5; mPF: n = 5]) in SM and mPF circuits. Each bar represents the mean ± SEM of n rats. Each dot represents the value from one neuron before and after drug administration. *P < 0.05, Student's two-tailed paired t test to analyse the parameters of the evoked responses and repeated-measures two-way ANOVA to compare the effect of Δ^9-THC in SM and mPF circuits

NMDA receptors (Ibáñez-Sandoval et al., 2007; Shen & Johnson, 2006), which in the SNr comes from the STN (Ding, Li, & Zhou, 2013; Murer, Riquelme, Tseng, & Pazo, 1997; Tseng et al., 2000, 2001). Retrograde and anterograde labelling studies performed by Parent and Smith (1987) showed a significant number of subthalamonigral fibres in the medial part of the SNr, while a moderate number were found in the lateral part.

Regarding the cortically-evoked responses, the percentages of responding cells agree with previous findings (Aliane et al., 2009; Kolomiets et al., 2003; Maurice et al., 1999). The latency of the responses recorded in the mPF pathways was found to be higher than those in the SM ones, likely due to the distance that cortical information has to travel until reaching the SNr. In this way, in the mPF circuits, the cortical projections must reach the dorsomedial and ventral tiers of the striatum, whereas in the case of the SM circuits, the projections of the motor cortex reach the dorsolateral area of the striatum (McGeorge & Faull, 1989). Thus, the motor cortex would be closer to its targets in the striatum and the STN than in the mPF cortex, resulting in lower latency values for the SM circuits. Moreover, additional modulatory synapses may be influencing information transmission through the different circuits. We found that the inhibitory response, which is related to the transmission through the direct trans-striatal pathway, had a longer duration in the SM than in the mPF circuits. This could be as a consequence of a higher activation of the SM circuits, since microdialysis studies have demonstrated a greater amount of glutamate coming from cortical afferents in the dorsal striatum than the ventral striatum (Gray, Rawls, Shippenberg, & McGinty, 1999; Pintor et al., 2004; Werkheiser, Rawls, & Cowan, 2006; Xi et al., 2006). In addition, binding experiments showed higher amounts of AMPA receptors in the dorsolateral striatum, in comparison to the dorsomedial striatum (Nicolle & Baxter, 2003).

4.2 | Effect of cannabinoids on cortico-nigral information transfer

The activation of CB_1 receptors located on presynaptic terminals leads to suppression of GABA and glutamate release in several brain areas, including BG nuclei (Gerdeman & Fernández-Ruiz, 2008; Wilson & Nicoll, 2002). Therefore, it is important to consider the different GABAergic and glutamatergic innervations of SM and mPF-BG

