SUPPLEMENTARY INFORMATION

Supplementary figure legends

Figure S1. Chicago sky blue diffusion after hippocampal injection, related to Figure 1

Representative sections of one rat brain at -2.12, -3.60 and -4.52 mm from bregma, analyzed under light microscopy. Rats (n=4) were injected with 1µl of Chicago sky blue (1%) and euthanized 1 hr after injection.

Figure S2. DAB perfused via microdialysis probe blocked long-term memory, related to Figure 2A

Hippocampal injections of DAB perfused by microdialysis probe before IA training significantly blocked long-term memory tested at 24 hr after training (n=3-4/group). Memory retention is expressed as mean latency ± SEM (in seconds, sec). Mean latency, n and detailed statistic are reported in Table S7.

Figure S3. Training-induced increase of pCREB is blocked by MCT1 antisense injection, related to Figure 7

Mean %, n and detailed statistic are reported in Table S7.

(A-C) Examples (A) and densitometric western blot analysis of pCREB (B), CREB (C) performed on dorsal hippocampal extracts from trained and untrained rats injected 1 h before training with MCT1-ODN or SC1-ODN and euthanized 12 hr after training. pCREB (B) expression were significantly increased after training. This increase was completely blocked by MCT1-ODN. There is no change in expression of CREB across samples (n = 6-10/group).

Data are expressed as mean percentage ± SEM of untrained, SC1-ODN-injected control (100%) mean values. All proteins values were normalized to those of actin. * $p < 0.05$.

Supplementary Tables

Table S1: Mean latencies of rats after training and treatment, related to Figure 1

Figure 1A	n	**Mean Latency (sec)**			
Vehicle	7	311.5 ± 51.5			
DAB	7	266.9 ± 38.4			
Figure 1B	n	**Mean Latency (sec)**			
		Test 1	**Test 2**	**Test 3**	**Test 4**
Vehicle	11	340.8 ± 51.9	301.9 ± 67.5	320.9 ± 58.7	-
DAB	11	88.5 ± 46.4	84.3 ± 27.7	105.5 ± 45.3	463.6 ± 31.9
Figure 1C	n	**Mean Latency (sec)**			
		Test 1	**Test 2**	**Test 3**	**Test 4**
Vehicle	9	365.3 ± 51.9	355.8 ± 47.2	363.8 ± 47.7	-
300 pmol DAB	7	253.0 ± 50.6	243.2 ± 25.0	229.7 ± 27.7	513.1 ± 25.1
1000 pmol DAB	8	106.0 ± 64.0	93.4 ± 38.2	98.5 ± 36.6	457.8 ± 29.0
Figure 1D	n	**Mean Latency (sec)**			
		Test 1		**Test 2**	
Vehicle	8	340.7 ± 39.5		352.9 ± 44.8	
DAB	8	334.6 ± 69.1		357.2 ± 68.6	
Figure 1E	n	**Mean Latency (sec)**			
Vehicle	8	380.7 ± 42.6			
Isofagomine	9	74.4 ± 14.0			

Statistics

Figure 1A- Test	$t_{12} = 0.95, p > 0.05$
	Treatment; $F_{(1,20)} = 13.04, p < 0.05$
Figure 1B- Test 1 and Test 2	Time; $F_{(1,20)} = 0.54, p > 0.05$
	Interaction; $F_{(1,20)} = 0.35, p > 0.05$
Figure 1B- Test 3	$t_{20} = 2.90, p < 0.05$
	Treatment; $F_{(2,22)} = 9.23, p < 0.05$
Figure 1C- Test 1 and Test 2	Time; $F_{(1,22)} = 0.27, p > 0.05$
	Interaction; $F_{(2,22)} = 0.01, p > 0.05$
Figure 1B- Test 3	$F_{(2,22)} = 11.85, p < 0.05$
	Treatment; $F_{(1,14)} = 0.001, p > 0.05$
Figure 1D- Test 1 and Test 2	Time; $F_{(1,14)} = 0.39, p > 0.05$
	Interaction; $F_{(1,14)} = 0.002, p > 0.05$
Figure 1E- Test	$t_{15} = 7.18, p < 0.05$

