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Hend Omara-Reda, Omar Ouachikh, Dhouha Hamdi, Mohamed Lashin, Aziz Hafidi. Reinforcing effect of tramadol in the rat. *Neuroscience Letters*, 2023, 796, pp.137053. 10.1016/j.neulet.2023.137053Get . hal-03936288

HAL Id: hal-03936288

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Reinforcing effect of tramadol in the rat

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Highlights

- Tramadol induced both behavioral (CPP) and motor (total movement) sensitizations in the rat.
- Tramadol promoted different molecular marker changes in the anterior cingulate cortex.
- All tramadol effects were significantly decreased by the administration of naltrexone, a μ opioid receptors antagonist.
- Tramadol constitutes a reinforcing substance in the rat.

Abstract

Tramadol is one of the most commonly prescribed analgesic opioids in various pharmacopeias. Tramadol has been linked to abuse in recent clinical investigations. However, the behavioral effects and neural substrates of the drug have not been well characterized in preclinical studies. As a result, the present study investigated the effects of tramadol on behavioral sensitizations in rats. Its impacts on cellular and molecular alterations in the brain were also investigated. In conditioned place preference (CPP) paradigm, tramadol induced behavioral as well as motor sensitizations. These effects were dramatically reduced by intraperitoneal administration of naltrexone, an opioid receptor antagonist. Tramadol caused changes in several molecular markers (pERK1/2, Δ -FosB, PKC γ , PKM ζ GAD67) in the anterior cingulate cortex, which could indicate an increase in excitation

within this structure. Tramadol is demonstrated in the present study to be a reinforcing drug in rats, as it increased both behavioral and motor sensitizations. Tramadol's effects are most likely due to the high levels of excitation it causes in the brain, which is mostly caused by the activation of opioid receptors.

1. Introduction

Tramadol is an opioid agonist that is often used alone or in combination with other medications to treat chronic pain. It is one of the most commonly prescribed analgesic opioids in various pharmacopeias due to its lower risk of addiction [1]. It delivers analgesia by two mechanisms: one, activation of opioid receptors, and the other, inhibition of central monoaminergic reuptake, which elevates monoaminergic neurotransmitter levels in the brain [2, 3]. Tramadol acts on different receptors and ion channels (GABAA, glycine, NMDA, adrenergic, nicotinic acetylcholine, sodium channels) [4, 5, 6, 7, 8].

There are differences in tramadol abuse effects in clinical research. Some studies showed a weak or no abuse liability for tramadol

[8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18]. Conversely, other studies linked an abuse effect to tramadol

[9, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34]. These discrepancies have been attributed to different doses, tramadol use in non-opioid dependent versus drug-dependent people, oral versus injectable administrations or its interaction with other drugs or medication.

Preclinical research on tramadol's potential for abuse have various discrepancies.

Tramadol has a mild reinforcing effect in rhesus monkeys [35], but a strong reinforcing effect in mice and rats [36], according to a self-administration studies.

In rodents, tramadol causes conditioned place preference (CPP)

[36, 37, 38, 39]. The CPP is a test that measure the motivational effects of a drug. Tramadol induces CPP via mu-opioid receptor [39], and an increase in dopamine release within the nucleus accumbens [37]. However, studies did not report that tramadol induces motor sensitization in rats [38]. This lack of motor sensitization during CPP test suggests that tramadol is not devoid of reinforcing effect but it has only limited abuse potential. Based on its interactions with morphine and buprenorphine, tramadol was found to cause CPP in rats [40].

The purpose of this study was to explore how tramadol affected behavioral sensitizations (CPP and actimetry). Both sensitizations must be present for a

molecule to be classified as an abuse drug [\[38\]](#), [\[41\]](#). Sensitization is defined generally as an amplification of the response to a specific repeated stimulus. After repeated exposure to addictive substances, rodents frequently experience locomotor sensitization, a common and important behavioral alteration that causes the animal to become noticeably more hyperactive in response to an acute drug challenge. The effects of tramadol on cellular and molecular alterations in the rat brain, were also studied. In addition, the opioid antagonist naltrexone was used to counteract the effects of tramadol.

The anterior cingulate cortex (ACC) constitutes an essential component of the limbic system, which is involved in a range of cognitive and emotional processing. The ACC plays major roles in pain [\[80\]](#) and drug reward [\[81\]](#). The ACC processes both acute and chronic pain, which makes this region hyperactive [\[44\]](#), [\[80\]](#). Contrarily, it has been reported that addiction causes an ACC hypoactivity [\[81,82\]](#). For each of these reasons, the ACC has been investigated in this study.

