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Editorial Open Access

(–)-Trans- Δ 9-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 vivo* assessment, the *in vitro* 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, affinity of gabapentin (3-cyclohexyl-GABA) for GABA receptor subtypes (no inhibition at up to 1,000,000 nM) [5,6] and low, if any, potency to inhibit the uptake of [^{3}H]-GABA (Ki value: 50,000 nM) [7] or [^{3}H]-leucine (Ki value: 30,000 nM) [8].

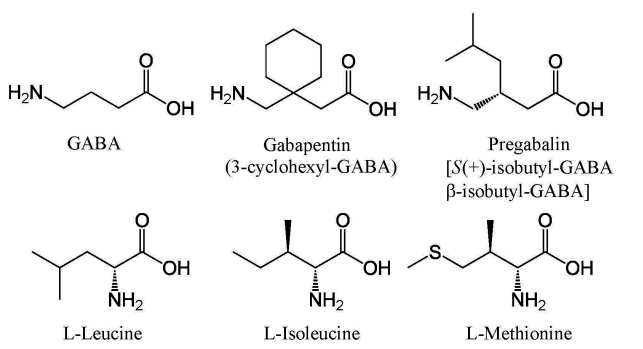

Figure 1: Chemical structures of gabapentin, γ-aminobutyric acid (GABA), pregabalin and three branched-chain γ-amino acids.

In marked contrast to GABA receptor subtypes, several *in vivo* studies on [^{3}H] gabapentin-binding sites have found a 26,300-fold higher affinity of gabapentin for auxiliary α2δ (α2δ-1 and α_2δ-2) subunits on voltage-dependent calcium (Ca^{2+}) 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 [^{3}H] gabapentin-binding site. These include pregabalin [12] and the three branched-chain γ-amino acids (L-isoleucine, L-leucine, and L-methionine) [5] (IC_{50} values: 50-80 nM). GABA, however, has at least a 7,630-fold lower affinity for the [^{3}H] gabapentin binding site *in vivo* (IC_{50} value: 610,000 nM) [5]. Based on the results from these studies using [^{3}H] 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 $CB_{1/2}$ receptor ($CB_{1/2}R$) partial agonist (–)-trans-Δ^9-tetrahydrocannabinol (Δ^9-THC) in Cannabis users trained to discriminate ingestion of Δ^9-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 $CB_{1/2}R$ 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 [^{3}H] gabapentin-binding site for any cannabinoid receptor subtypes or endocannabinoid [e.g. anandamide and 2-arachidonoylglycerol (2-AG)] uptake enzymes. Δ^9-THC [27,28] and BAY 59-3074 [29] have been reported to have substantial, high affinity for cannabinoid CB_1 and CB_2 receptor subtypes (Ki values: 15.3-55.4 nM). Δ^9-THC also is known to exert potent action that is mediated through non-CB1/2R, 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 Ca^{2+} levels [31] and a recent *in vitro* study using a Bioluminescence Resonance Energy Transfer (BRET) assay

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 CB_2R 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 Δ^9-THC-like DS effects of gabapentin in Cannabis users [26] might result from a blocking action of gabapentin and Δ^9-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 Δ^9-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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