Table S2: Lactate concentration and mean latencies of rats after training and treatment, related to Figure 2

Figure 2A	n	**Concentration (% of baseline)**			
		-10 min	**0 min**	**10 min**	**20 min**
Vehicle	4	105.8 ± 3.9	94.2 ± 3.9	170.2 ± 27.8	190.7 ± 22.6
DAB	3	102.3 ± 7.0	97.7 ± 7.0	102.3 ± 7.0	114.6 ± 6.9
		30 min	**40 min**	**50 min**	
Vehicle		151.7 ± 15.4	131.0 ± 16.8	155.1 ± 14.4	-
DAB		118.0 ± 2.7	97.3 ± 7.7	102.4 ± 7.4	-
Figure 2B		**Mean Latency (sec)**			
		Test 1		**Test 2**	
Vehicle	7	396.8 ± 60.6		347.73 ± 50.6	
DAB	7	91.9 ± 31.2		102.5 ± 32.7	
DAB+L-lactate	7	106.1 ± 44.4		87.5 ± 23.8	
Figure 2C		**Mean Latency (sec)**			
		Test 1		**Test 2**	
Vehicle	12	368.2 ± 57.8		353.0 ± 58.2	
DAB	12	102.2 ± 25.8		79.9 ± 24.2	
DAB+L-lactate	12	295.3 ± 65.2		273.3 ± 66.8	
Figure 2D		**Mean Latency (sec)**			
Vehicle	7	451.5 ± 36.3			
D-lactate	8	202.0 ± 62.8			

Statistics

Figure 2A	Treatment; $F_{(1,33)} = 23.15, p < 0.05$
	Time; $F_{(1,33)} = 3.70, p < 0.05$
	Interaction; $F_{(1,33)} = 2.13, p > 0.05$
Figure 2B- Test 1 and Test 2	Treatment; $F_{(1,18)} = 15.88, p < 0.05$
	Time; $F_{(1,18)} = 1.28, p > 0.05$
	Interaction; $F_{(1,18)} = 1.05, p > 0.05$
Figure 2C- Test 1 and Test 2	Treatment; $F_{(2,33)} = 7.39, p < 0.05$
	Time; $F_{(1,33)} = 1.73, p > 0.05$
	Interaction; $F_{(2,33)} = 0.02, p > 0.05$
Figure 2D- Test	$t_{13} = 3.31, p < 0.05$

Table S3: Fold change of MCTs protein levels and mean latencies of rats after training and treatment, related to Figure 4

Figure 4B	n	**% of Untrained SC1-ODN**			
		Untrained		**Trained**	
		SC1-ODN	**MCT1-ODN**	**SC1-ODN**	**MCT1-ODN**
MCT1	6	100.0 ± 6.1	99.3 ± 8.1	124.2 ± 8.5	83.0 ± 7.4
MCT2	6	100.0 ± 5.4	102.2 ± 7.3	99.9 ± 10.6	97.9 ± 9.6
MCT4	6	100.0 ± 7.2	95.9 ± 12.4	93.0 ± 3.7	100.4 ± 7.3
Figure 4C		**SC1-ODN**		**MCT1-ODN**	
MCT1	4	100.0 ± 7.9		54.6 ± 10.8	
MCT2	4	100.0 ± 2.9		96.6 ± 3.7	
MCT4	4	100.0 ± 4.6		92.3 ± 2.5	
Figure 4D	n	**Mean Latency (sec)**			
SC1-ODN	7	242.6 ± 39.6			
MCT1-ODN	7	182.7 ± 47.1			
Figure 4E		**Test 1**	**Test 2**	**Test 3**	**Test 4**
SC1-ODN	11	399.3 ± 46.2	365.9 ± 53.6	463.1 ± 39.9	-
MCT1-ODN	10	107.2 ± 32.5	84.3 ± 27.7	124.9 ± 50.6	526.3 ± 13.7
Figure 4F		**Test 1**		**Test 2**	
SC1-ODN+Vehicle	13	344.7 ± 31.7		316.3 ± 31.8	
SC1-ODN+L-lactate	7	378.7 ± 57.7		339.0 ± 56.5	
SC1-ODN+Glucose	7	487.1 ± 33.9		422.5 ± 53.8	
MCT1-ODN+Vehicle	13	99.4 ± 18.1		93.8 ± 15.2	
MCT1-ODN+L-lactate	7	253.4 ± 59.9		251.9 ± 44.4	
MCT1-ODN+Glucose	7	98.4 ± 35.7		95.1 ± 27.9	
Figure 4G		**Test 1**		**Test 2**	
SC1-ODN+Vehicle	8	349.4 ± 63.2		330.3 ± 48.8	
MCT1-ODN+Vehicle	11	98.1 ± 24.4		88.0 ± 23.4	
MCT1-ODN+Glucose	10	273.5 ± 60.5		117.1 ± 33.0	