2. Materials and methods

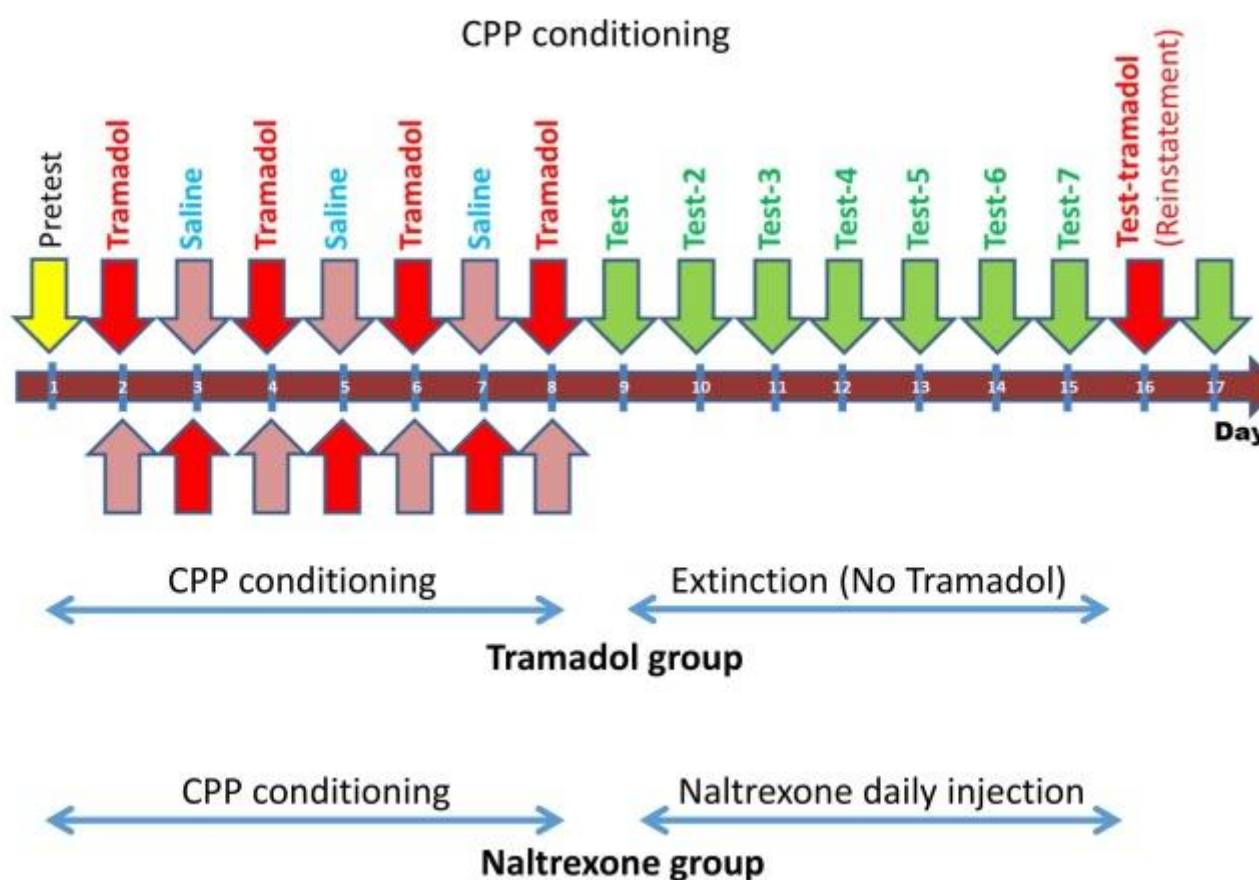
2.1. Animals

Fifty-one adult male Sprague Dawley rats (Charles Rivers, L'Arbresle, France) were used. Rats were maintained in a controlled environment (lights on 07:00–19:00 h, 22 °C) with *ad libitum* access to food and water. The experiments followed the ethical guidelines of the animal ethics committee of the University of Auvergne (APAFIS#19965-20190325052285).

The CPP test was conducted as previously indicated [\[42\]](#), [\[43\]](#). A software application (Imetronic, Pessac, France) was used to analyze rat movements within each compartment of the apparatus, and measure the number of entries and the time the rats spent in each compartment. Briefly, for habituation, the rats were placed in the central alley and were free to explore the entire apparatus for 15 min. During the pretest day, rats received only vehicle injection then placed in the central alley and the time spent in each compartment during a 15 min session was recorded. The conditioning period consisted of a session of 30 min per day for 8 days. Each animal had one session with a tramadol (10 mg/kg) intraperitoneal injection (15 min before the CPP session) alternated on the second day by an injection of a vehicle (saline). During the conditioning phase of the CPP, the rats received four tramadol (10 mg/kg)-paired sessions and four vehicles paired sessions ([Fig. 1](#)). This

procedure ruled out that place preference would result from response bias. By doing this, one group had its last tramadol injection 24 h before the test day while the other had it 48 h before the test day. In the test day, rats were introduced (during 15 min) into the apparatus by placing them in the central alley and did not receive any drug or vehicle. This group is referred to as tramadol-group. This group was continuously tested until the extinction of the tramadol-induced CPP. A second group was tramadol sensitized during the CPP and received naltrexone (1 mg/kg) intraperitoneal injection just before the test in the test day. This group is referred to as naltrexone group. This group continued to be naltrexone administered each day until the extinction of the CPP. The time spent in each compartment during a 15 min session was measured. Data were presented as means of individual differences between times spent in the drug-paired compartment during the pretest phase and the test day. Positive values reflected a CPP. To mention that the CPP experimenter was unaware of the treatment given to the animals.

Conditioned Place Preference time course



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Fig. 1. The figure represents the time course of the CPP experiments. The rats were divided into two groups: tramadol group, which was conditioned with tramadol and had been CPP-tested after the test day for 7 additional days until the extinction of the behavioral sensitization (CPP) was obtained. The second group named the naltrexone group, which has been conditioned with tramadol and after the test was daily administered a naltrexone for additional 7 days. During the conditioning, the rats were split into two groups, one receiving tramadol while the other receiving a saline administration and there were switched the next day. As a result, one group had their last tramadol injection 24 h before the test, whereas the other received it 48 h before the test.

Software from the CPP apparatus gave information's on the number of entries on each compartment, the movement made at the back, front, and back and forth in each compartment. Locomotors activity performance (actimetry) represents the sum of movements performed in each compartment for each animal (mean \pm SD) in 15 min. The input number is the sum of entries in the compartments made for each animal (mean \pm SD) in 15 min.

2.2. Immunohistochemistry

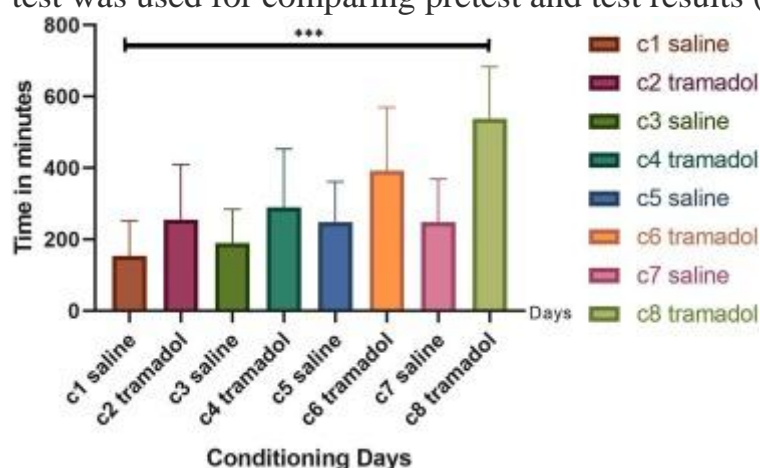
At the end of behavioral studies (CPP extinction), rats were deeply anesthetized with 1 % ketamine and Xylazine. Rats were perfused through the heart with saline followed by 4 % paraformaldehyde in phosphate-buffered saline (PBS). The brains were then removed and placed in 30 % sucrose and 0.05 % sodium azide solution overnight at 4 °C. Coronal sections (30 μ m) were obtained using a freezing microtome and collected in 0.05 M Tris-buffered saline (TBS). Free-floating sections were placed in 1 % normal goat serum for 1 h before overnight incubation in primary monoclonal antibody solution (1:5000 mouse anti-PKC γ , Sigma-Aldrich, France; anti-phosphoPKM ζ 1/1000, rabbit, Clinisciences, France; anti-GAD67, 1/1000, rabbit, Cell-Signaling, Netherland; anti- Δ -FosB, 1/1000, rabbit, Clinisciences, France) at 4 °C. After several rinses, sections were incubated with a corresponding secondary antibody (1:400 for goat anti-mouse Cy2or Cy3; Vector Lab, France) for 3 h at room temperature. All antibodies were diluted in TBS containing 0.25 % bovine serum albumin and 0.3 % TritonX-100. The sections were finally rinsed in TBS, mounted onto gelatin-coated slides, dehydrated in alcohol, cleared in xylene, and cover-slipped with distyrene-plasticizer-xylene. The specificity of the immunostaining was assessed by omitting the primary antibody or protein pre-adsorbed antibody, which resulted in the absence of a signal. Photomicrographs of immuno-stained sections were captured and image intensity

analysis was completed using ImageJ software (ImageJ v1.41, National Institute of Health, USA).

The number of Δ -FosB positive cells or the intensity of the labeling were counted using ImageJ software as previously reported [[42], [43], [44]]. For each animal group, data were the total number of cells or the labeling intensity per identical used square of the sections ($n = 12$ per animal).

