Supporting Information

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SI Methods

Tissue Processing and Lipid Extraction for Endocannabinoid Measurement. After rapid decapitation, the hippocampus was dissected and placed in precooled tubes and frozen in liquid nitrogen within 3 min of decapitation. Tissue samples were stored at −80 °C until extraction. For detection of endocannabinoids, the collected hippocampal tissue was weighed and homogenized in 2-mL polypropylene tubes (Sarstedt). For lipid extraction, internal standards consisting of the stable isotope-labeled endocannabinoids arachidonyl ehanolamide-d4, 2-arachidonoyl glycerol-d5, palmitoyl ethanolamide-d4, *N*-arachidonoyl dopamine-d8, and arachidonoyl glycine-d8 (synthesized by Roche Diagnostics, and Cayman) were added to the tubes. The purity of these materials was >97.2%. Then, 1 mL methyl tertiary butyl ether (Sigma-Aldrich) was added, and the mixture was vortexed for 30 s and centrifuged at 12,000 × *g* for 6 min. The clear supernatant was transferred into clean 2-mL polypropylene tubes (Sarstedt) and evaporated under N2 at 37 °C. Dried organic phases were then reconstituted in 100 μL acetonitrile, vortexed for 30 s, and centrifuged at 12,000 × *g* for 6 min; endocannabinoid levels were determined with HPLC and tandem MS.

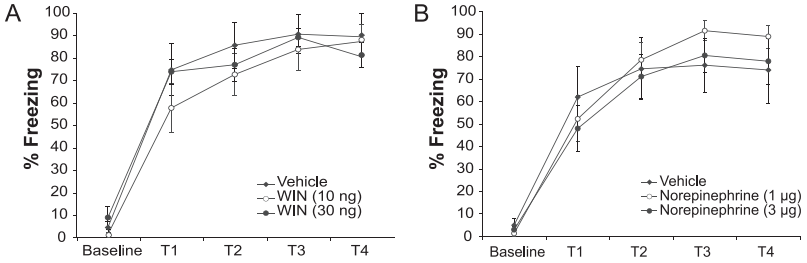

Fig. S1. The effect of intrahippocampal administration of WIN55,212–2 (WIN) or norepinephrine on freezing behavior during retention of auditory fear conditioning. (*A*) Effect of WIN (10 or 30 ng in 0.5 μL) infused into the dorsal hippocampus 1 h before retention of auditory fear conditioning during baseline and tone trials (T1–T4). Results represent mean ± SEM (*n* = 9–11 per group). (*B*) Effect of norepinephrine (1 or 3 μg in 0.5 μL) infused into the dorsal hippocampus 1 h before retention of auditory fear conditioning during baseline and tone trials (T1–T4). Results represent mean ± SEM (*n* = 7–12 per group).

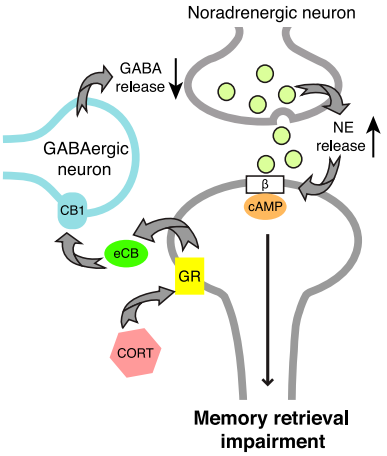

Fig. S2. Model on the role of the endocannabinoid system in the hippocampus in mediating glucocorticoid effects on the noradrenergic system in inducing memory retrieval impairment. Corticosterone (CORT) binds to a membrane-bound glucocorticoid receptor (GR) that activates a pathway to induce endocannabinoid (eCB) synthesis. Endocannabinoids are then released into the synapse, where they bind to CB1 receptors on GABAergic interneurons and thereby, inhibit the release of GABA. This suppression of GABA release subsequently disinhibits norepinephrine (NE) release, resulting in an activation of the postsynaptic β-adrenoceptor and downstream signaling pathways.

