Neuropharmacology 114 (2017) 168–171

Contents lists available at ScienceDirect

Neuropharmacology

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

Commentary

A novel inhibitor of endocannabinoid catabolic enzymes sheds light on behind the scene interplay between chronic pain, analgesic tolerance, and heroin dependence

Josée Guindon

Department of Pharmacology and Neuroscience, Texas Tech University Health Sciences Center, 3601 4th Street STOP 6592, Lubbock, TX, 794304, USA

ARTICLE INFO

Article history:
Accepted 21 November 2016
Available online 25 November 2016

Keywords:
Cannabinoid
Fatty-acid amide hydrolase (FAAH)
Monoacylglycerol lipase (MAGL)
Morphine
Heroin
Self-administration
Addiction
Reward
Chronic pain

ABSTRACT

From the Aristotelian ancient Greece, pain has been associated with appetites or emotions and is opposite to pleasure. Reward and addiction is also linked to pleasure and compulsive drug seeking reinstates pleasure. Alleviation of chronic pain can induce a euphoric phase similar to what is found in addiction. Both chronic pain and addiction are recognized as a disease of the central nervous system. They share many characteristics and brain regions/mechanisms. Evidence points to the usefulness of cannabinoids as a new class of agents to add to the pharmaceutical toolbox in the management of chronic pain. Wilkerson and colleagues, in this issue, examine SA-57, an inhibitor of two different endocannabinoid catabolic enzymes FAAH and MAGL, demonstrating its analgesic effectiveness and morphine-sparing properties in a chronic pain model, as well as its ability to reduce heroin seeking behavior in a self-administration paradigm in mice. This timely study emphasizes the need for development of more efficacious chronic pain therapeutics with minimized abuse potential and/or reinforcing properties. It also highlights the need for better understanding of the overlapping circuitry of chronic pain, reward, and addiction.

Pain comes from the Latin word *peona* defined as punishment or penalty. Pain is an unpleasant, complex, personal, and subjective sensation originating from ongoing or impending tissue damage that can range in intensity from slight to severe to indescribable. Its definition has evolved greatly through advancement in both our understanding of the neuronal circuitry contributing to pain transmission/modulation as well as ongoing improvements in the evaluation of its effects, reviewed by Vardeh et al. (2016). However, pain is a complex multi-dimensional experience associated with sensory-discriminative, cognitive-evaluative, and motivational-affective dimensions that further its complexity (Apkarian et al., 2009; Neugebauer, 2015). Despite improvement in our understanding of pain pathways through breakthrough discoveries, the scourge of the affliction for chronic pain patients continues unabated. Indeed, chronic pain afflicts more than 120 million Americans and costs $600 billion annually in medical expenses, loss of work productivity, and long-term insurance disability (Gaskin and Richard, 2012; Nahin, 2015). Management of moderate and severe chronic pain is clinically challenging due to absence of long-term effective therapies lacking major side effects, with current analgesics inefficient in ~70% of patients (Kremer et al., 2016). This lack of efficacy could be due to our primary focus of alleviating the sensory component of pain without fully considering its cognitive and affective dimensions. Chronic pain is an entity on its own that integrates the three dimensions of pain and these dimensions need to be addressed as a whole for optimal treatment.

The ancient Greeks had defined and associated pain with the emotions or appetites. They considered pain to be the opposite of pleasure (Boring, 1942; Livingstone, 1998). Throughout the years, our understanding of pain pathways has evolved from the specificity (Descartes, 1664), gate-control (Melzack and Wall, 1965), and body-self matrix (Melzack, 1999) theories. Chronic pain is defined as pain that persists after all possible healing has occurred and last more than 3 months and has no survival value (Kehlet et al., 2006; Apkarian et al., 2009). In this modern era where multiple sources of technology, through special application (e.g., measurement of heart rate, activity levels, sleep patterns, or assessment of pain levels), are used on a daily basis, we are still in need of developing long-lasting, highly efficacious and personalized therapies for chronic pain.