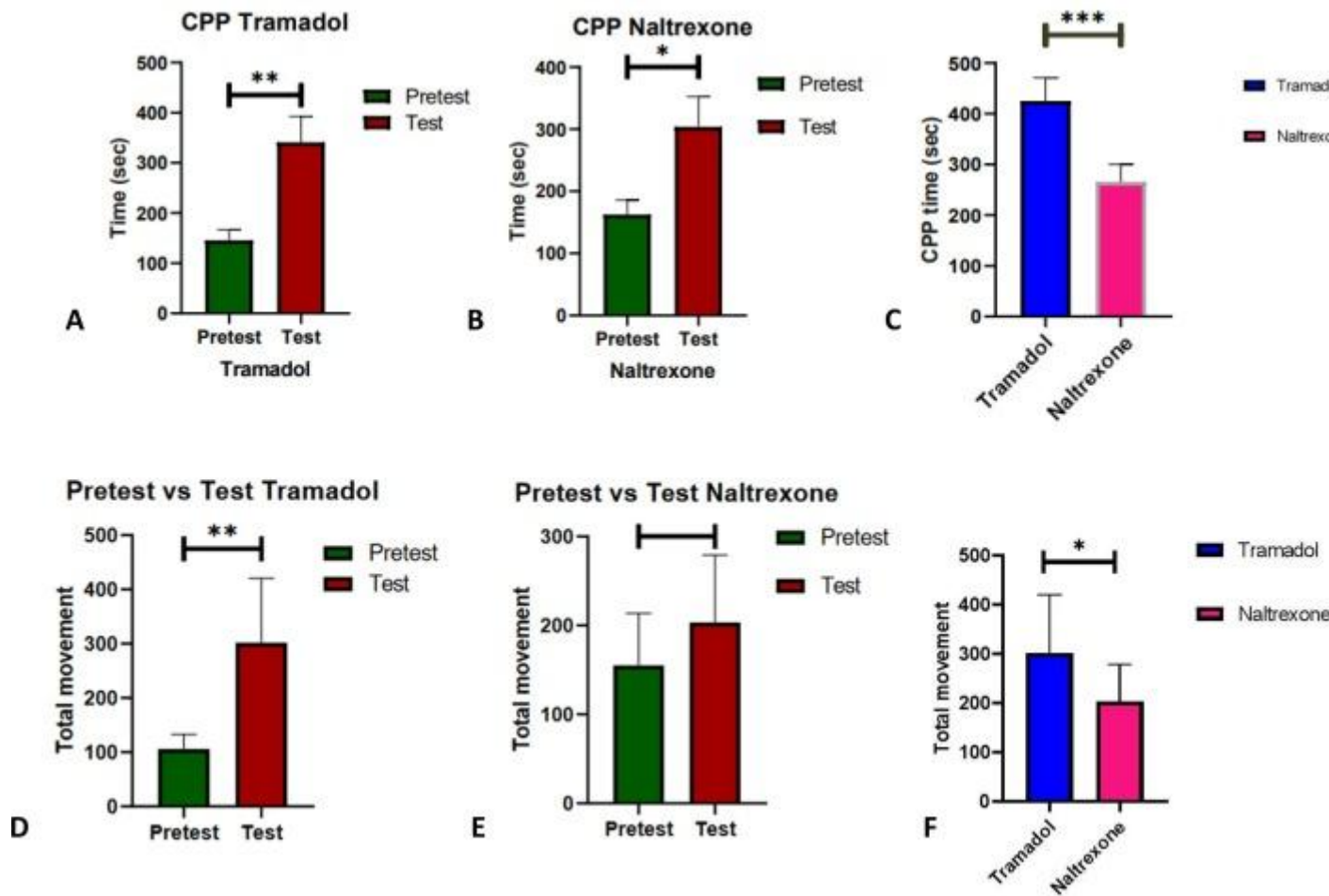
2.3. Statistics

Data analysis and statistical comparisons were performed using GraphPad Prism 8 (GraphPad Software Inc.). The results are expressed as mean \pm SEM. Level of significance was set as $P \leq 0.05$. Brown Forsythe ANOVA one way and Bartlett's test were used to compare between three and more groups. Otherwise, Student's t -test was used for comparing pretest and test results (Fig. 3).



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Fig. 2. The diagram illustrates how tramadol's impact on motor sensitization during conditioning changed over time. Tramadol generated a considerable ($p < 0.01$) increase in motor sensitization after the third injection, and this increase became significantly more pronounced ($p < 0.001$) by the fourth dosage. Data are means \pm SEM.



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Fig. 3. The figure represents the tramadol effect on the CPP and the motor sensitization (actimetry) as well as the effect of naltrexone on the CPP-induced by tramadol. Tramadol significantly ($p < 0.01$) induces a CPP (A) as revealed by the time spent in the tramadol associated compartment when compared to the pretest one. The injection of naltrexone significantly ($p < 0.05$) decreased the CPP induced by tramadol (B). The naltrexone effect was highly significant ($p < 0.001$) (C). Tramadol also induced a significant motor (total movements) sensitization (D) when compared to the pretest day. However, naltrexone administration did not result in a significant difference in motor sensitization (E) when compared to the pretest day, while it did reduce motor sensitization generated by tramadol considerably ($p < 0.05$) (F). Data are means \pm SEM.

3. Results

3.1. Tramadol effect on behavioral (CPP) and motor (actimetry) sensitizations

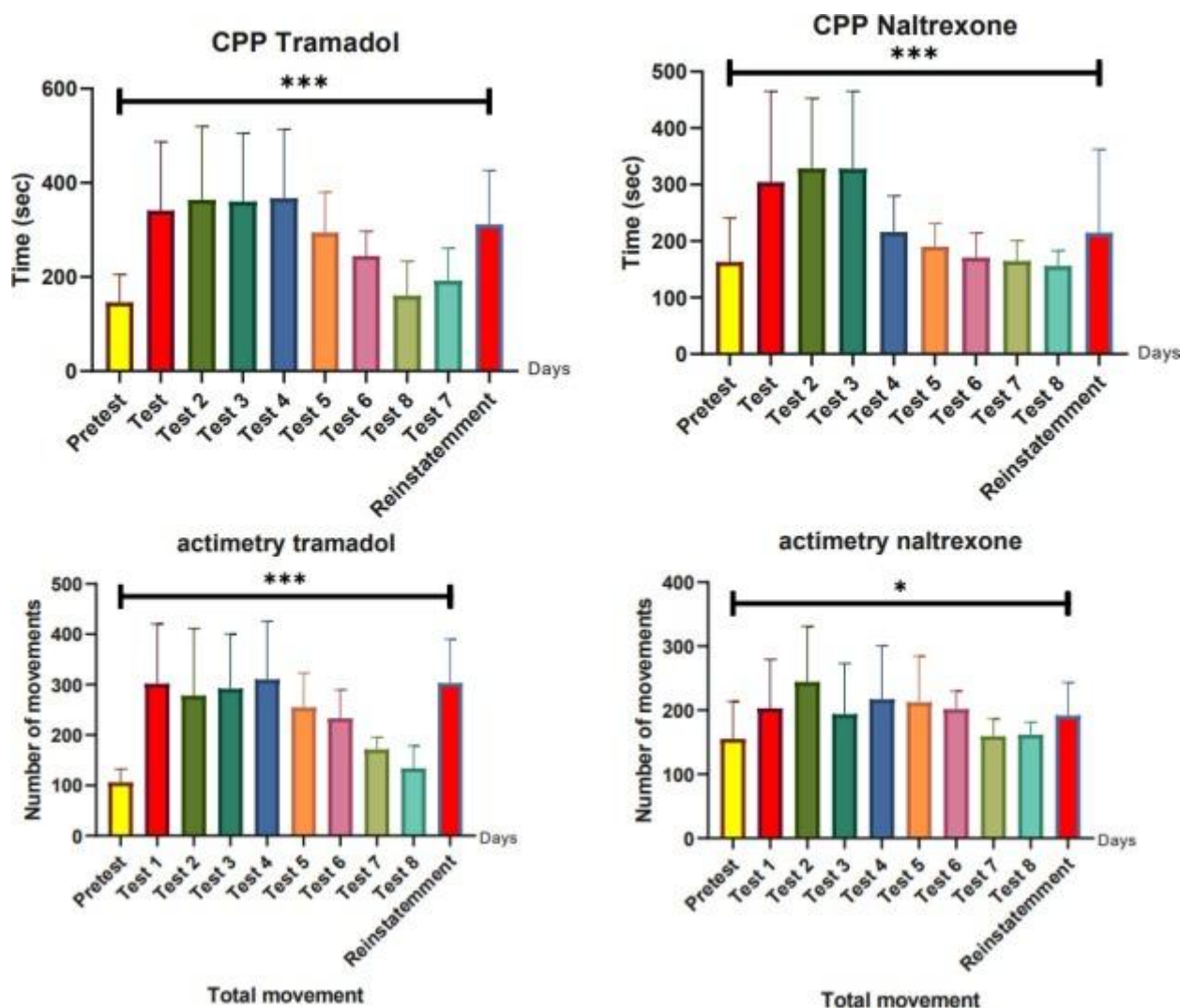
The ANOVA one way revealed a very significant difference ($p < 0.001$) between groups during conditioning (Fig. 2). Tramadol produced a significant ($p < 0.01$) CPP starting with the third injection and became more significant ($p < 0.001$) at the fourth tramadol injection.