Table S1. Percentage freezing during training of contextual fear conditioning in animals later administered corticosterone

	Shock trials				
Drug groups (mg/kg)	1	2	3	4	5
Vehicle	8 ± 5	27 ± 7	38 ± 5	51 ± 9	63 ± 8
CORT 0.3	7 ± 2	32 ± 8	43 ± 8	43 ± 8	51 ± 8
CORT 1	6 ± 3	20 ± 7	29 ± 7	54 ± 9	51 ± 11
CORT 3	2 ± 1	17 ± 7	37 ± 11	44 ± 10	59 ± 10

There was no difference in the acquisition rate between later drug groups. Data are expressed as mean ± SEM (n = 10–15 per group). CORT, corticosterone.

Table S2. Percentage freezing during training of contextual fear conditioning in animals later administered corticosterone and AM251

	Shock trials				
Drug groups	1	2	3	4	5
Vehicle					
Vehicle	29 ± 9	52 ± 10	54 ± 9	62 ± 8	66 ± 9
CORT (3 mg/kg)	27 ± 15	40 ± 13	44 ± 15	44 ± 13	60 ± 13
AM251					
Vehicle	31 ± 8	47 ± 12	67 ± 9	58 ± 8	67 ± 6
CORT (3 mg/kg)	28 ± 5	44 ± 5	53 ± 5	67 ± 11	81 ± 3

There was no difference in the acquisition rate between later drug groups. Values are expressed as mean ± SEM (n = 7–11 per group). CORT, corticosterone.

Table S3. Effects of corticosterone administration before the nontraining context exposure on the hippocampal tissue content of palmitoylethanolamine and oleoylethanolamine

	PEA (pmol/g tissue)	OEA (pmol/g tissue)
Vehicle	542 ± 54	96 ± 10
CORT 0.3	539 ± 33	93 ± 10
CORT 1	521 ± 52	94 ± 8.2
CORT 3	528 ± 43	90 ± 7.1

There was no effect of corticosterone (CORT; 0.3, 1, or 3 mg/kg) administration on hippocampal tissue content of either palmitoylethanolamide (PEA) or oleoylethanolamine (OEA). Values are expressed as mean ± SEM (n = 10–15 per group).

Table S4. Percentage freezing during training of contextual fear conditioning in animals later administered WIN55,212-2 and propranolol

	Shock trials				
Drug groups	1	2	3	4	5
Vehicle					
Vehicle	25 ± 6	48 ± 7	52 ± 9	57 ± 8	52 ± 8
WIN (10 ng)	11 ± 8	21 ± 10	24 ± 12	24 ± 11	42 ± 11
WIN (30 ng)	30 ± 6	51 ± 7	59 ± 8	64 ± 7	63 ± 8
Propranolol					
Vehicle	14 ± 7	33 ± 8	42 ± 9	44 ± 8	40 ± 9
WIN (10 ng)	17 ± 6	24 ± 7	43 ± 8	53 ± 7	65 ± 8
WIN (30 ng)	34 ± 6	43 ± 7	60 ± 8	54 ± 7	56 ± 7

There was no difference in the acquisition rate between later drug groups. Values are expressed as mean ± SEM (n = 10–14 per group). WIN, WIN55,212-2.

Table S5. Percentage freezing during training of contextual fear conditioning in animals later administered norepinephrine and AM251

	Shock trials				
Drug groups	1	2	3	4	5
Vehicle					
Vehicle	26 ± 7	37 ± 8	50 ± 9	57 ± 7	66 ± 6
NE (1 μg)	19 ± 8	32 ± 9	43 ± 12	53 ± 9	61 ± 9
NE (3 μg)	20 ± 6	32 ± 9	44 ± 10	59 ± 7	66 ± 9
AM251					
Vehicle	29 ± 8	45 ± 8	60 ± 9	63 ± 7	54 ± 9
NE (1 μg)	32 ± 7	48 ± 7	53 ± 6	58 ± 6	52 ± 8
NE (3 μg)	19 ± 5	31 ± 8	38 ± 9	50 ± 10	49 ± 10

There was no difference in the acquisition rate between later drug groups. Values are expressed as mean ± SEM (n = 11–15 per group). NE, norepinephrine.