Statistics

Figure 4B	MCT1; $F_{(3,20)} = 3.78$, $p < 0.05$ MCT2; $F_{(3,20)} = 0.04$, $p > 0.05$ MCT4; $F_{(3,20)} = 0.19$, $p > 0.05$
Figure 4C	MCT1; $t_{6} = 3.40$, $p < 0.05$ MCT2; $t_{6} = 0.42$, $p > 0.05$ MCT4; $t_{6} = 0.91$, $p > 0.05$
Figure 4D- Test	$t_{12} = 0.97$, $p > 0.05$
Figure 4E- Test 1 and Test 2	Treatment; $F_{(1,19)} = 25.15$, $p < 0.05$ Time; $F_{(1,19)} = 0.81$, $p > 0.05$ Interaction; $F_{(1,19)} = 0.04$, $p > 0.05$
Figure 4E- Test 3	$t_{19} = 5.30$, $p < 0.05$
Figure 4F- Test 1 and Test 2	Treatment; $F_{(5,48)} = 18.01$, $p < 0.05$ Time; $F_{(1,48)} = 3.91$, $p > 0.05$ Interaction; $F_{(5,48)} = 0.67$, $p > 0.05$
Figure 4G- Test 1 and Test 2	Treatment; $F_{(2,26)} = 10.97$, $p < 0.05$ Time; $F_{(1,26)} = 5.89$, $p < 0.05$ Interaction; $F_{(2,26)} = 3.60$, $p < 0.05$

Table S4: Fold change of MCTs protein levels and mean latencies of rats after training and treatment, related to Figure 5

Figure 5A	n	**% of Untrained SC4-ODN**	
		SC4-ODN	**MCT4-ODN**
MCT4	4	100.0 ± 5.1	54.5 ± 2.9
MCT1	4	100.0 ± 5.1	104.0 ± 7.4
MCT2	4	100.0 ± 3.6	96.4 ± 4.0
		Mean Latency (sec)	
Figure 5B		**Test 1**	**Test 2**
SC4-ODN+Vehicle	10	317.4 ± 38.7	287.1 ± 40.3
MCT4-ODN+Vehicle	10	125.6 ± 34.3	117.3 ± 29.2
MCT4-ODN+L-lactate	12	283.6 ± 68.7	265.5 ± 37.9
MCT4-ODN+Glucose	10	120.3 ± 11.3	118.3 ± 17.3

Statistics

Figure 5A	MCT4; $t_6 = 4.45, p < 0.05$
	MCT1; $t_6 = 0.44, p > 0.05$
	MCT2; $t_6 = 0.39, p > 0.05$
Figure 5B- Test 1 and Test 2	Treatment; $F_{(3,38)} = 8.50, p < 0.05$
	Time; $F_{(1,38)} = 3.41, p > 0.05$
	Interaction; $F_{(3,38)} = 0.58, p > 0.05$