After the conditioning period, tramadol induced a significant ($p < 0.01$) CPP (as evidenced by the time spent in the tramadol related compartment as compared to the pretest) (Fig. 3A). Naltrexone decreased significantly ($p < 0.05$) the CPP induced by tramadol conditioning (Fig. 3B). The naltrexone effect on tramadol induced conditioning was highly significant ($p < 0.001$) (Fig. 3C).

In addition, when compared to the pretest total movement within the apparatus room, tramadol had a significant ($p < 0.01$) motor sensitization (actimetry, total movement within the apparatus room) (Fig. 3D). Although naltrexone treatment reduced overall movement, the difference was not significant when compared to the baseline (pretest) (Fig. 3E). When compared to tramadol, however, naltrexone had a significant ($p < 0.05$) effect on motor sensitization (Fig. 3F). When compared to the pretest, motor sensitization became non-significant after the fifth day after naltrexone injection, indicating that naltrexone had an effect on tramadol-induced activity.

3.2. CPP extinction and naltrexone effect (effect of NTX on tramadol induced-CPP)

From the first test day to the extinction of behavioral sensitization, tramadol-induced CPP was assessed (Fig. 4A). It is worth noting that the rats were not given tramadol beyond the first test day (eighth day after the pretest). The tramadol-induced CPP remained significant ($p < 0.01$) for four days following the test day, declined by the fifth day although still significant ($p < 0.05$), and subsequently became non-significant. Tramadol re-induced a substantial ($p < 0.01$) CPP when injected 7 days following the last test day.



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Fig. 4. The figure represents the extinction of tramadol-induced CPP and the naltrexone effect on this CPP. Tramadol-induced behavior was significant for up to 7 days after the test day (A). Tramadol injections on day 7 after the test resulted in a significant ($p < 0.01$) increase in CPP. The tramadol-induced CPP was reduced significantly ($p < 0.01$) by naltrexone treatment in the first three days after the test day, and it was blocked after that (B). A CPP was not induced by tramadol injection 24 h after naltrexone injection on day 7 after the test. Tramadol-induced motor sensitization was considerable 6 days following the test day, but not by the 7th day (C). When tramadol was administered on the eighth day after the test, it caused a significant ($p < 0.001$) increase in CPP. For the first four days after the test day, naltrexone reduced tramadol-induced motor sensitization (D) and ultimately blocked it. Tramadol did not cause motor sensitization in this animal group on the eighth day after the test day (naltrexone-treated). Data are means \pm SEM.

From the day of the CPP test, the Naltrexone group received naltrexone injections every day. Naltrexone administration reduced the CPP generated by tramadol

considerably ($p < 0.01$) for the first three days after the test day ([Fig. 4B](#)) and then blocked it. There was no significant tramadol-induced CPP behavior in the naltrexone group when tramadol was reinjected 7 days after the test day.

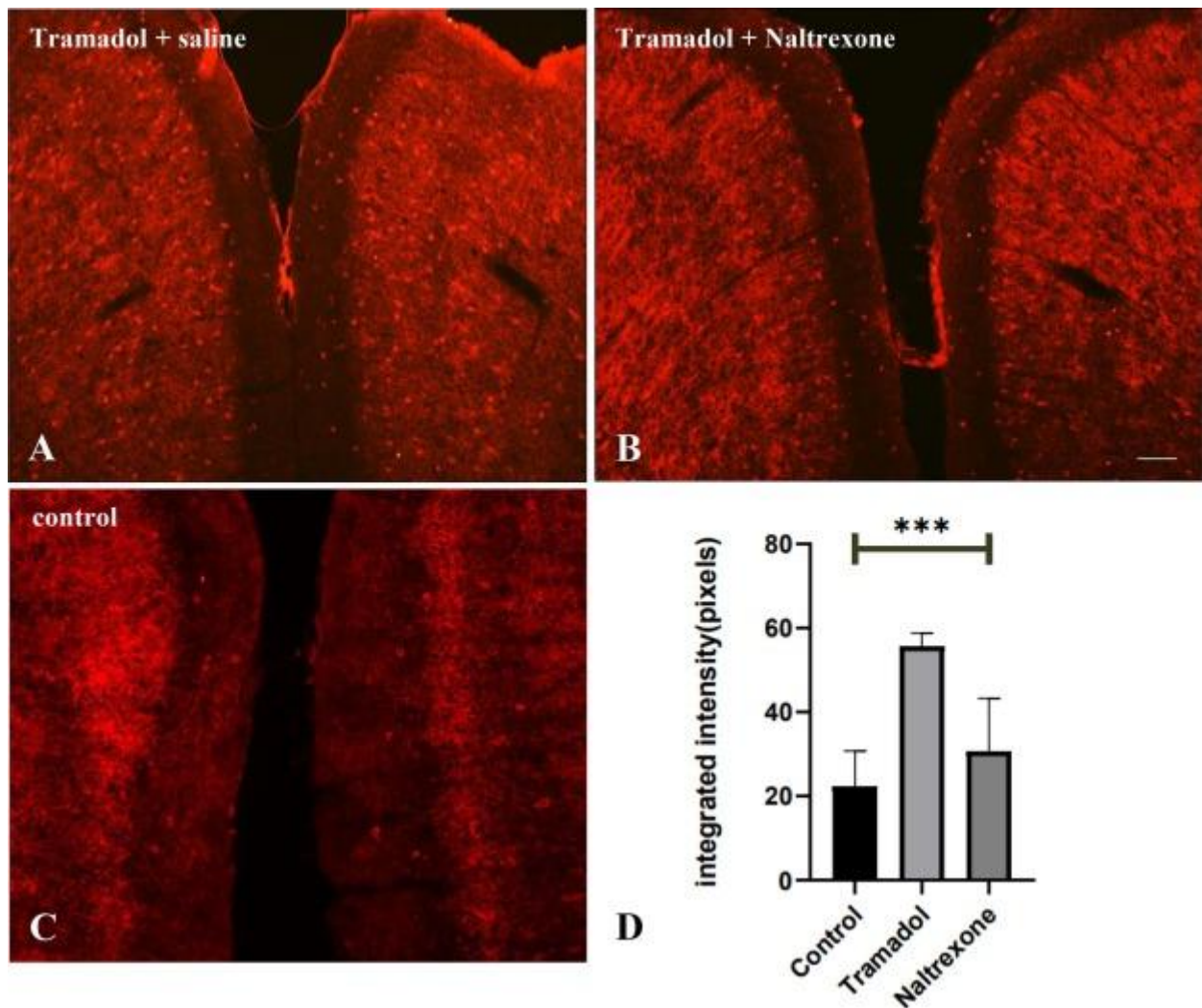
A significant tramadol-induced motor sensitization paralleled that of the CPP behavior, lasted for 6 days after the test day, and subsequently disappeared ([Fig. 4C](#)). The injection of tramadol eight days after the test day re-induced a significant ($p < 0.01$) motor sensitization.

