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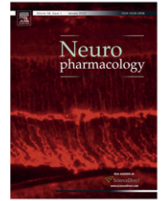

Pharmacological elevation of anandamide impairs short-term memory by altering the neurophysiology in the hippocampus

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In rodents, many exogenous cannabinoid agonists including Δ^9-THC and WIN55,212-2 (WIN-2) have been shown to impair short-term memory (STM) by inhibition of hippocampal neuronal assemblies. However, the mechanisms by which endocannabinoids such as anandamide and 2-arachidonyl glycerol (2-AG) modulate STM processes are not well understood. Here the effects of anandamide on performance of a Delayed-Non-Match-to-Sample (DNMS) task (i.e. STM task) and concomitant hippocampal ensemble activity were assessed following administration of either URB597 (0.3, 3.0 mg/kg), an inhibitor of the Fatty Acid Amide Hydrolase (FAAH), AM404 (1.5, 10.0 mg/kg), a putative anandamide uptake/FAAH inhibitor, or *R*-methanandamide (3.0, 10.0 mg/kg), a stable analog of anandamide. Principal cells from hippocampal CA3/CA1 were recorded extracellularly by multi-electrode arrays in Long-Evans rats during DNMS task (1–30 s delays) performance and tracked throughout drug administration and recovery. Both *R*-methanandamide and URB597 caused dose- and delay-dependent deficits in DNMS performance with suppression of hippocampal ensemble activity during the encoding (sample) phase. *R*-methanandamide-induced effects were not reversed by capsaicin excluding a contribution of TRPV-1 receptors. AM404 produced subtle deficits at longer delay intervals but did not alter hippocampal neuronal activity during task-specific events. Collectively, these data indicate that endocannabinoid levels affect performance in a STM task and their pharmacological elevation beyond normal concentrations is detrimental also for the underlying physiological responses. They also highlight a specific window of memory processing, i.e. encoding, which is sensitive to cannabinoid modulation.

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1. Introduction

Systemic administration of phytocannabinoids or synthetic receptor agonists such as Δ^9-Tetrahydrocannabinol (Δ^9-THC), WIN55,212-2 and HU-210 impair working memory (WM) and short-term memory (STM) in rodents (Heyser et al., 1993; Lichtman et al., 1995; Ferrari et al., 1999; Hampson and Deadwyler, 2000; Mishima et al., 2001; Varvel and Lichtman, 2002; Hampson et al., 2003; Goonawardena et al., 2010a,b; Robinson et al., 2010). Unexplored, however, remains the role(s) played by endogenous cannabinoids such as arachidonoyl ethanolamide (anandamide) and 2-arachidonyl glycerol (2-AG) on these different memory processes. Their presence in memory-relevant areas of the rodent brain (Di Marzo et al., 2001) together with the localization of cannabinoid (CB1) receptors on different cell types (Marsicano and Lutz, 1999; Domenici et al., 2006) in hippocampus and pre-frontal cortex (Herkenham et al., 1991) suggests that the endocannabinoid system could play a pivotal role in modulating both WM and STM processes. Typically, endocannabinoid function has been probed by administration of SR141716A , a well-known CB1 receptor antagonist. When given alone SR141716A enhanced STM in a radial-arm maze at long, but not short delays (Lichtman, 2000; Wolff and Leander, 2003), short-term social recognition memory (Terranova et al., 1996) and passive avoidance retention (Mazzola et al., 2003). More recently, we provided evidence for an intriguing prolongation of long-term spatial memory in rats (Robinson et al., 2008) suggesting that the time course of memory is normally curtailed by the activation of CB1 receptors. This is in line with evidence that

Abbreviations: 2-AG, 2-Arachidonyl glycerol; DNMS, Delayed-non-match-to-sample; FAAH, Fatty acid amide hydrolase; STM, Short-Term Memory; WIN-2, WIN55,212-2; WM, Working memory; SR, Sample response; NR, Non-match response; TRPV-1, Transient-receptor-potential-vanilloid type-1.

