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Self-Administration of an Endogenous Cannabinoid 2-Arachidonoylglycerol in Experimentally Naïve Rats

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A recent study by Dr. Maria Antonietta De Luca demonstrated intravenous (IV) self-administration responding (nose-poking) of an endogenous compound in an experimentally naïve, adult rat species [1]. Surprisingly, response-dependent changes of visual stimulus were not presented in the study when the compound was injected. This finding is very unique since there is few if any endogenous compounds that have been reported to maintain self-administration responding above vehicle levels through an IV route of administration (i.e. not intracranial self-injections) in rodent species. Further, it is also likely that a phytocannabinoid (–)-trans-9-tetrahydrocannabinol (9-THC, Figure 1), a primary psychoactive constituent in marijuana, is not an effective reinforcer in rat [2,3] and rhesus monkey species [4-6] relative to standard drugs of abuse [7].

The use of marijuana has been legalized in two states of the U.S as of today. Despite high effectiveness of 9-THC in experimentally naïve squirrel monkeys [8], 9-THC has been reported to fail to maintain IV self-administration responding above vehicle levels in rats [2,3] and rhesus monkeys [4-6]. On the other hand, there continues to be an increase in the abuse and non-medical use of a number of ‘designer’ drugs [9-11]. Among these drugs are synthetic cannabinoids that are frequently found in many K2/Spice preparations [9-11]. Several synthetic cannabinoids have been found to maintain IV self-administration responding in experimentally naïve rats [12-16], and mice [17-20]. For endocannabinoids, only anandamide has been demonstrated to maintain IV self-administration responding in a squirrel monkey species [21]. However, the sample size was only one to draw any conclusion [21]. Using IV drug self-administration procedures in squirrel monkeys, another endocannabinoid 2-arachidonoylglycerol (Figure 1) has been shown to substitute for anandamide or (–)-nicotine [22]. These findings may suggest the reinforcing effects of endocannabinoid in rats. Importantly, the IV self-administration of endocannabinoid anandamide in an experimentally naïve squirrel monkey [21] and of synthetic cannabinoids in experimentally naïve rats [13,14] and mice [17,19,20] occurred when response-dependent changes of visual stimulus were presented. Despite the low effectiveness of phytocannabinoid 9-THC in rats as a positive reinforcer and a lack of response-dependent

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changes of visual stimulus, the endocannabinoid 2-arachidonoylglycerol maintained IV self-administration responding above vehicle levels in all six of six experimentally naïve rats assessed (i.e., 100% of rats assessed) [1]. The finding should be appreciated because endogenous monoamine dopamine, an important neurotransmitter for induction of reinforcing effects of stimulants [23,24], failed to maintain IV self-administration responding above vehicle levels when substituted for (-)-cocaine in rats [25]. Further, a dopamine D2-like agonist quinpirole has been found to fail to induce IV self-administration responding above vehicle levels in experimentally naïve rats even when a response-dependent injection-paired visual stimulus was presented [26,27]. In addition, (-)-nicotine has been found to fail to induce IV self-administration responding above vehicle levels in experimentally naïve rats when an injection-paired visual stimulus was absent [28]. Finally a synthetic cannabinoid WIN 55,212-2 was reinforcing in only a maximum of 85.7% of experimentally naïve rats assessed (=12/14) among a range of several injection doses [13]. Thus it appears that the endocannabinoid 2-arachidonoylglycerol is a relatively effective positive reinforcer in rats.

As mentioned above, the abuse of synthetic cannabinoids is increasing [9,10]. Despite the low effectiveness of a phytocannabinoid 9-THC in a rat species [2,3], Dr. De Luca found a relatively high capacity of an endocannabinoid 2-arachidonoylglycerol to induce reinforcing effects in experimentally naïve rats [1]. The self-administration model of 2-arachidonoylglycerol may be useful to study pharmacology of endocannabinoids. In addition, the finding may lead to further development of medications for cannabinoid abuse in humans using a rat species.

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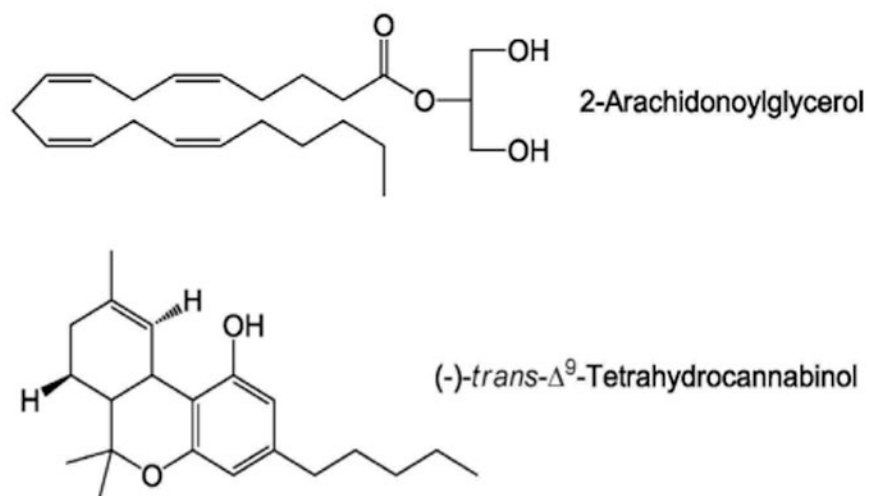


Figure 1. Chemical structures of 2-arachidonoylglycerol (1,3-dihydroxy-2-propanyl (5Z,8Z,11Z,14Z)-5,8,11,14-eicosatetraenoate) and (-)-trans- Δ^9 -tetrahydrocannabinol [($-$)-(6aR,10aR)-6,6,9-trimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6H-benzo[c]chromen-1-ol].