After the test day, naltrexone was given every day until the CPP behavior was no longer present. The first four days of tramadol-induced motor sensitization were reduced by naltrexone, but the motor sensitization was still significant when compared to the pretest. When compared to the pretest, motor sensitization became non-significant after the fifth day after naltrexone injection, indicating that naltrexone had an effect on tramadol-induced motor activity ([Fig. 4D](#)). There was no substantial motor sensitization when tramadol was re-injected on day 8 after the test day in the naltrexone group.

3.3. Molecular changes induced by tramadol in the anterior cingulate cortex

3.3.1. GAD67 staining:

In tramadol- ([Fig. 5A](#)), naltrexone- ([Fig. 5B](#)), and control rats, a comparable pattern of GAD67 immunostaining ([Fig. 5](#)) was found in cell bodies and processes within the ACC ([Fig. 5C](#)). In tramadol-treated ACC, the intensity of GAD67 staining was more higher, particularly within cell processes, than in naltrexone-treated and control ACC. Quantification of GAD67 immunostaining revealed a significant ($p < 0.001$) difference between tramadol-treated and naltrexone-treated or control ACC ([Fig. 5D](#)). Although the GAD67 staining intensity was higher in naltrexone-treated rats than in control rats, this difference was not significant.



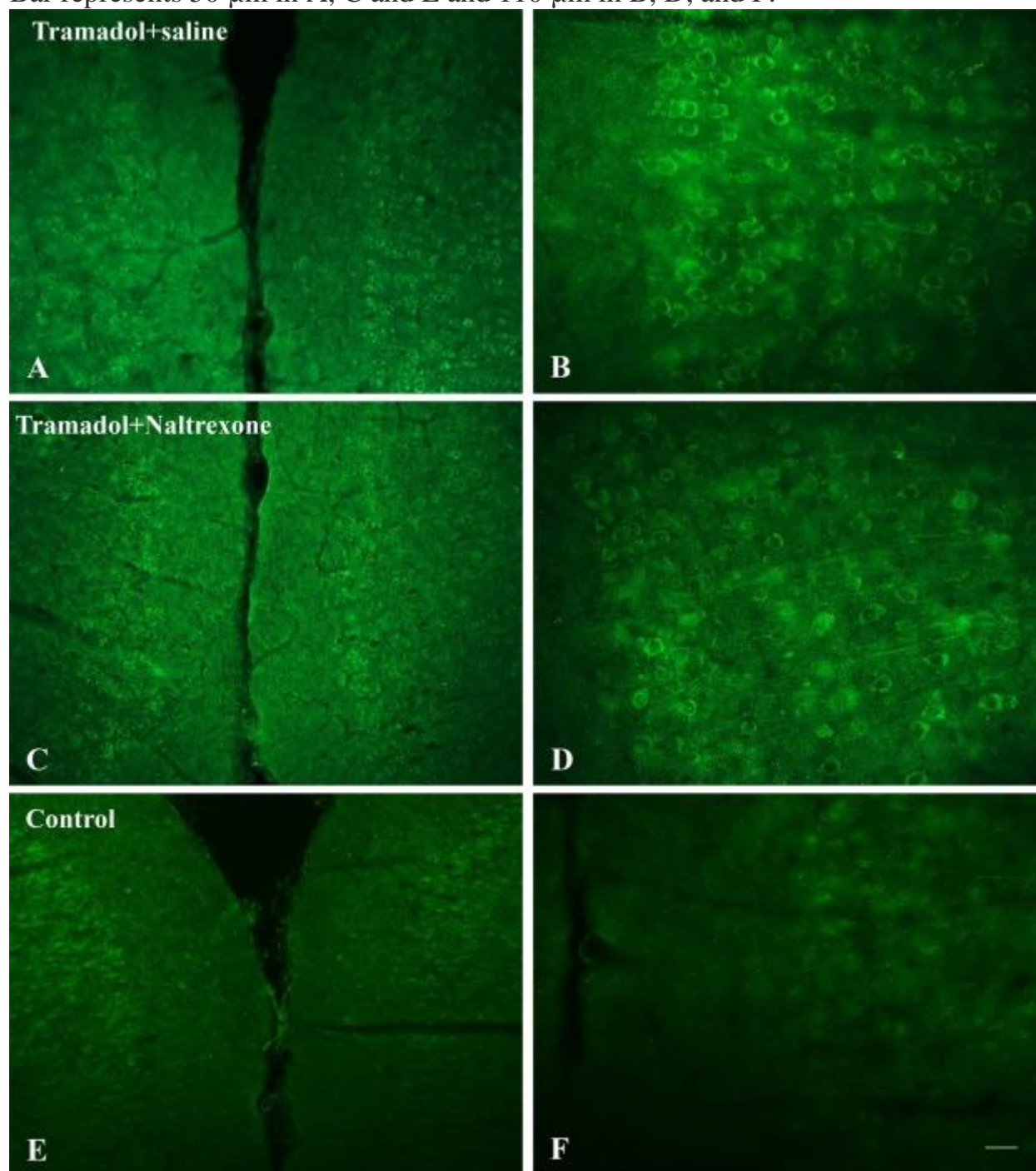
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Fig. 5. The figure represents the effect of tramadol and naltrexone on GAD67 expression in the ACC. Within the ACC of tramadol- (A), naltrexone-treated (B), and control rats, GAD67 staining can be seen in various cell bodies and processes (C). The GAD67 staining quantification indicated a significant ($p < 0.001$) difference in staining between tramadol and control rats, as well as tramadol and naltrexone treated rats. There is no significant change in staining between the naltrexone-treated and control rats. The bar represents 200 μm in A, C and E; and 50 μm in B, D and F. Data are means \pm SEM.

