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Structure activity relationship studies on chemically non-reactive glycine sulfonamide inhibitors of diacylglycerol lipase

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ABSTRACT

N-Benzylic-substituted glycine sulfonamides that reversibly inhibit diacylglycerol (DAG) lipases are reported. Detailed herein are the structure activity relationships, profiling characteristics and physicochemical properties for the first reported series of DAG lipase (DAGL) inhibitors that function without covalent attachment to the enzyme. Highly potent examples are presented that represent valuable tool compounds for studying DAGL inhibition and constitute important leads for future medicinal chemistry efforts.

1. Introduction

Regulation of the endocannabinoid signaling system is an emerging strategy for potential therapeutic intervention in a variety of diseases,[1] including; anxiety,[2] depression,[3] pain,[4] inflammation,[5] hepatic steatosis and obesity.[6] Here we describe efforts to regulate the endocannabinoid signaling system by modulating the levels of the endogenous cannabinoid agonist, 2-arachidonoylglycerol (2-AG) through inhibition of the enzymes predominantly responsible for its biosynthesis.

The endocannabinoid signaling system consists of the cannabinoid receptors CB_1 and CB_2, the endogenous agonists (endocannabinoids) anandamide (ANA) and 2-AG, and the enzymes that regulate endocannabinoid synthesis and degradation. CB_1 and CB_2 are G-protein coupled receptors (GPCRs) that are widely distributed throughout the body. CB_1 is one of the most abundant GPCRs in the brain and is also located to a lesser extent in the liver, adipose tissue, gastrointestinal tract, as well as in vagal nerves, pancreas and skeletal muscle. In contrast, CB_2 is found mainly in cells of the immune system.[7–12]

Attempts to prepare compounds that modulate the CB_1 or CB_2 receptors without inducing significant side effects have met with limited success. For example, the synthetic cannabinoid agonist nabilone is approved for the treatment of chemotherapy-induced nausea and vomiting that has not responded to conventional antiemetics. However, nabilone produces psychoactive side effects similar to those observed with marijuana.[13] The CB_1 antagonist rimonabant and the inverse agonist taranabant inhibit food intake and reduce body weight in obese animals and humans. However, these agents are known to induce central nervous system (CNS) side effects including anxiety and depression.[14]

An emerging alternative strategy to receptor agonism or antagonism is to regulate tissue levels of the endocannabinoids.[12,5,15] Presented here are the SAR, profiling properties and pharmacokinetics of the first reported chemically non-reactive inhibitors of 2-AG synthesis.[16,17] Diminished 2-AG levels are expected to produce a corresponding reduction in cannabinoid receptor (CR) activation. Unlike many typical neurotransmitters, 2-AG is not stored in vesicles; rather, it is rapidly synthesized (in an on-demand fashion) in response to rising cellular calcium levels, or alternatively, by activation of $G_{q/11}$ protein coupled receptors.[12,15,18,19] 2-AG is produced by the reaction sequences depicted in Figure 1.[20] Initial cleavage of the sugar moiety from membrane associated phosphatidyl inositol by phosphatidyl lipase C (PLC) results in the for-

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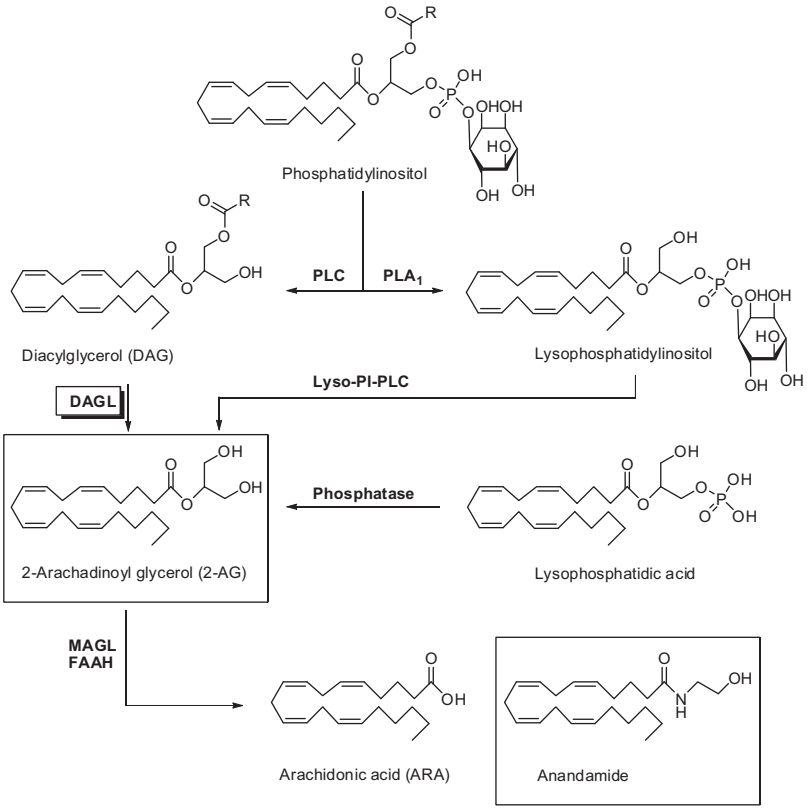