Table S5: Fold change of MCTs protein levels and mean latencies of rats after training and treatment, related to Figure 6

Figure 6A	n	**% of Untrained SC2-ODN**			
		SC2-ODN		**MCT2-ODN**	
MCT2	4	100.0 ± 3.0		70.1 ± 5.1	
MCT1	4	100.0 ± 4.2		103.8 ± 7.8	
MCT4	4	100.0 ± 2.7		104.0 ± 6.1	
Figure 6B		**Mean Latency (sec)**			
SC2-ODN	8	287.4 ± 78.2			
MCT2-ODN	8	254.6 ± 64.9			
Figure 6C	n	**Mean Latency (sec)**			
		Test 1	**Test 2**	**Test 3**	**Test 4**
SC2-ODN	11	265.2 ± 54.5	273.5 ± 61.3	473.4 ± 51.6	-
MCT2-ODN	10	64.6 ± 18.0	35.2 ± 13.9	102.0 ± 27.9	540 ± 0.0
Figure 6D	n	**Mean Latency (sec)**			
		Test 1		**Test 2**	
SC2-ODN+Vehicle	8	440.3 ± 53.4		392.4 ± 47.6	
MCT2-ODN+Vehicle	6	164.6 ± 44.3		82.3 ± 24.3	
MCT2-ODN+L-lactate	6	137.6 ± 50.5		75.2 ± 24.8	
MCT2-ODN+Glucose	7	174.7 ± 53.9		130.5 ± 38.9	

Statistics

	MCT2; $t_6 = 2.81, p < 0.05$
Figure 6A	MCT1; $t_6 = 0.43, p > 0.05$
	MCT4; $t_6 = 0.35, p > 0.05$
Figure 6B- Test	$t_{14} = 0.32, p > 0.05$
	Treatment; $F_{(1,14)} = 36.93, p < 0.05$
Figure 6C- Test 1 and Test 2	Time; $F_{(1,14)} = 0.05, p > 0.05$
	Interaction; $F_{(1,14)} = 0.15, p > 0.05$
Figure 6C- Test 3	$t_{14} = 7.31, p < 0.05$
	Treatment; $F_{(3,23)} = 13.51, p < 0.05$
Figure 6D- Test 1 and Test 2	Time; $F_{(1,23)} = 10.02, p < 0.05$
	Interaction; $F_{(3,23)} = 0.21\ p > 0.05$

Table S6: Fold change of Arc, pCREB, CREB, pcofilin and cofilin protein levels of rats after training and treatment, related to Figure 7

Figure 7B	**% of Untrained Vehicle**			
	Untrained		Trained	
	n		n	
Vehicle+Vehicle	7	100.0 ± 19.2	5	195.2 ± 24.1
DAB+Vehicle	5	111.2 ± 14.8	5	116.1 ± 17.3
DAB+L-lactate		-	5	171.0 ± 10.5
Figure 7C				
Vehicle+Vehicle	6	100.0 ± 7.9	6	171.3 ± 16.1
DAB+Vehicle	4	97.2 ± 5.6	6	114.1 ± 5.5
DAB+L-lactate		-	5	150.0 ± 10.4
Figure 7D				
Vehicle+Vehicle	6	100.0 ± 7.0	6	98.2 ± 9.7
DAB+Vehicle	4	97.1 ± 10.9	6	94.3 ± 4.5
DAB+L-lactate		-	5	102.8 ± 10.6
Figure 7E				
Vehicle+Vehicle	6	100.0 ± 11.2	5	178.3 ± 11.9
DAB+Vehicle	4	125.3 ± 30.2	6	106.0 ± 8.6
DAB+L-lactate		-	5	160.7 ± 7.6
Figure 7F				
Vehicle+Vehicle	6	100.0 ± 3.8	5	92.0 ± 3.2
DAB+Vehicle	4	104.0 ± 6.4	6	98.4 ± 8.1
DAB+L-lactate		-	5	92.6 ± 5.8

