ONLINE METHODS

Cell culture. PC12 cells were obtained from American Type Culture Collection and cultured as described by the source. Cells (2×10^5 per well) were grown in 12-well plates precoated with poly-D-lysine (BD Biosciences). One day later, cells were replaced with 0.5 ml of serum-free RPMI 1640 and subject to drug treatments. Primary VTA neuron preparations and culture were carried out as described[37]. Cells were plated at a density of 5×10^4 cells per cm^2 on 24-well plates or eight-well slides precoated with poly-D-lysine and laminin (BD Biosciences) and incubated at 37 °C with 5% CO_2, 95% air. Half of the medium was changed every 4 d. Experiments were carried out on day 10 after plating.

Immunochemistry and microscopy. We performed immunostaining and confocal microscopy for tyrosine hydroxylase in VTA neurons. Details can be found in the **Supplementary Methods**.

Cell fractionation and western blotting. We isolated cytosol and membrane fractions from VTA neurons by ultracentrifugation and performed western blotting to detect translocation of PKA and εPKC. For western blotting, the relative intensity of individual bands was quantified with ImageJ software and normalized to glyceraldehyde 3-phosphate dehydrogenase or tyrosine hydroxylase. The ratio of target protein to glyceraldehyde 3-phosphate dehydrogenase or tyrosine hydroxylase was assigned a value of 1. Details can be found in the **Supplementary Methods**. Primary antibodies for tyrosine hydroxylase, phosphorylated tyrosine hydroxylase at Ser19, Ser31 or Ser40, εPKC and glyceraldehyde 3-phosphate dehydrogenase were purchased from Santa Cruz Biotechnology. Primary antibody for PKA Cα was purchased from BD Sciences. Horseradish peroxidase–linked secondary antibodies were purchased from PerkinElmer Life and Analytical Sciences. FITC- and Texas red–conjugated secondary antibodies were purchased from Santa Cruz Biotechnology.

Dopamine and THP sample preparation. We collected PC12 or VTA culture medium in Eppendorf tubes containing 10 µl of 5 M perchloric acid. We then washed cells twice with PBS before addition of 0.5 ml of 0.1 M perchloric acid and lysis by freezing on dry ice and thawing at 37 °C three times. We centrifuged medium and lysates at 14,000 r.p.m. in a benchtop centrifuge (Eppendorf 5417R) for 5 min. We collected the supernatant for dopamine and THP analysis. To measure brain dopamine and THP, we dissected out the VTA and nucleus accumbens from naive or cocaine-addicted rats treated with or without ALDH2i (15 mg per kg body weight i.p.) immediately after the conclusion of a 2-h cue-reinstatement session and weighed and homogenized them with a Tissue Tearer (Glas-Col) on ice in 1 ml of PBS buffer with the addition of 5 ng of d_4-dopamine·HCl (Sigma-Aldrich) as an internal standard and 20 µl of 1M phenylhydrazine (Sigma-Aldrich) as an aldehyde-trapping agent. Tissue homogenates were acidified with 1 ml of 1 M $HClO_4$ solution containing 0.02% EGTA, 0.02% semicarbazide hydrochloride and 0.02% sodium metabisulfite. We then centrifuged the samples at 2,000*g* for 10 min at 4 °C and collected the supernatant. We isolated THP and dopamine by solid-phase extraction with a phenyl boronic acid cartridge and analyzed by liquid chromatography-tandem mass spectrometry after pentafluorobenzyl derivatization. Details can be found in the **Supplementary Methods**.

Enzyme preparations. We purified DBH, tyrosine hydroxylase and DOPA decarboxylase from PC12 cells. Details can be found in the **Supplementary Methods**.

Enzyme activity assays. Enzyme activity assays for tyrosine hydroxylase, DOPA decarboxylase and DBH were performed as previously described[38–40]. MAO activity assay was performed as described by the manufacturer (Invitrogen). Details can be found in the **Supplementary Methods**.

Cocaine self-administration and reinstatement. Male Sprague Dawley rats (Charles River) with implanted jugular vein catheters were trained to self-administer cocaine on a fixed-ratio 1 schedule of reinforcement as previously described[41]. Each active lever press produced a 0.05-ml infusion of 0.35 mg per kg body weight per infusion of cocaine over 3 s with a cue light and tone signaled during the drug delivery. ALDH2i (10, 15, 30 and 45 mg per kg body weight) or vehicle was administered i.p. 30 min before the self-administration session in a counterbalanced order. For reinstatement, rats underwent extinction training procedures, whereby activation of the lever that had previously delivered cocaine was recorded but did not result in cocaine infusions. After extinction, rats received i.p. ALDH2i (3.75, 7.5, 15 or 30 mg per kg body weight) or vehicle (0.5% methylcellulose) 30 min before a single injection of cocaine (10 mg per kg body weight i.p.); or ALDH2i (1, 3.75, 7.5 and 15 mg per kg body weight) or THP (15 mg per kg body weight) 30 min before an auditory (tone) and visual (cue light) cue immediately before the beginning of the 2-h session. The session was conducted identically to the extinction training sessions without cocaine delivery. Active and inactive lever presses were recorded, and the number of active lever presses was the measure of reinstatement. All experiments were approved by the Gilead Institutional Animal Care and Use Committee following criteria outlined in the US National Institutes of Health Guide for the Care and Use of Laboratory Animals. Details can be found in the **Supplementary Methods** for methamphetamine-induced reinstatement.

Statistical analyses. Data from rat studies were analyzed by repeated measures of analysis of variance followed by Fisher's *post hoc* test to determine statistical significance. Data from cell studies were expressed as means ± s.e.m. of three independent experiments and evaluated with one-way analysis of variance and Dunnett's test.

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