Figure 1. Principal endocannabinoids 2-AG and anandamide. The major routes for the anabolism and catabolism of 2-AG are shown. Enzymes exist to catalyze the reverse reactions depicted in most of the anabolic steps shown, and the transient tissue concentrations of 2-AG represent the balance between the rates of these competing reactions. Fatty acid amide hydrolaze (FAAH), phosphatidylinositol-specific phospholipase C (Lyso-PI-PLC), Phospholipase A1 (PLA_1).

mation of diacylglycerol (DAG). DAG is subsequently hydrolyzed by diacylglycerol lipase (DAGL) resulting in the formation of 2-AG. Once formed, 2-AG acts as a retrograde messenger by activating CRs on presynaptic neurons. Alternatively, 2-AG can be synthesized by the phosphatase mediated cleavage of lysophosphatidic acid, though this pathway is thought to be a minor contributor to tissue levels. In relation to its catabolism, 2-AG is cleared by the action of several enzymes, with the major pathway thought to involve monoacylglycerol lipase (MAGL). Thus the levels of 2-AG are tightly controlled primarily by the actions of DAGL and MAGL. Consistent with this observation is that genetically-modified animals that lack DAGL-α exhibit decreased tissue concentrations of 2-AG.[21,22]

In this manuscript, we focus on inhibiting the activity of DAGL as a point of potential therapeutic intervention. Inhibition of DAGL should lead to reduced levels of 2-AG and a corresponding reduction in CR activation.[23] Consequently, it is anticipated that a DAGL inhibitor will be functionally equivalent to a CR antagonist. However, the effects of a DAGL inhibitor would be localized to sites where 2-AG is actively being synthesized, and thus it might be anticipated to have an improved side-effect profile relative to a CR antagonist.

DAGLs are serine hydrolases that exist as membrane associated proteins. There are two known isoforms of the enzyme, DAGL-α and DAGL-β.[24] DAGL-α is predominantly found in the CNS where it is localized in post-synaptic neurons (Fig. 2), in contrast to DAGL-β that is found mainly in the periphery.[21,25,26] Postsynaptic neurons generate and release 2-AG which acts as a retrograde messenger by activating CRs on presynaptic neurons.[27,28] Activation of the presynaptic CR regulates the release of the neurotransmitters GABA and glutamate. In certain disease states, tissue levels of 2-AG can be altered and result in changes to the activation level of

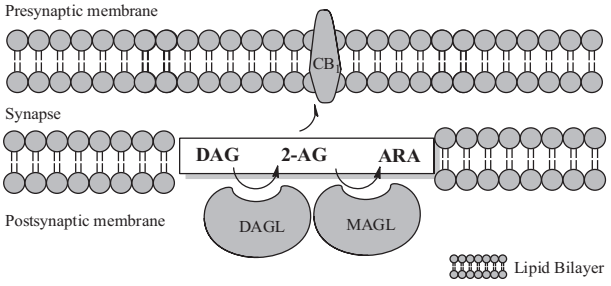

Figure 2. Sites of synthesis and degradation of 2-AG and a depiction of its role as a retrograde neurotransmitter; activation of presynaptic CB_1 receptors can result in a variety of responses dependent on the G-protein to which the receptor is coupled.

the CRs.[9–11,29–31] This activation can impact the functional output of the GABAergic and glutamatergic systems, as is the case in Alzheimer's or Parkinson's diseases where the regulatory function of 2-AG is thought to be disrupted.[29] 2-AG also functions in the periphery, where DAGL inhibitors are anticipated to have therapeutic potential in the treatment of diseases such as obesity, metabolic syndrome, liver fibrosis and allergic contact dermatitis.[5,10,11,32]

Prior to our initial disclosure[16,17] and a subsequent related publication,[25] the only reported inhibitors of DAGL were chemically reactive molecules that function by covalently modifying DAGL. Such irreversible inhibitors are expected to display several potential liabilities related to toxicity and a lack of selectivity. For example, tetrahydrolipstatin (**1**) covalently modifies both DAGL-α and DAGL-β (Fig. 3).[33] In addition, **1** blocks several brain serine hydrolases with similar potencies to those observed against DAGL-α and