Statistics

Figure 7B- Arc	$F_{(4,22)} = 3.78, p < 0.05$
Figure 7C- pCREB	$F_{(4,22)} = 5.02, p < 0.05$
Figure 7D- CREB	$F_{(4,22)} = 0.14, p > 0.05$
Figure 7E- pcofilin	$F_{(4,21)} = 6.17, p < 0.05$
Figure 7F- cofilin	$F_{(4,21)} = 0.66, p > 0.05$

Table S7: Mean latencies and fold change of pCREB and CREB protein levels of rats after training and treatment, related to Figures S2 and S3

Figure S2	n	**Mean Latency (sec)**
Vehicle	7	383.6 ± 90.5
DAB	7	71.7 ± 19.6

Figure S3B	**% of Untrained Vehicle**			
	Untrained		Trained	
	n		n	
Vehicle	10	100.0 ± 10.3	10	199.8 ± 42.8
MCT1	6	118.7 ± 18.4	6	116.6 ± 18.1
Figure S3C				
Vehicle	10	100.0 ± 11.9	10	96.0 ± 15.4
MCT1	6	106.2.2 ± 17.7	6	93.0 ± 8.6

Statistics

Figure S2 Test	$t_5 = 2.88, p < 0.05$

Figure S3B- pCREB	$F_{(3,28)} = 4.32, p < 0.05$
Figure S3C- CREB	$F_{(3,28)} = 0.18, p > 0.05$

EXTENDED EXPERIMENTAL PROCEDURES

Animals

Adult male Long-Evans rats weighing between 200 and 250 g were used for all behavioral and biochemical studies. Adult male Sprague-Dawley rats (250-300 g) were used for electrophysiological studies. Animals were individually housed and maintained on a 12 hr light/dark cycle. Experiments were performed during the light cycle. All rats were allowed ad libitum access to food and water and were handled for 3 min per day for 5 days prior any procedure. All protocols complied with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and were approved by the Mt. Sinai School of Medicine Animal Care Committees.

Cannulae implants

Bilateral hippocampal surgeries were performed as described by Taubenfeld et al. (2001a). Rats were anesthetized with ketamine (65 mg/kg) and xylazine (7.5 mg/kg), and stainless steel cannulas (22 gauge) were stereotactically implanted bilaterally into either their hippocampi (4 mm posterior to Bregma, 2.6 mm lateral from midline, and 2 mm ventral). After surgery, rats recovered for 7 days before undergoing any procedure.

Inhibitory avoidance (IA)

IA was carried out as described previously (Taubenfeld et al. 2001a). The IA chamber (Med Associates, St. Albans, Vermont) consisted of a rectangular-shaped Perspex box, divided into a safe compartment and a shock compartment. The safe compartment was

white and illuminated by a light fixture fastened to the cage lid. The shock compartment was dark and made of black Perspex. Foot shocks were delivered to the grid floor of this chamber via a constant current scrambler circuit. The two compartments were separated by an automatically operated sliding door. During training sessions, each rat was placed in the safe compartment with its head facing away from the door. After 10 sec, the door was automatically opened, allowing the rat access to the shock chamber. The door closed 1 sec after the rat entered the shock chamber, and a brief foot shock (0.9 mA for 2 sec) was administered to the rat. Latency to enter the shock compartment was taken as a measure of acquisition. The rat was then returned to its home cage and tested for retention 24 hr and 7 days later. Retention tests were performed by placing the rat back into the safe compartment and measuring the latency to enter the shock compartment. Foot shock was not administered on the retention test, and testing was terminated at 540 s. Reminder footshocks were of identical duration and intensity to that of training but in a novel, neutral chamber with transparent walls that resided in a separate, well-lit room. Training and testing procedures were performed blind to treatments.

