(-)-Trans-Δ⁹-Tetrahydrocannabinol-Like Discriminative-Stimulus Effects of Gabapentin in Cannabis Users

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Editorial

A recent study by Dr. Joshua Lile and his colleagues demonstrated the capability of gabapentin to produce marijuana-like effects in humans. The finding is unexpected since the primary binding site of gabapentin is not thought to be any of the cannabinoid receptor subtypes. Gabapentin (Neurontin®) (Figure 1) is an FDA-approved medication for the treatment of epilepsy and neuropathic pain and several cases of its off-label use are also known. Several case reports have indicated gabapentin misuse/abuse [1-4] but the in vivo pharmacology and abuse potential of gabapentin have not yet been directly characterized. Thus, there is a clear need to characterize the in vivo pharmacology of gabapentin including its abuse potential.

In contrast to the in vitro assessment, the in vivo pharmacology of gabapentin has relatively been characterized. Gabapentin is a structural analogue of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) and 3 branched-chain γ-amino acids (L-isoleucine, L-leucine, and L-methionine) (Figure 1). Despite its structural similarity to GABA and these branched-chain γ-amino acids, several studies using radio ligand binding assays have reported low, if any, potency to GABA and these branched-chain γ-amino acids. Despite its structural similarity to GABA, pregabalin [12] and the three branched-chain γ-amino acids (L-isoleucine, L-leucine, and L-methionine) [5] (IC₅₀ values: 50-80 nM). Gabapentin, however, has at least a 7,630-fold lower affinity for the [³H]gabapentin binding site in vivo (IC₅₀ value: 610,000 nM) [5]. Based on the results from these studies using [³H]gabapentin, it is not surprising that gabapentin can influence a VDCC-mediated effect [13].

Drug discrimination procedures have high human predictive validity with respect to the subjective effects of various test articles across pharmacological classes and have served as the gold standards for characterizing drug pharmacology in vivo because of their high pharmacological specificity [14-17]. Assessment of the capacity of gabapentin to induce a discriminative-stimulus (DS) in drug naïve subjects has not been reported. Interestingly, several L-VDCC blockers (nifedipine and verapamil) by themselves have been demonstrated to condition place preference in drug naïve rats using a place-conditioning procedure [18]. Considering the potential of gabapentin to serve as a functional L-VDCC antagonist [13,19,20], gabapentin alone at an appropriate dose and treatment time may exert an in vivo action indicative of its abuse potential.

Several studies using drug discrimination procedures have assessed the capacity of gabapentin or pregabalin to substitute for various psychoactive compounds from different pharmacological classes [21-26]. Among them is a double-blind, placebo-controlled, clinical study that found gabapentin capable of full substitution for the cannabinoid CB₂ receptor (CB₂-R) partial agonist (-)-trans-Δ⁹-tetrahydrocannabinol (Δ⁹-THC) in Cannabis users trained to discriminate ingestion of Δ⁹-THC from ingestion of placebo [26]. However, this clinical result is inconsistent with preclinical findings that indicate a lack of cannabinoid-like DS effects for gabapentin in rats trained to discriminate another cannabinoid CB₁-R partial agonist, BAY 59-3074 [23]. There is currently no literature on the assessment of the binding affinity of gabapentin and other high-affinity ligands at the [³H]gabapentin-binding site for any cannabinoid receptor subtypes or endocannabinoid [e.g. anandamide and 2-arachidonoylglycerol (2-AG)] uptake enzymes. Δ⁶-THC [27,28] and BAY 59-3074 [29] have been reported to have substantial, high affinity for cannabinoid CB₁ and CB₂ receptor subtypes (Ki values: 15.3-55.4 nM). Δ⁶-THC also is known to exert potent action that is mediated through non-CB₁/2, cannabinoid G protein-coupled receptor 55 (GPR55) [30,31] that is expressed in human [32] and rat [33,34] brains while it is unknown whether BAY 59-3074 has actions at the cannabinoid GPR55. Importantly, cannabinoid GPR55 has been found to increase intracellular Ca²⁺ levels [31] and a recent in vitro study using a Bioluminescence Resonance Energy Transfer (BRET) assay

Figure 1: Chemical structures of gabapentin, γ-aminobutyric acid (GABA), pregabalin and three branched-chain γ-amino acids.