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SR141716A impairs extinction learning in the Morris water maze (Varvel et al., 2005) and extinction of conditioned freezing either to a tone or context (Marsicano et al., 2002; Suzuki et al., 2004) suggesting that an endocannabinoid tone is crucial for various forms of learning and memory.

Anandamide, the first endocannabinoid to be isolated (Devane et al., 1992) produces WM deficits in rats trained to perform a non-match-to-position operant conditioning task (Mallet and Beninger, 1998). Around the same time, Murillo-Rodriguez et al. (1998) confirmed that intra-cerebroventricular (icv) administration of anandamide weakens memory consolidation. Such a direct role of the hippocampal endocannabinoid system was proven in long-term memory since intra-hippocampal infusions of anandamide produced anterograde amnesia in rats trained to perform a one trial, step-down inhibitory avoidance task (Barros et al., 2004), and chronic infusions of rimonabant (CB1 receptor antagonist/inverse agonist) via minipumps enhanced acquisition learning and prolonged spatial memory possibly by preventing extinction learning (Robinson et al., 2008).

Since anandamide is rapidly metabolized and/or recycled into the cell, other studies have used *R*-methanandamide, a metabolically stable analog of anandamide, to better understand how this particular endocannabinoid modulates learning and memory.

R-methanandamide dose-dependently disrupted operant conditioning through a CB1 receptor mediated mechanism (Brodkin and Moerschbaecher, 1997), impaired recognition memory in rats (Kosiorek et al., 2003), and disrupted WM in the water maze in mice (Varvel and Lichtman, 2002; Varvel et al., 2006). These data strongly implicate endogenous cannabinoids in several forms of memory and warrant its use in this study. However, *R*-methanandamide may also activate transient-receptor-potential-vanilloid type-1 (TRPV-1) receptors in the hippocampus (Chavez et al., 2010; Bhaskaran and Smith, 2010) and any drug-related action may not be specific to CB1 receptor mediated functions. Consequently, *R*-methanandamide was also assessed in the presence of capsazepine in an attempt to define a putative involvement of the TRPV-1 receptor in this STM task.

An alternative approach to modulate endocannabinoid levels is by interference with the metabolism of anandamide. It is metabolized by Fatty Acid Amide Hydrolase (FAAH), an integral membrane protein widely distributed in the rodent brain including the hippocampus (Freund et al., 2003). Various FAAH inhibitors have been developed including the well characterized URB597, known to deactivate FAAH and increase anandamide levels in the rodent brain at a dose of 0.3 mg/kg (Fegley et al., 2004). The same dose caused WM deficits in a delayed-alternation task in a T-maze (Seillier et al., 2010) without producing side effects (e.g. hypomotility, hypothermia, etc.) that often accompany exogenously administered CB1 receptor agonists. Such a pharmacological approach is thus preferred over synthetic cannabinoids.

A third possibility for pharmacological elevation of brain levels of anandamide is via the inhibition of its putative transporter protein. AM404 is an inhibitor of this transporter and lacks any direct action on cannabinoid receptors (Kelley and Thayer, 2004; Fegley et al., 2004; Fowler et al., 2004). However, AM404 may also act as a FAAH inhibitor (Glaser et al., 2003; Abush and Akirav, 2010) thereby inhibiting two possible mechanisms that physiologically can curtail the actions of anandamide. Systemic injections of AM404 (5 mg/kg) impaired spatial learning in the water maze (Abush and Akirav, 2010), but it dose-dependently (2–10 mg/kg) enhanced extinction (i.e. block reconsolidation) of conditioned fear memory in rodents (Chhatwal et al., 2005; Pamplona et al., 2008) suggesting effectiveness of treatment in terms of mnemonic systems.

Here, we reasoned that if these compounds were applied to rats trained in a delayed-non-match-to-sample (DNMS) task, the resulting effects on STM and hippocampal ensemble firing in DNMS relevant phases (Hampson and Deadwyler, 2000; Goonawardena et al., 2010b) could shed new light on the physiological role of the endocannabinoid system in behaviorally defined situations.