3.3.2. PKM ζ staining

PKM ζ immunostaining in the ACC ([Fig. 6](#)) was primarily observed in neuronal cell bodies and processes in the tramadol- ([Fig. 6A-B](#)), naltrexone- ([Fig. 6C-D](#)) and control rats ([Fig. 6E-F](#)). The intensity of staining was more important in tramadol and naltrexone-treated when compared to control ACC. PKM ζ staining

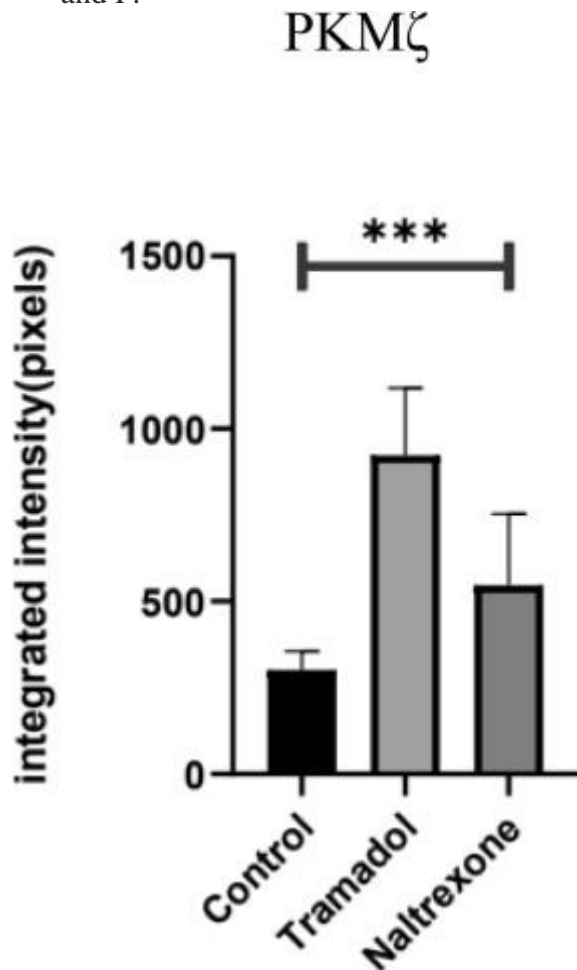
quantification ([Fig. 7](#)) revealed a significant staining difference between tramadol, naltrexone ($p < 0.01$) and control ($p < 0.001$) rats. There was also a significant ($p < 0.01$) PKM ζ staining difference between naltrexone-treated and control ACC. Bar represents 50 μm in A, C and E and 110 μm in B, D, and F.



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Fig. 6. Represents phospho-PKM ζ staining in the ACC. The staining can be seen in neuronal cell bodies and processes within the ACC of tramadol-treated rats at low magnification (A). The staining can be seen throughout somata and processes across

the width of the cortex of tramadol-treated rats at high magnification (B). The intensity of the staining was decreased in naltrexone-treated animals (C, D), but it can be seen at high magnification in neuronal somata and processes inside the ACC (D). Similar staining is observed in the ACC (E) in the control, where it is localized in neuronal cell bodies (F). The bar represents 200 μ m in A, C and E; and 50 μ m in B, D and F.



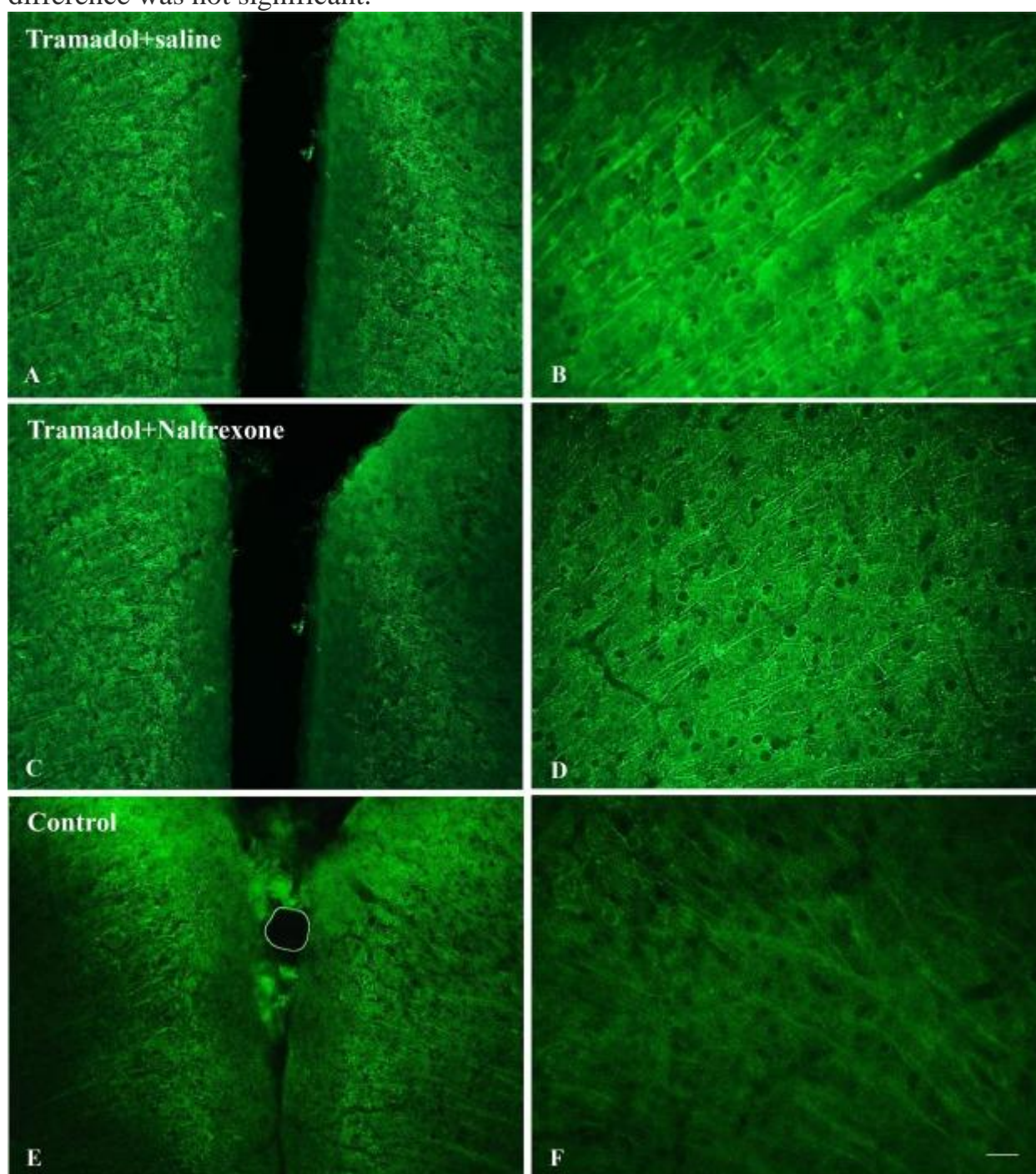
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Fig. 7. phospho-PKM ζ intensity of staining quantification revealed a significant staining difference between tramadol treated and naltrexone-treated ($p < 0.01$) or control ($p < 0.001$) ACC. There was also a significant ($p < 0.01$) staining difference between naltrexone-treated and control ACC. Data are means \pm SEM.