Different pharmacological approaches exist to alleviate pain such as nonsteroidal anti-inflammatory drugs (NSAIDs), opioids,

E-mail address: josee.guindon@ttuhsc.edu.

http://dx.doi.org/10.1016/j.neuropharm.2016.11.018
0028-3908/

anticonvulsants, antidepressants, local anesthetics, cannabinoids and others (Guindon et al., 2007; Vardeh et al., 2016). Evidence is mounting that the use of cannabinoids for the treatment of chronic pain constitutes a new class of agents to add to the pharmaceutical toolbox in the management of chronic pain (Eisenberg et al., 2014; Lynch and Ware, 2015). Indeed, it has been demonstrated that selective fatty-acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL) inhibitors produce antinociceptive effects in acute, inflammatory and neuropathic (Guindon et al., 2013; Grim et al., 2014) pain models. Moreover, simultaneous inhibition of these enzymes produce enhanced antinociceptive effects in different pain models (Long et al., 2009; Adamson Barnes et al., 2016).

In this issue, Wilkerson et al. (2017) report that SA-57 (a dual FAAH-MAGL inhibitor) reduces inflammation in the carrageenan inflammatory pain model and partially reduces edema through increases in endocannabinoid levels (AEA and 2-AG). SA-57 also alleviates mechanical allodynia, and these anti-allodynic properties are mediated by both CB_1 and CB_2 receptors as demonstrated by the use of CB_1 and CB_2 knockout mice. However, the anti-edematous effect of SA-57 is only found in $CB_1-/-$ mice and $CB_2-/-$ are resistant to this effect. These results set the tone to the investigation of the effect of combining this dual FAAH-MAGL inhibitor with an opioid in a chronic pain model.

Clinical studies suggest that cannabinoids used in combination with opioids reduce opioid dosing, thereby contributing to lower side effects (Abrams et al., 2011; Johnson et al., 2013). Wilkerson et al. (2017) demonstrate the morphine-sparing effect of SA-57 in the chronic constriction injury (CCI) neuropathy model (Fig. 1). They show that SA-57 and morphine individually reverse allodynia while their combinations, at equivalent doses (1:1), produce a leftward shift of the dose-response curve and demonstrate an additive anti-allodynic effect. Importantly, the combination of threshold doses of SA-57 and morphine fully reversed CCI-induced allodynia and thermal hyperalgesia following either acute or repeated administration. Moreover, this combination of SA-57 with morphine produces anti-allodynic, but no other cannabimimetic effects.

Recent studies have highlighted the overlap between chronic pain circuitry and reward pathways (Elman and Borsook, 2016; Navratilova et al., 2015). However, the conceptual premise of pain being a disorder of the reward function has been analyzed and debated for millennia. Indeed, Aristotle claimed in his rhetoric that human beings will move toward pleasure (gratification of immediate needs) and away from painful stimuli. Here, Wilkerson et al. have demonstrated that SA-57, in addition to its morphine sparing effect in alleviating chronic pain symptoms, also exhibited suppression of escalated opioid (heroin) self-administration. This reinforces the link between chronic pain and escalation of drug use in terms of common behavioral characteristics and brain mechanisms.

Previous studies showed that URB597, a selective FAAH inhibitor, did not affect reinforcing efficacy of heroin at any doses (0.01–0.3 mg/kg ip) tested (Solinas et al., 2005). By contrast, Wilkerson et al. demonstrate that SA-57, a dual FAAH-MAGL inhibitor, significantly diminishes escalated self-administration in mice trained to nose poke for intravenous administration of heroin from day 4 until day 15 (Fig. 1). Moreover, mice subjected to a progressive ratio procedure (increases in nose-pokes required to obtain each subsequent infusion of 0.25 mg/kg of heroin) and treated with 1, 2.5, or 5 mg/kg of SA-57 demonstrate reduced break point (the mice stop responding which correspond to end point) compared to vehicle-treated mice (Fig. 1). However, SA-57 did not change the extinction or reinstatement phase of heroin behavior.