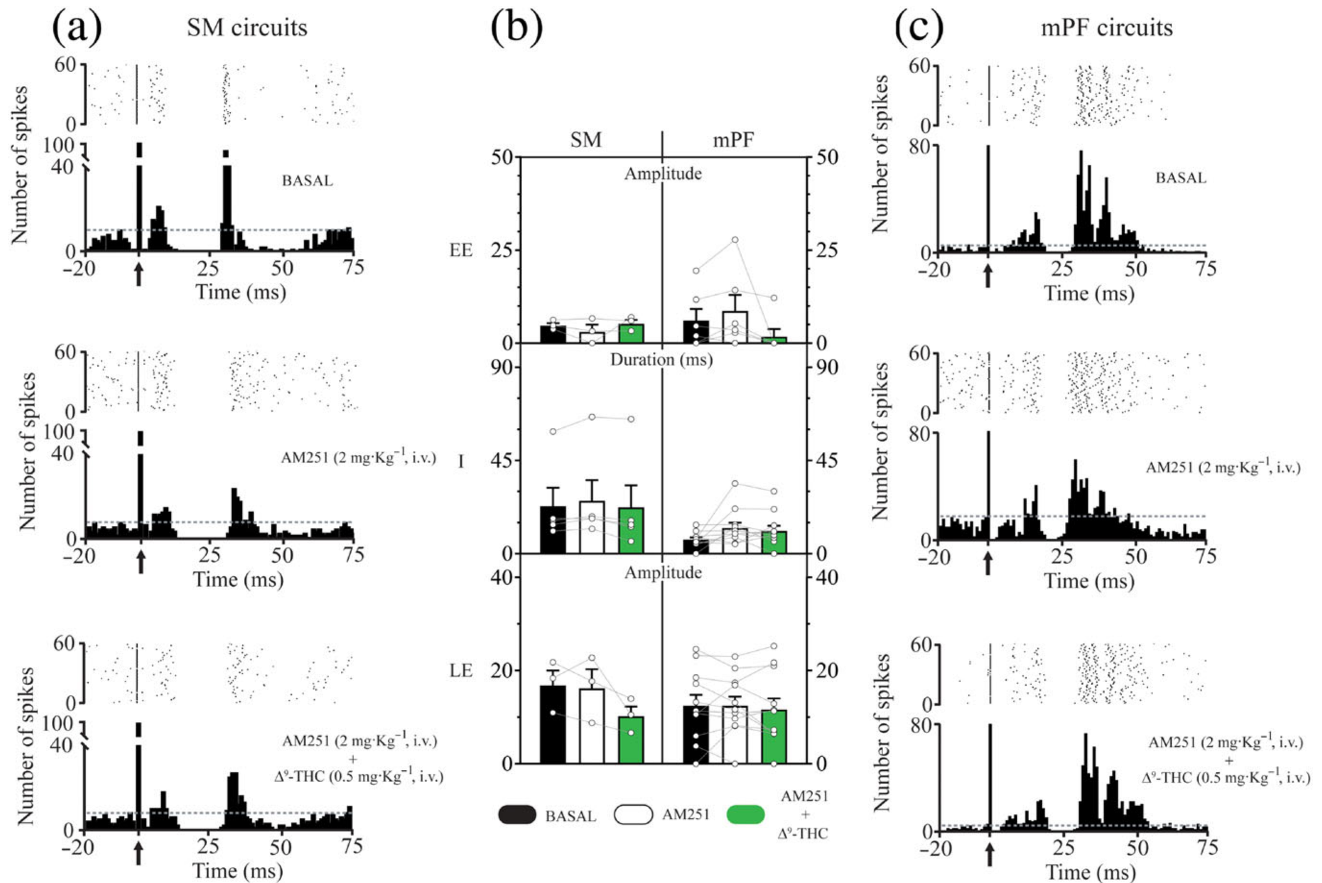

FIGURE 6 Blockade of Δ^9-THC-induced effects on cortico-nigral information transmission in SM and mPF BG circuits by pretreatment with the selective CB_1 antagonist AM251 (2 mg·kg^{-1}, i.v.). (a) Top: raster plot and peristimulus time histogram showing a representative example of a triphasic response evoked in a SNr neuron by stimulation of the motor cortex under basal conditions. AM251 administration did not modify the characteristics of the three components of the cortically-evoked response (middle) but blocked the effects mediated by Δ^9-THC (bottom). Arrows indicate a stimulation artefact. (c) Top: raster plot and peristimulus time histogram showing a representative example of a triphasic response evoked in a SNr neuron by stimulation of the mPF cortex under basal conditions. As in the SM circuit, AM251 administration did not modify the characteristics of the cortically-evoked triphasic response (middle) but blocked the effects induced by Δ^9-THC (bottom). Arrows indicate a stimulation artefact. (b) Bar graphs showing the mean effect of AM251 (2 mg·kg^{-1}, i.v.) and Δ^9-THC (0.5 mg·kg^{-1}, i.v.) on cortically-evoked responses in SNr neurons (amplitude of early [EE; SM: n = 3; mPF: n = 6] and late [LE; SM: n = 3; mPF: n = 11] excitations and duration of inhibition [I; SM: n = 5; mPF: n = 11]) in SM and mPF circuits. Each bar represents the mean ± SEM of n rats. Each dot represents the value from one neuron before and after drug administration

circuits mentioned previously, which, together with the fact that CB_1 receptors are also differently distributed along these circuits, may help to explain the cannabinoid-induced effects observed in the present study.

Our results show that the systemic administration of CB_1 receptor agonists profoundly disrupts the cortical information transmission along the BG circuits. These data are in line with previous in vivo and in vitro electrophysiological studies demonstrating that cannabinoid agonists inhibit GABAergic and glutamatergic neurotransmissions along the BG circuitry. Specifically, cannabinoids reduce corticostriatal (Gerdeman & Lovinger, 2001) and subthalamonigral glutamatergic neurotransmission (Sañudo-Peña & Walker, 1997; Szabo, Wallmichrath, Mathonia, & Pfreundtner, 2000), as well as striatopallidal and striatonigral GABAergic signalling (Miller & Walker, 1996; Wallmichrath & Szabo, 2002). However, the present results show that the modulatory role of CB_1 receptors on SM and mPF circuits of the BG is different. In the SM circuits, after cannabinoid agonist administration (WIN 55,212-2 or Δ^9-THC), cortico-nigral information transmission via the direct and indirect trans-striatal pathways was strongly reduced. By contrast, the information transmitted via the hyperdirect trans-subthalamic pathway remained globally unchanged. Interestingly, in the mPF circuits, cannabinoid agonist administration induced a marked reduction in cortical information transfer in all the trans-BG pathways, including the trans-striatal and trans-subthalamic pathways.