3.3.3. PKC γ staining

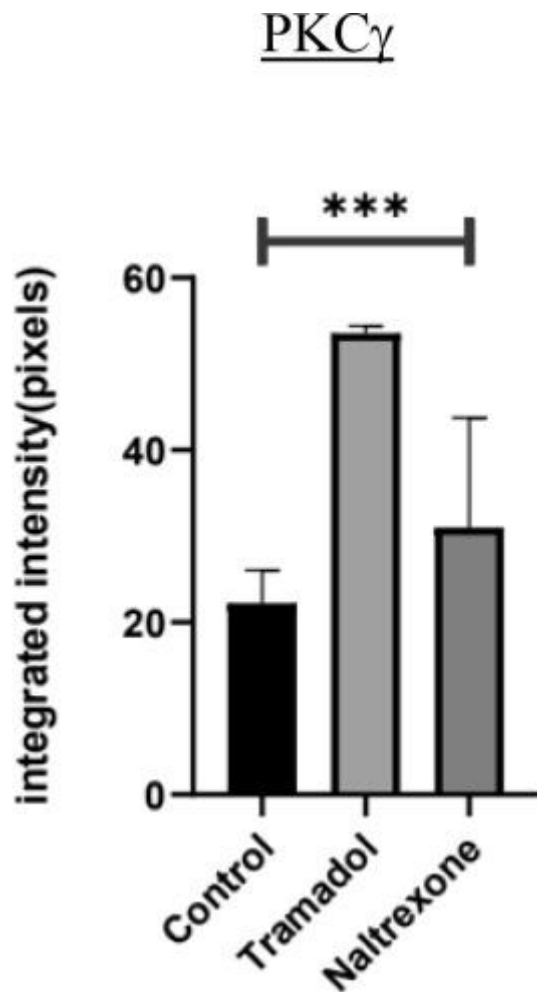
In tramadol ([Fig. 8A-B](#)), naltrexone ([Fig. 9C-D](#)), and control ([Fig. 8 E-F](#)) groups, PKC γ labeling ([Fig. 8](#)) was found in cell bodies and processes across the ACC. The processes were thick and resembled the dendritic subtype in appearance. In the ACC, PKC γ immunostaining quantification revealed a significant ($p < 0.001$)

difference between tramadol and naltrexone or control ([Fig. 9](#)). Although the intensity of PKC γ staining in naltrexone was higher than in control ACC, the difference was not significant.



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Fig. 8. PKC γ staining within the ACC in tramadol- (A, B), naltrexone-treated (C, D) and control rats (E, F). PKC γ staining is observed in cell bodies and processes. The intensity of staining is high in tramadol and naltrexone-treated rats when compared to control. The bar represents 200 μ m in A, C and E; and 50 μ m in B, D and F.

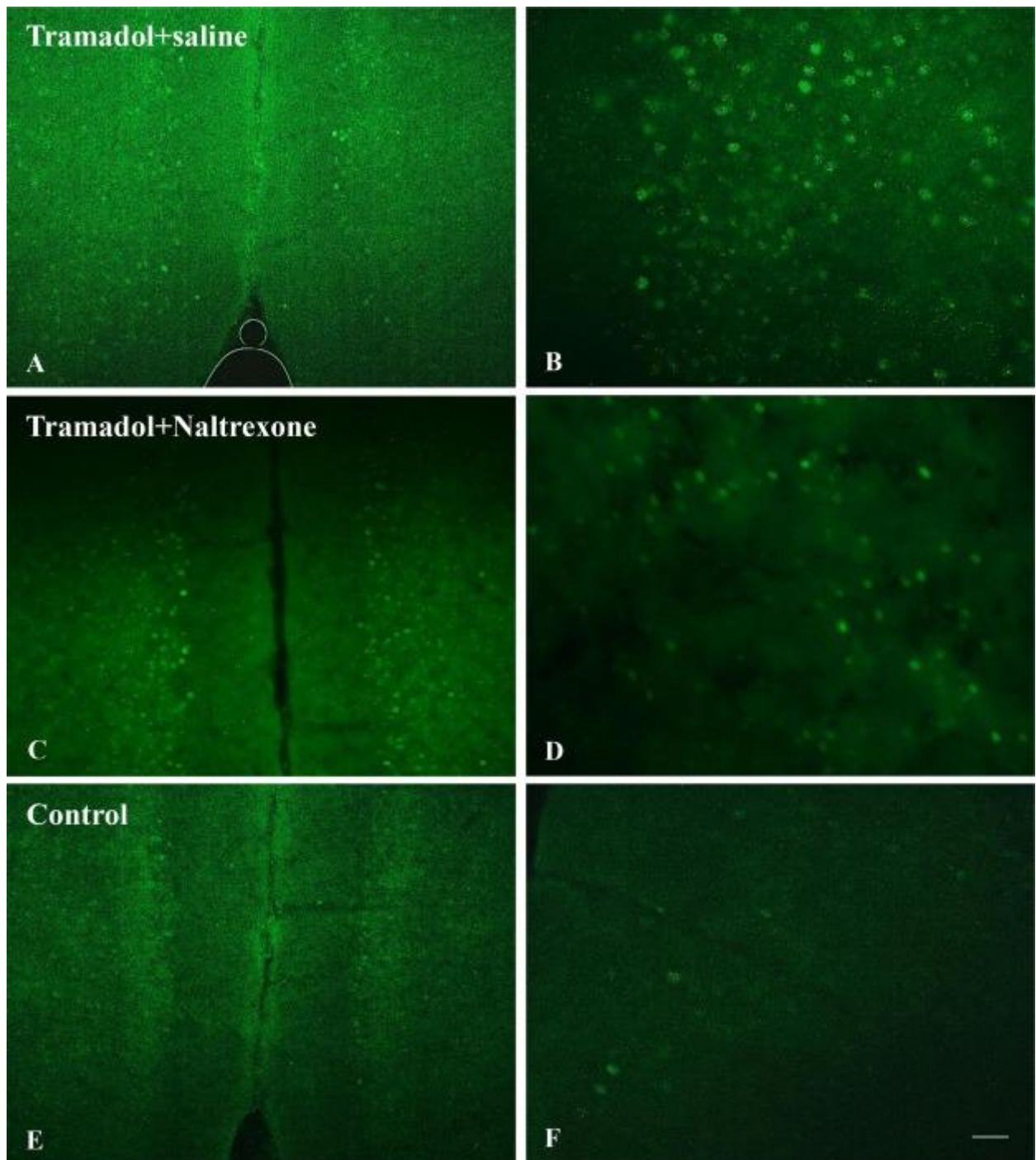


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Fig. 9. PKC γ intensity of staining quantification in the ACC revealed a significant ($p < 0.001$) staining difference between tramadol-treated when compared to naltrexone-treated or control. No significant staining difference is observed between naltrexone-treated and control ACC. Data are means \pm SEM.