2. Material and methods

2.1. Animals

Adult male, Long-Evans rats (Harlan, USA) aged between 6 and 8 months (280–350 g) were individually housed in a temperature-controlled (20–22 °C) environment with a 12 h light/dark cycle (lights on 7 am–7 pm). All animals were water-restricted throughout training and drug testing, but allowed free access to food (regular rat-chow). The volume of water consumed and weights was monitored daily to maintain ∼83% of *ad libitum* body weight. Water consumption during behavioral testing was recorded, and a supplemental volume given immediately after the session to provide 20–22 h of water deprivation. All animal care and experimental procedures including water regulation and surgery were approved by the Wake Forest University Institutional Animal Care and Use Committee and were in concordance with the National Institutes of Health (NIH) Guide for the Care and use of Laboratory Animals (NIH Publications No. 8023, revised 1978).

2.2. Apparatus

The apparatus as described previously (Heyser et al., 1993; Deadwyler et al., 2007; Goonawardena et al., 2010a,b) consisted of a $43 \times 43 \times 50$ cm Plexiglass behavioral testing chamber with two retractable levers (left and right) positioned on either side of a water trough in the front panel and a nose-poke device mounted at the center of the back panel. A cue light (28-V) was located immediately above the nose-poke device. The test chamber was illuminated by two 28-V incandescent house lights mounted into the ceiling next to a video camera which recorded the behavior of rats continuously. The entire apparatus was computer-controlled and housed inside a commercially built sound-attenuated cubicle (Industrial Acoustics Co., Bronx, New York, USA).

2.3. Behavioral training procedure

All animals were trained to perform the DNMS task (Deadwyler and Hampson, 2004; Deadwyler et al., 2007; Goonawardena et al., 2010a,b). Each trial consisted of three main phases: *Sample*, *Delay* and *Non-match*. It was initiated at the *Sample* phase in which either the left or right lever was selected at random and extended (counterbalanced design). The animal responded by pressing the lever (Sample Response; SR), which was immediately retracted, thereby initiating the *Delay* phase of the task (1–30 s). In the *Delay* phase a cue light over the nose-poke device on the opposite wall was illuminated and the animal was required to respond with at least one nose-poke to terminate the delay phase. The last nose-poke at the end of the delay phase also turned out the cue light and extended both levers in the front panel, signaling the onset of the *Non-match* phase. Only a Non-match Response (NR) on the lever opposite to the position of the SR was rewarded. Reinforcement consisted of a drop of water (40 μL) delivered to the trough immediately after the NR occurred. At the termination of the *Non-match* phase both levers were retracted for a 10 s inter-trial interval (ITI) with house lights on, after which one lever was extended again and the next trial started with the onset of the *Sample* phase. An error consisting of a 'Match Response' resulted in no water reward and caused the house lights to be turned off for 5 s with both levers retracted, after which house lights were re-illuminated for another 5 s, and the next trial started. All animals were trained to criterion of 90% correct responding on trials with delays of 1–5 s in sessions of 100 trials; delays varied from 1 to 30 s prior to surgery (i.e. implantation of electrode arrays), and animals were re-trained to the same level after surgical recovery and before drug testing.

2.4. Surgery

Following training, animals were anesthetized under a constant flow of isoflurane (3% for induction, 1.5% for maintenance)/O_2 (100%) mixture and placed in a stereotaxic frame. A craniotomy (5 mm diameter) was performed over the dorsal hippocampus so that the center pair of array electrodes consisting of sixteen stainless steel micro-wires (diameter: 40 μm each; Neurolinc Corp., NJ, USA) was positioned 3.4 mm posterior and 3.0 mm lateral to Bregma (Paxinos and Watson, 1998). The longitudinal axis of the array was angled 30° to the midline, with posterior electrodes more lateral than anterior sites. The array was lowered in 25–100 μm steps to a depth of 3.0–4.0 mm from the cortical surface for CA3 leads (eight long wires), and CA1 leads (eight short wires) automatically positioned 1.2 mm higher along the longitudinal axis of the hippocampus. Electrodes were spaced 200 μm apart within each row and 400 μm between rows. Recordings from all micro-wire electrodes were monitored throughout surgery to ensure correct placement in appropriate hippocampal cell layers and the exposed cortex was kept moist with 0.9% sodium chloride. After array placement, the cranium was sealed

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