Drug and oligodeoxynucleotide injections

DAB, sodium L-lactate, sodium D-lactate, D-glucose (Sigma-Aldrich, St. Louis, MO) and isofagomine (Santa Cruz Biotechnology, Santa Cruz, CA) were dissolved in phosphate-buffered saline (PBS, pH 7.4). All injections were performed at 1 μl of volume per hippocampal side. The infusion needles extended 1.5 mm beyond the cannula. At the indicated time points before or after IA training, the rats received bilateral hippocampal injections at a rate of 0.333 μl/min with an infusion pump. The injection needle was left

in place for 3 min following the injection to allow for complete dispersion of the solution. Concentrations: DAB: 300 or 1000 μM. Similar concentrations of DAB have been previously used in chick brain and found to dose-dependently inhibit bead discrimination memory retention (Gibbs et al., 2006). Given the diffusion (Figure S1), which spread approximately 1.7 mm across the injection site, the final average concentration within the diffusion space is calculated to be approximately 15 and 50 μM, respectively. Isofagomine: 40 mM; L-lactate: 10 mM (final estimated average concentration 0.5 mM), and 100 mM (final estimated average concentration 5 mM); D-lactate: 20 mM; D-glucose: 50, 150 mM. ODNs: MCT1 antisense oligodeoxynucleotide (MCT1-ODN; 5'-CAATCGCAGGTGGCATCTTAGG-3') or relative scrambled ODN (SC1-ODN; 5'-ACTTAGGGGTCTTCAGGCACGA-3'), MCT2 antisense oligodeoxynucleotide (MCT2-ODN; 5'-GACTCTGATGGCATTTCTGAG-3') or relative scrambled ODN (SC2-ODN; 5'-GGTTTACGAGTCGTCCGTAAT-3'), MCT4 antisense oligodeoxynucleotide (MCT4-ODN; 5'- CACAGCTCCTCCCATGGCCAGG -3') or relative scrambled ODN (SC4-ODN; 5'- GTCACGCATCTCGCACCAGCGC -3') were dissolved in PBS pH 7.4. MCT1-ODN, MCT2-ODN and MCT4-ODN were specific for the sequence that includes MCT1, MCT2 and MCT4 translational starting site, respectively. Both SC-ODNs contained relative MCTs-ODN base composition but in a randomized order and showed no homology to any mammalian sequence in the GenBank database, as confirmed by a BLAST (basic local alignment search tool) search. All ODNs were phosphorothioated on the three terminal bases at each end to protect against nuclease degradation. ODNs were reverse phase cartridge-purified and purchased from

Gene Link (Hawthorne, NY). Two nmol in 1 μl of ODNs were injected in each hippocampus.

Microdialysis

Microdialysis cannulae (CMA 12), probes (CMA 12 elite, 2 mm long), and FEP tubing were all purchased from CMA Microdialysis, Inc., Stockholm, Sweden. Rats underwent surgery as described, but were implanted with microdialysis cannulae unilaterally targeting the left dorsal hippocampus. Rats were handled for 10 minutes a day for 5 days prior to microdialysis. On the day of microdialysis, the probe was inserted into the guide cannula and perfused with artificial cerebrospinal fluid (aCSF containing: 119 mM NaCl, 26 mM $NaHCO_3$, 2.5 mM KCl, 1 mM NaH_2PO_4, 1.25 mM Na_2HPO_4, 2 mM $CaCl_2$, 4 mM $MgCl_2$) or DAB dissolved in aCSF (300 μM) at a rate of 3 μl/min, collected every 10 minutes. The first 2 samples were discarded, and then after 20 minutes of baseline collection, rats were trained in IA with a 0.9 mA footshock, and sample collection was continued for 1h after training. Samples were subsequently analyzed using the AbCam Lactate Fluorescence Assay Kit. Results are presented as means ± SEM. As baseline lactate concentrations showed interindividual differences, data from each animal were expressed as percentages, and the individual values were calculated accordingly for each animal. The microdialysis data were analyzed using a two-way repeated measures ANOVA followed by the post hoc Bonferroni multiple comparisons test.