The different effects of the cannabinoid drugs on cortico-nigral transmission through the hyperdirect pathway observed in both circuits, could be explained by considering the differential distribution of the CB_1 receptor within them. The regional comparison of CB_1 receptor expression in the cortex shows that mPF cortical areas have a higher expression of CB_1 receptors than SM cortical areas (Heng et al., 2011). Moreover, CB_1 receptor expression has been detected

in the STN, but no topographical variations in the expression between its motor and limbic/associative areas were demonstrated (Mailleux & Vanderhaeghen, 1992). Previous electrophysiological studies show that CB_1 receptor agonists have different effects on STN neurons from the motor territories and limbic/associative territories of the STN (Morera-Herreras, Ruiz-Ortega, & Ugedo, 2010). Therefore, differences in the sensitivity of the hyperdirect pathway to CB_1 receptor agonists may underlie differences in cortical CB_1 expression between mPF and SM cortical areas. These differences in CB_1 receptor expression along SM and mPF circuits could determine the site at which WIN 55,212-2 and Δ9-THC act. The regional comparison of CB_1 receptor expression at the cortical and striatal level indicates that SM areas of the striatum, which have a higher expression of the CB_1 receptor (dorsolateral territory) receive afferents from cortical areas with a low expression (motor cortex). The opposite is observed in mPF areas of the striatum that show a low CB_1 receptor expression (ventromedial territory), which receive afferents from cortical areas with a high expression (mPF cortex; Van Waes et al., 2012). Based on this distribution and according to the hypothesis proposed by Van Waes et al. (2012), the cannabinoid agonist would largely inhibit the striatal GABA release in the SM circuits, while in the mPF circuits, the cortical glutamate release would be reduced. In our study, as hypothesized in Figure 7, in the SM circuits, both cannabinoid agonists tested, WIN 55,212-2 and Δ^9-THC, would inhibit the striatal GABA release more efficiently, interrupting cortico-nigral transmission at the level of the trans-striatal pathways. However, in the mPF circuit, the inhibition of cortical glutamate release induced by these drugs would lead to disruption of the cortical drive and, consequently, almost complete