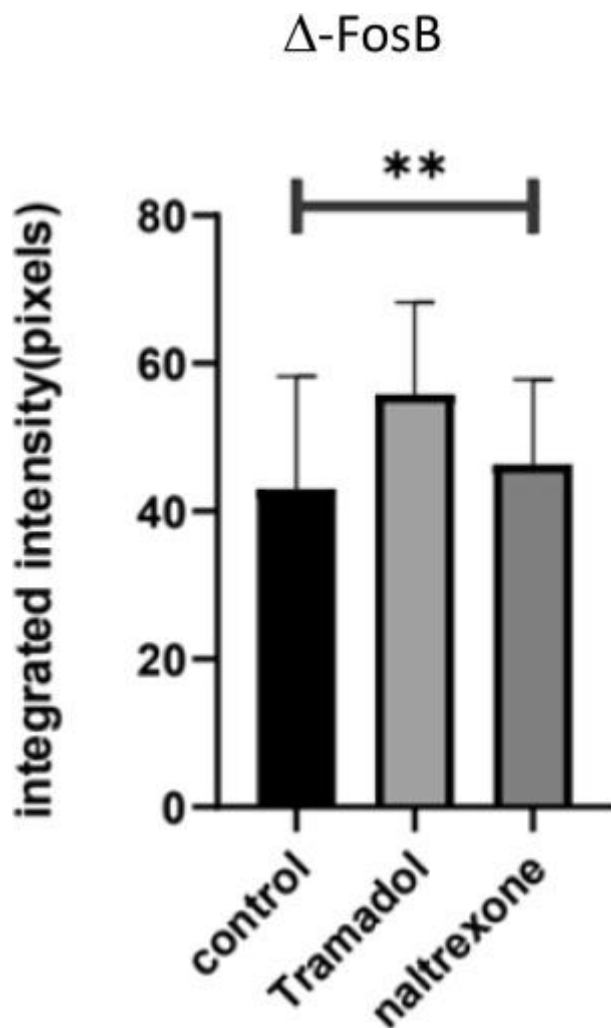
3.3.4. Δ -FosB staining

Δ -FosB staining ([Fig. 10](#)) was observed in cell nuclei within the ACC of tramadol- ([Fig. 10A, B](#)), naltrexone- ([Fig. 10C, D](#)) and control ([Fig. 10E, F](#)) rats. There was a more cell staining in tramadol and naltrexone-treated ACC than in control. Cell count ([Fig. 11](#)) reveals a significant difference in the positive cell number between tramadol ($p < 0.01$), naltrexone ($p < 0.05$) and control rat. There is also a significant ($p < 0.05$) difference in cell number between tramadol and naltrexone ACC.



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Fig. 10. Δ -FosB staining in the ACC. Δ -FosB staining is observed in cell nuclei of the cortex in tramadol- (A, B), naltrexone- (C, D) and control (E, F) rats. The bar represents 200 μ m in A, C and E; and 50 μ m in B, D and F.



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Fig. 11. Δ -FosB cell count reveals a significant difference between tramadol ($p < 0.01$), naltrexone ($p < 0.05$) -treated and control rat. There is also a significant staining difference in cell number in the anterior cingulate cortex between tramadol and naltrexone treated rats. Data are means \pm SEM.

4. Discussion

The main results of the present study were that tramadol administration promoted both behavioral (CPP) and motor (actimetry) sensitizations making it a drug of abuse in the rat. Tramadol administration caused a high level of excitation in the ACC, as evidenced by an increase in markers such PKC γ , phospho-PKM ζ , and Δ -FosB.

CPP caused by tramadol has already been demonstrated [[36], [37], [38]]. Only one study, however, shows a minor motor sensitivity [38]. During the conditioning

period in the current investigation, motor sensitization mirrored behavioral sensitization. During the conditioning, tramadol caused significant motor sensitization after the third injection. Also, motor sensitization followed behavioral sensitization in the tramadol-group (rats get tramadol under CPP training) after the test day (CPP). Furthermore, on the day of CPP extinction, motor sensitization was still evident and significant (behavior). In the naltrexone group, similar results were obtained. These findings support the fact that tramadol causes both motor and behavioral sensitization. Tramadol delivery-two weeks after CPP extinction resulted in an increase in both behavioral and motor sensitizations (unpublished data), while the differences were not statistically significant when compared to the pretest.

The ACC is a structure that is important for cognitive control of decision-making, in reward [46], learning, emotion, and memory [48]. In drug addicts, there is a decrease in ACC activity [49]. These characteristics make the ACC an ideal structure for studying tramadol's molecular and cellular effects.

The Δ FosB finding is consistent with a recent study that found that tramadol enhanced Δ FosB in the nucleus accumbens and prefrontal cortex after both acute and chronic treatment [50]. This effect is due to the tramadol activation of mu-opioid receptors as well as an increase in their expression [[39], [50]]. Δ FosB is known to be elevated during chronic exposure to drug abuse and to play a key role in the neuroplasticity that underlay addiction [51]. Increased psychomotor sensitivity to psychostimulants is promoted by Δ FosB expression [[52], [53]]. As a result, the current study's rise in Δ FosB expression provides more evidence of tramadol's misuse potential in rats.

Δ FosB may have a role in tramadol-induced behavioral and motor sensitizations by modulating the expression of Glutamate receptor subunits [[52], [54], [55]]. In both CPP and self-administration paradigms, inducing Δ FosB expression in the striatum's medium spiny neurons improves locomotor sensitivity and reward responses to cocaine [[52], [56], [57]].

In addition, tramadol administration increased two important synaptic plasticity proteins, PKC γ and PKM ζ [[58], [59]]. Within the brain, synaptic plasticity occurs at glutamatergic synapses. Tramadol induces an increase in glutamate release and a decrease in GABA system [[60], [61]] causing seizure [[62], [63]]. Tramadol may suppress this cell type by acting on mu-opioid receptors, which are only found in

GABA-ergic interneurons [64, 65, 66, 67, 68]. Within the ACC, this can help excitatory inputs to pyramidal cells or GABAergic afferent target cells. In addition, mu-opioid stimulation inhibits GABA release [69]. This decrease in GABA inhibition is most likely reflected in the current study by an increase in PKC γ [70] and PKM ζ expression in the tramadol-treated group's ACC. Both of these markers are found in excitatory cells, including pyramidal cells. Also, tramadol inhibits GABA receptors [71, 72]. The fact that GAD67 increased in the ACC of the tramadol group is probably due to an increase in general excitation within the cortex. GAD67 expression is regulated by activity [73, 74, 75, 76]. It could be due also to disinhibition within GABAergic circuitry within the ACC [77]. The expression of GAD67 is highly correlated with the amount of intracellular GABA [78].

The CPP generated by tramadol was dramatically reduced by naltrexone, a mu-opioid antagonist. It reduces behavioral as well as motor sensitizations. Furthermore, naltrexone accelerated the extinction of the tramadol-induced CPP by two days (at four days following the test day instead of 6 days in tramadol-treated rats). Tramadol-induced CPP (reinstatement) was totally prevented by continuous naltrexone (8 days after the test day) treatment. Both motor and behavioral sensitization were inhibited (Fig. 5A and B). Furthermore, naltrexone reduced all of the studied markers.

Although, naltrexone decreased significantly most of tramadol effects it did not reverse them at the control levels. This revealed that some of tramadol's effects are due to its activity other than through mu-opioid receptors [2, 3, 4, 5, 6, 7, 8] may be at central serotonergic transmission level [79].

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This study was funded by Clermont Auvergne University and all authors declare that there is no conflict of interest.

Data availability

The data that has been used is confidential.

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