Synaptoneurosomal preparation

Synaptoneurosomal preparation was carried out as described in Villasana et al. (2006).

Briefly, dorsal hippocampi were rapidly dissected in ice-cold cortical dissection buffer followed by homogenization in buffer containing 10mM HEPES, 2mM EDTA, 2mM EGTA, 0.5mM DTT, phosphatase and protease inhibitor cocktails (Sigma-Aldrich, St. Louis, MO). Glass-teflon homogenizer was used and homogenates were filtered through 100 μm nylon mesh filter and 5 μm nitrocellulose filters sequentially. Synaptoneurosomes were obtained by centrifugating the filtrate at 1000g for 10 min.

Western blot analysis

Fifty micrograms of total protein extract/lane were resolved using 10 or 15% SDS-PAGE and analyzed by western blot as described previously (Taubenfeld et al., 2001b). Primary antibodies [rabbit anti-MCT1, rabbit anti-MCT2, rabbit anti-MCT4, rabbit anti-pCREB and rabbit anti-CREB (1:1000; Millipore, Billerica, MA), rabbit anti-pcofilin (1:3000; Abcam, Cambridge, MA), rabbit anti-cofilin (1:2000; Millipore, Billerica, MA), rabbit anti-Arc (1:1000; Synaptic System, Gottingen, Germany), mouse anti-PSD95 and rabbit anti-GFAP (1:5000; Millipore, Billerica, MA)] were used. Actin (1:5000; Santa Cruz Biotechnology, Santa Cruz, CA) was used for loading normalization. Horseradish peroxidase-coupled specific secondary antibodies (1:4000; Santa Cruz Biotechnology, Santa Cruz, CA) were incubated in TBS containing 5% skim milk for 1 h at room temperature. The detection system used was ECL detection reagents (GE Healthcare Bio-Sciences). Quantitative densitometric analysis was done using NIH Image software.

Electrophysiology

Rats were anaesthetized using an isoflurane vaporizer (isoflurane concentration: 1–2%, O2 flow rate: 1 l/min) and placed in a stereotaxic frame for electrophysiological recordings. Rectal temperature was maintained at 37°C during the experiments. A monopolar tungsten electrode was used to stimulate the Schaffer-commissural projection (from bregma, in mm: AP: 3.5, ML: 3.0, DV: 2.3). Field excitatory postsynaptic potentials (fEPSPs) were recorded in area CA1 stratum radiatum (in mm: AP: 4, ML: 2.8, DV: 2.5) with a glass micropipette filled with 3 M NaCl. Test pulses (100 μs duration) were collected every 30 sec; their intensity was adjusted to evoke fEPSP amplitudes that were ~ 50% of the maximal response. The slope of the fEPSPs was used to generate an input-output (I/O) relationship ranging from subthreshold to maximal response. All responses were expressed as percent change from the average responses recorded during the 20-30 min immediately before drug application or LTP-inducing tetanic stimuli. LTP was induced with 4 trains of 100 Hz, 1 sec stimulation separated by 5 min. Paired-pulse facilitation (PPF) was induced by delivering two stimuli with a 50 ms interstimulus interval.

DAB (300 μM), lactate (100 mM) or lactate+DAB (2x concentration from each) were delivered into area CA1 using controlled pressure-pulses of nitrogen (20 psi, 1 min period, 1 μl total volume) applied via a Picospritzer to one barrel of a double-barrel glass micropipette in which the other barrel was used for recording fEPSPs. N-methyl-D-aspartate (NMDA) receptor antagonist MK-801 (3mg/kg) was intraperitoneally (i.p.) injected 30 min before tetanic stimulation. The onset and duration of drug administration are indicated in individual figures. At the termination of the experiments, rats were killed by intracardiac perfusion (4% paraformaldehyde, 10 min). Brain sections (50 μm) were

sliced on a freezing sliding microtome and were used to verify placement of stimulating/recording electrodes histologically.