Chronic pain is a multidimensional entity interconnecting the cognitive, sensory, and affective dimensions of pain and frequently

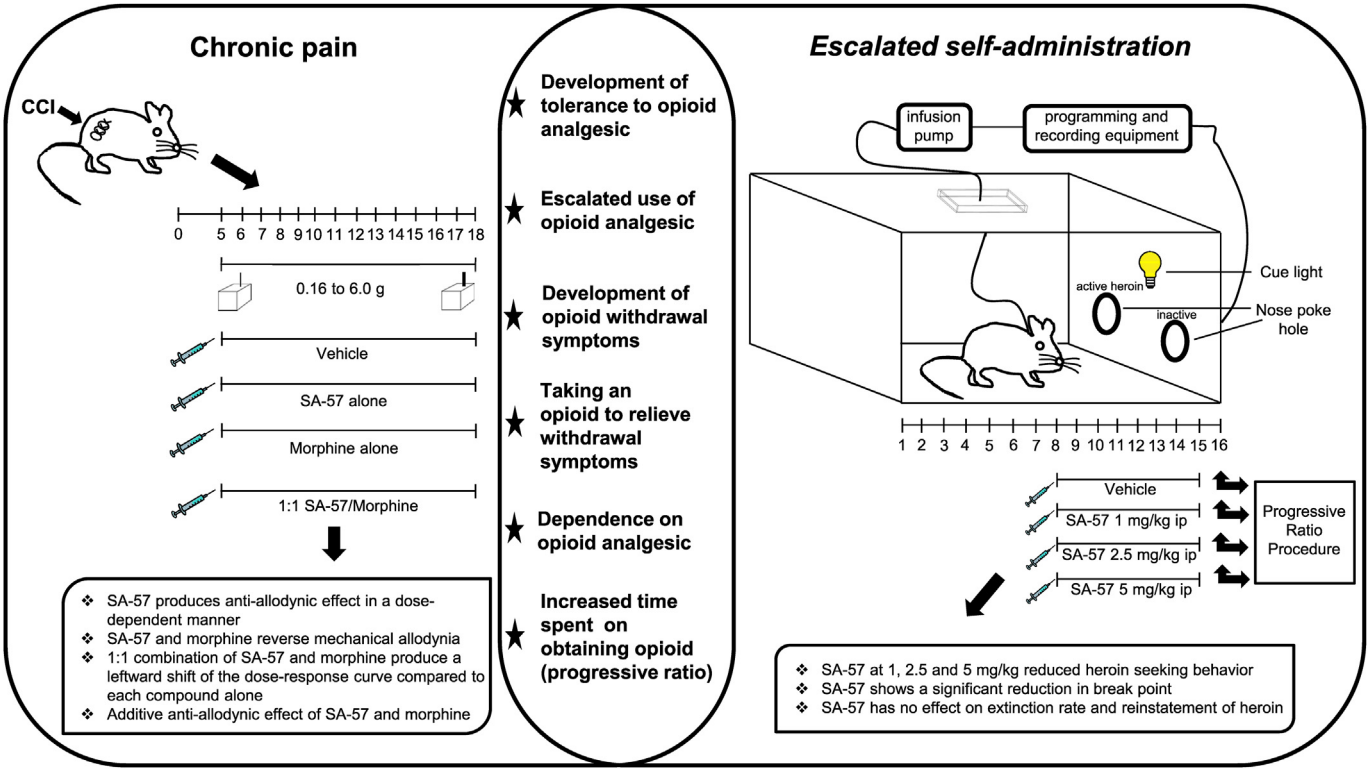

Fig. 1. Schematic representation of SA-57, a dual FAAH-MAGL inhibitor used in chronic pain and self-administration models. The two models show common characteristics detailed in the middle (oval defined as merging point). The simultaneous study of this dual FAAH-MAGL inhibitor in both chronic pain and self-administration paradigms highlight the common pattern of escalated use of analgesic opioids in chronic pain states.