In marked contrast to GABA receptor subtypes, several in vivo studies on [³H]gabapentin-binding sites have found a 26,300-fold higher affinity of gabapentin for auxiliary α₂δ (α₂δ-1 and α₂δ-2) subunits on voltage-dependent calcium (Ca²⁺) channels (VDCCs) [9,10] in cerebral cortices of rats [5] and mice [11] (Kd values: 38 and 23 nM, respectively). Consistent with their structural similarity to gabapentin, several compounds (Figure 1) have been shown to be high-affinity ligands at the [³H]gabapentin-binding site. These include pregabalin [12] and the three branched-chain γ-amino acids (L-isoleucine, L-leucine, and L-methionine) [5] (IC₅₀ values: 50-80 nM). Gabapentin, however, has at least a 7,630-fold lower affinity for the [³H]gabapentin binding site in vivo (IC₅₀ value: 610,000 nM) [5]. Based on the results from these studies using [³H]gabapentin, it is not surprising that gabapentin can influence a VDCC-mediated effect [13].

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demonstrated that cannabinoid GPR55 can form a heteromer with cannabinoid CB1R [34] in the rat striatum. In addition, another study identified a heteromer consisting of cannabinoid CB2R and GPR55 [35]. Considering the well-characterized effect of cannabinoid CB1R agonists as L-VDCC blockers [36-42] and the potential of gabapentin to serve as a functional L-VDCC blocker [13,19,20], the full Δ⁹-THC-like DS effects of gabapentin in Cannabis users [26] might result from a blocking action of gabapentin and Δ⁹-THC at L-VDCCs.

In summary, it does appear pharmacologically important comprehensively to assess the L-VDCC-blocker- and cannabinoid-like DS effects of gabapentin and pregabalin for regulatory purposes. Further it may be important to assess whether gabapentin and pregabalin can enhance reinforcing and toxic effects of Δ⁹-THC and cannabinoid products. Given the clinical use of L-VDCC blockers against hypertension, such studies would also have significant impact on their safer use.

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References:

1. Satish R, Kandasamy A, Jayarajan D, Benegal V (2015) Gabapentin dependence in a patient with opioid dependence syndrome. J Neuropsychiatry Clin Neurosci 27: e64.
2. Häkkinen M, Vuori E, Kalso E, Gergov M, Ojanperä I (2014) Profiles of pregabalin and gabapentin abuse by postmortem toxicology. Forensic Sci Int 241: 1-6.
3. Schifano F (2014) Misuse and abuse of pregabalin and gabapentin: cause for concern? CNS Drugs 28: 491-496.
4. Howland RH (2014) Gabapentin: can it be misused? J Psychosoc Nurs Ment Health Serv 52: 12-25.
5. Suman-Chauhan N, Webdale L, Hill DR, Woodruff GN (1993) Characterisation of [3H]gabapentin binding to a novel site in rat brain: homogenate binding studies. Eur J Pharmacol 244: 293-301.
6. Larneau C, Green A, Hirst WD, Wise A, Brown JT, et al. (2001) Gabapentin is not a GABA receptor agonist. Neuropharmacology 41: 965-973.
7. Eckstein-Ludwig U, Fei J, Schwarz W (1999) Inhibition of uptake, steady-state currents, and transient charge movements generated by the neuronal GABA transporter by various anticonvulsant drugs. Br J Pharmacol 128: 92-102.
8. Belliotti TR, Caprini T, Ekhato IV, Kinsora JJ, Field MJ, et al. (2005) Structure-activity relationships of pregabalin and analogues that target the alpha(2)delta protein. J Med Chem 48: 2294-2307.
9. Marais E, Klugbauer N, Hofmann F (2001) Calcium channel alpha(2)delta subunits-structure and Gabapentin binding. Mol Pharmacol 59: 1243-1248.
10. Field MJ, Cox PJ, Stott E, Melrose H, Oloff J, et al. (2006) Identification of the alpha2-delta-1 subunit of voltage-dependent calcium channels as a molecular target for pain mediating the analgesic actions of pregabalin. Proc Natl Acad Sci U S A 103: 17537-17542.
11. Bian F, Li Z, Oloff J, Davis MD, McCormick J, et al. (2006) Calcium channel alpha2-delta type 1 subunit is the major binding protein for pregabalin in neocortex, hippocampus, amygdala, and spinal cord: an ex vivo autoradiographic study in alpha2-delta type 1 genetically modified mice. Brain Res 1075: 68-80.
12. Taylor BK, Peterson MA, Basbaum AI (1997) Early nociceptive events influence the temporal profile, but not the magnitude, of the tonic response to subcutaneous formalin: effects with remifentanil. J Pharmacol Exp Ther 280: 876-883.
13. Fink K, Dooley DJ, Meder WP, Suman-Chauhan N, Duffy S, et al. (2002) Inhibition of neuronal Ca(2+)- influx by gabapentin and pregabalin in the human neocortex. Neuropharmacology 42: 229-236.
14. Holtzman SG (1985) Drug discrimination studies. Drug Alcohol Depend 14: 263-282.
15. Schuster CR, Johanson CE (1988) Relationship between the discriminative stimulus properties and subjective effects of drugs. Psychopharmacol Ser 4: 161-175.
16. Hiranita T, Soto PL, Tanda G, Katz JL (2011) Lack of Cocaine-Like Discriminative-Stimulus Effects of a Receptor Agonists in Rats. Behav Pharmacol 22:525-530.
17. Kohut SJ, Hiranita T, Hong SK, Ebbis AL, Tronci V, et al. (2014) Preference for distinct functional conformations of the dopamine transporter alters the relationship between subjective effects of cocaine and stimulation of mesolimbic dopamine. Biol Psychiatry 76: 802-809.
18. Niala G, Langwinski R (1996) Effects of calcium channel antagonists on the reinforcing properties of morphine, ethanol and cocaine as measured by place conditioning. J Physiol Pharmacol 47: 497-502.
19. Stefani A, Spadoni F, Bernardi G (1998) Gabapentin inhibits calcium currents in isolated rat brain neurons. Neuropharmacology 37: 83-91.
20. Sutton KG, Martin DJ, Pinnock RD, Lee K, Scott RH (2002) Gabapentin inhibits high-threshold calcium channel currents in cultured rat dorsal root ganglion neurons. Br J Pharmacol 135: 257-265.
21. Besheer J, Frisbee S, Randall PA, Jaramillo AA, Masciello M (2016) Gabapentin potentiates sensitivity to the interoceptive effects of alcohol and increases alcohol self-administration in rats. Neuropharmacology 101: 216-224.
22. McDonald LM, Sheppard WR, Staveley SM, Sohal B, Tattersall FD, et al. (2008) Discriminative stimulus effects of tiagabine and related GABAergic drugs in rats. Psychopharmacology (Berl) 197: 591-600.
23. De Vry J, Jentsch KR (2004) Discriminative stimulus effects of the structurally novel cannabinoid CB1/CB2 receptor partial agonist Bay 59-3074 in the rat. Eur J Pharmacol 505: 127-133.
24. Filip M, Frankowska M, Zajewska M, Golda A, Przegalinski E, et al. (2007) Diverse effects of GABA-mimetic drugs on cocaine-evoked self-administration and discriminative stimulus effects in rats. Psychopharmacology (Berl) 192: 17-26.
25. Field MJ, Oles RJ, Lewis AS, McCleary S, Hughes J, et al. (1997) Gabapentin (neurontin) and S-(+)-3-isobutylgaba represent a novel class of selective antihyperalgesic agents. Br J Pharmacol 121: 1513-1522.
26. Lile JA, Wesley MJ, Kelly TH, Hays LR (2015) Separate and combined effects of gabapentin and [INCREMENT]³-tetrahydrocannabinol in humans discriminating [INCREMENT]³-tetrahydrocannabinol. Behav Pharmacol.
27. Brents LR, Reichard EE, Zimmerman SM, Moran JH, Fantegrossi WE, et al. (2011) Phase I hydroxylated metabolites of the K2 synthetic cannabinoid JWH-018 retain in vitro and in vivo cannabinoid 1 receptor affinity and activity. PLoS One 6: e21917.
28. Showalter VM, Compton DR, Martin BR, Abood ME (1996) Evaluation of binding in a transfected cell line expressing a peripheral cannabinoid receptor (CB2): identification of the cannabinoid receptor subtype selective ligands. J Pharmacol Exp Ther 278: 989-999.
29. De Vry J, Denzer D, Reissmueller E, Eijckenboom M, Heil M, et al. (2004) -2-[3-(trifluoromethyl)phenoxy]-4,4,4-trifluoro-1-butanesulfo nate (BAY 59-3074): a novel cannabinoid Cb1/Cb2 receptor partial agonist with antihyperalgesic and antiallodynic effects. J Pharmacol Exp Ther 310: 620-632.
30. Ryberg E, Larsson N, Stigren S, Hjorth S, Hermansson NO, et al. (2007) The orphan receptor GPR55 is a novel cannabinoid receptor. Br J Pharmacol 152: 1092-1101.
31. Lauckner JE, Jensen JB, Chen HY, Lu HC, Hille B, et al. (2008) GPR55 is a cannabinoid receptor that increases intracellular calcium and inhibits M current. Proc Natl Acad Sci U S A 105: 2699-2704.
32. Sawzdargo M, Nguyen T, Lee DK, Lynch KR, Cheng R, et al. (1999) Identification and cloning of three novel human G protein-coupled receptor genes GPR52, PsiGPR53 and GPR55: GPR55 is extensively expressed in human brain. Brain Res Mol Brain Res 64: 193-198.