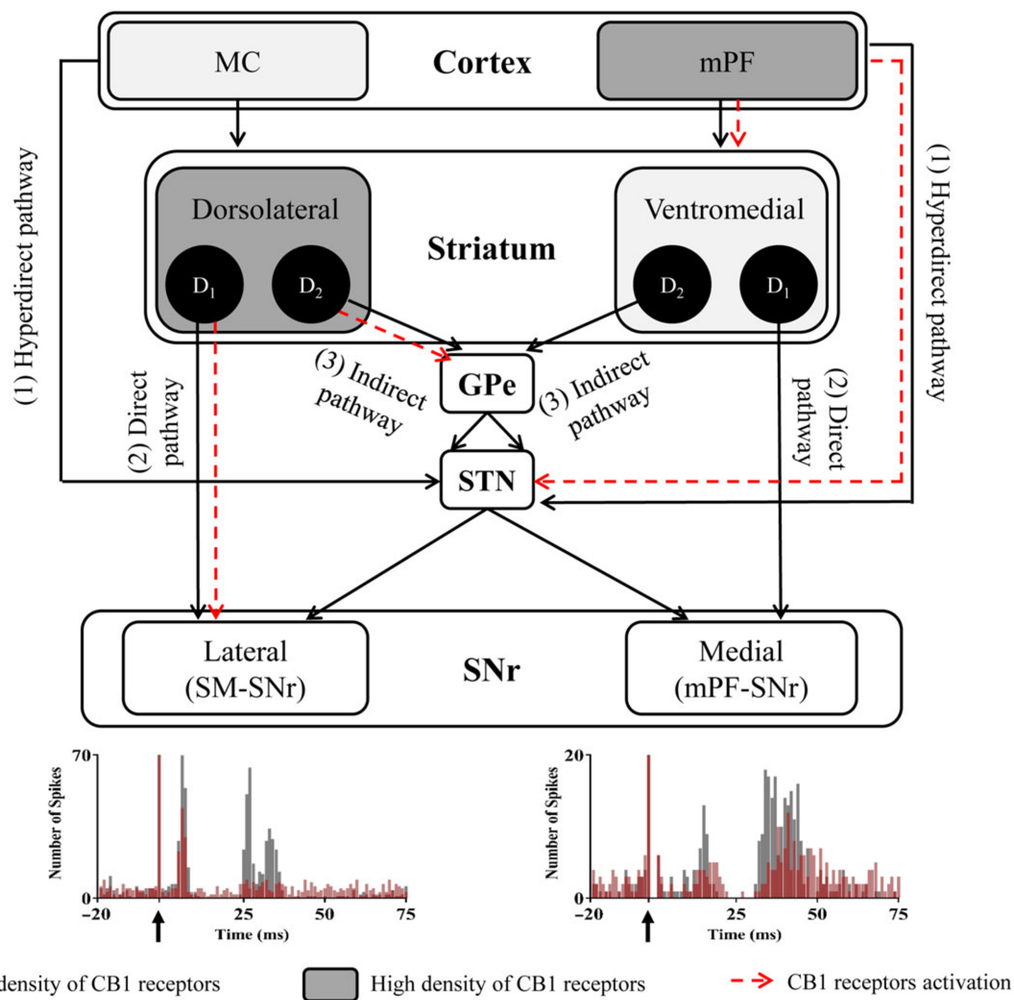

FIGURE 7 Simplified diagram explaining the effect of CB_1 receptor activation on cortico-nigral information transfer through the SM and mPF BG circuits. Under basal conditions, SM and mPF cortical information are transmitted to the SNr through three pathways: (1) cortex-subthalamus-SNr hyperdirect pathway (that evokes an early excitation in the SNr); (2) cortex-striatum-SNr direct pathway (that induces inhibition in the SNr), and (3) cortex-striatum-external *globus pallidus*-subthalamus-SNr indirect pathway (that induces late excitation in the SNr). The activation of CB_1 receptors by cannabinoid agonists (red dashed lines) mainly reduces the transmission through the trans-striatal direct and indirect pathways in SM circuits, whereas in mPF circuits, the activation of CB_1 receptors by cannabinoid agonists affects the corticostriatal and cortico-subthalamic transmissions more. D_1: medium spiny neurons expressing D_1 dopamine receptors; D_2: medium spiny neurons expressing D_2 dopamine receptors; GPe: external *globus pallidus*; MC: motor cortex; STN: subthalamic nucleus

inhibition of the cortico-nigral information transfer through the three pathways.

Regarding the cannabinoid drugs tested, although both WIN 55,212-2 and Δ^9-THC activate CB_1 receptors and although the magnitude of the effects they induce is similar, their pharmacological profiles are different. The synthetic compound WIN 55,212-2 is a potent full CB_1/CB_2 agonist. However, Δ^9-THC is a partial CB_1/CB_2 agonist and **GPR55** and **GPR18** agonist, although it seems to exert its effects principally via CB_1 receptors (Pertwee, 2006). In fact, in the present study, all the effects observed seem to be mediated by the CB_1 receptor since they were blocked by the pretreatment with AM251, a selective CB_1 antagonist and GPR55/GPR18 agonist. Moreover, the administration of AM251 at the dose tested did not have any effect on the triphasic responses, indicating no tonic endocannabinoid control of these circuits.

4.3 | Functional considerations

Under normal conditions, BG output SNr neurons receive convergent synaptic input from the STN and striatum and exert a tonic inhibition on thalamic and brainstem structures. Thus, each SNr neuron receives stimulatory inputs from hyperdirect and indirect pathways (STN) as well as a direct inhibitory input from the striatum. In the SM circuit, hyperdirect and indirect pathways mediate the suppression of movement, while the direct pathway promotes movement (Bevan, Crossman, & Bolam, 1994). Our results show that after CB_1 activation, only the information through the hyperdirect pathway remained unaltered. Consequently, movement inhibition may result, which agrees with previous data showing that cannabinoids impair motor coordination, inducing hypokinesia, and catalepsy in rodents (Anderson, Anderson, Chase, & Walters, 1995; Crawley et al., 1993; de Lago, de Miguel, Lastres-Becker, Ramos, & Fernández-Ruiz, 2004; Navarro et al., 1993; Prescott, Gold, & Martin, 1992; Romero et al., 1995) as well as motor performance deficits in humans smoking marijuana (reviewed in Prashad & Filbey, 2017). Regarding the mPF circuit involved in decision making and goal-directed behaviour (Everitt & Robbins, 2005), after CB_1 activation, cortico-nigral information processing is disrupted almost completely. This mechanism may underlie the deficits in neurocognitive functioning that are well documented in frequent cannabis users (Grant et al., 2003; Schreiner & Dunn, 2012).

In summary, the cannabinoid system represents a promising target in the development of new therapies for several pathologies such as those related to motor disorders. Here, we show how CB_1 receptor agonists modulate the cortical-SNr transmission that comes from motor- and motivation-related cortical areas, which may contribute to a better understanding of the CB_1 receptor-mediated modulation of cortico-BG information processing.

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AUTHOR CONTRIBUTIONS

T.M.H. designed the study. M.A., A.G.C., and I.B. performed the experiments and analysis. M.A., L.U., and T.M.H. wrote the manuscript. L.U. and T.M.H. supervised the whole study.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DECLARATION OF TRANSPARENCY AND SCIENTIFIC RIGOUR

This Declaration acknowledges that this paper adheres to the principles for transparent reporting and scientific rigour of preclinical research as stated in the *BJP* guidelines for Design & Analysis, and Animal Experimentation, and as recommended by funding agencies, publishers and other organisations engaged with supporting research.

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