33. Coria SM, Roura-Martínez D, Ucha M, Assis MA, Miguéns M, et al. (2014) Strain differences in the expression of endocannabinoid genes and in cannabinoid receptor binding in the brain of Lewis and Fischer 344 rats. Prog Neuropsychopharmacol Biol Psychiatry 53: 15-22.

34. Martínez-Pinilla E, Reyes-Resina I, Olatubia-Astibia A, Zamarbide M, Ricobaraza A, et al. (2014) CB1 and GPR55 receptors are co-expressed and form heteromers in rat and monkey striatum. Exp Neurol 261: 44-52.

35. Moreno E, Andradas C, Medrano M, Caffarel MM, Pérez-Gómez E, et al. (2014) Targeting CB2-GPR55 receptor heteromers modulates cancer cell signaling. J Biol Chem 289: 21960-21972.

36. Ross HR, Napier I, Connor M (2008) Inhibition of recombinant human T-type calcium channels by Delta9-tetrahydrocannabinol and cannabidiol. J Biol Chem 283: 16124-16134.

37. Muntoni AL, Pillolla G, Melis M, Perra S, Gessa GL, et al. (2006) Cannabinoids modulate spontaneous neuronal activity and evoked inhibition of locus coeruleus noradrenergic neurons. Eur J Neurosci 23: 2385-2394.

38. Rao GK, Kaminski NE (2006) Kaminski, Cannabinoid-mediated elevation of intracellular calcium: a structure-activity relationship. J Pharmacol Exp Ther 317: 820-829.

39. Oz M, Tchugunova Y, Dinc M (2004) Differential effects of endogenous and synthetic cannabinoids on voltage-dependent calcium fluxes in rabbit T-tubule membranes: comparison with fatty acids. Eur J Pharmacol 502: 47-58.

40. Begg M, Mo FM, Offertaler L, Bátkai S, Pacher P, et al. (2003) G protein-coupled endothelial receptor for atypical cannabinoid ligands modulates a Ca2+-dependent K+ current. J Biol Chem 278: 46188-46194.

41. Nadler V, Biegon A, Beit-Ya’annai E, Adamchik J, Shohami E (1995) 45Ca accumulation in rat brain after closed head injury; attenuation by the novel neuroprotective agent HU-211. Brain research 685: 1-11.

42. Lozovaya N, Min R, Tsintsadze V, Burnashev N (2009) Dual modulation of CNS voltage-gated calcium channels by cannabinoids: Focus on CB1 receptor-independent effects. Cell Calcium 46: 154-162.

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