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LETTER TO THE EDITOR

Attenuating the persistence of fear memory storage using a single dose of antidepressant

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Enhanced memory for emotionally arousing events is a highly adaptive phenomenon that helps us remember both dangerous and favorable situations.[1] However, under certain conditions, intrusive and persistent traumatic memories can lead to anxiety disorders, like posttraumatic stress disorder. Current therapies for anxiety disorders involve pharmacological or behavioral manipulations of long-lasting fear memories in which patients explicitly recall the painful traumatic experience.[2,3] Despite recent advances, a major question of how to effectively attenuate persistent fear memories in a safe and less distressful manner remains unresolved.

Following up our earlier work on the mechanisms of memory persistence,[4,5] here we show in rats that a single systemic injection of the antidepressant venlafaxine (10 mg kg^{-1}; i.p.) given 11 h after training attenuated the persistence of inhibitory avoidance (IA) memory tested 7 (Figure 1a) or 14 days after training (oral administration) (Supplementary Figure S1D). No changes in memory retention were observed 2 days after IA training (Figure 1a, Supplementary Figure S1D), indicating that acute antidepressant treatment does not modify memory formation or its expression. Similar effects on memory persistence were obtained using fluoxetine, a widely prescribed antidepressant (10 mg kg^{-1}; i.p.) (Supplementary Figure S1A). No alterations in memory maintenance were found when antidepressants were injected systemically immediately after training (Supplementary Figure S1B) or 25 h after training (Supplementary Figure S1C), indicating that their effects on memory persistence are time-dependent. Attenuation of memory persistence was also observed when venlafaxine or fluoxetine were administered orally (12 mg kg^{-1}; p.o.) or infused into the CA1 region of the dorsal hippocampus 12 h after IA training (Supplementary Figure S1D, E). A similar selective impairment on memory storage was obtained using contextual fear conditioning, another hippocampus-dependent task (Supplementary Figure S1F).

In addition, systemic administration of venlafaxine or fluoxetine 11 h after IA training impeded training-induced increase in hippocampal brain-derived neurotrophic factor (BDNF) levels (Figure 1b). A similar pattern of effects was observed when TrkB phosphorylation was determined using pTrkB/TrkB ratio by immunoblotting (Supplementary Figure S2B). This is consistent with recent findings showing that an increased expression of hippocampal *BDNF* is crucial for memory persistence.[4,5] Moreover, venlafaxine-induced impairment of IA memory persistence is reverted by the bilateral infusion of BDNF (0.5 μg/0.5 μl) into the CA1 region of the dorsal hippocampus (Figure 1c).

Acute administration of different antidepressants increases extracellular 5-hydroxytryptamine (5-HT) levels, activates 5-HT2A receptors and decreases *BDNF* gene expression in the hippocampus.[6] We found that antidepressant-induced attenuation of IA memory persistence is prevented by the intrahippocampal infusion of MDL11939 (0.3 μg/0.5 μl each side), a 5-HT2A receptor antagonist (Figure 1c), but not by SB242084, a selective 5-HT2C receptor antagonist (Supplementary Figure S1G). MDL11939 also prevented the deleterious effect of venlafaxine on IA training-induced increase in *BDNF* expression (Figure 1d). To further substantiate that the effect of venlafaxine on memory persistence is mediated by activating 5-HT2A receptors in a way that ensures more specificity, we utilized knockout mutant mice for 5-HT2A receptors (*5HT-2AR*$^{-/-}$).[7] We observed that venlafaxine (10 mg kg^{-1}; i.p.) induced a clear-cut impairment of memory retention at 7 days after training in *5HT-2AR*$^{+/+}$, but it did not affect memory in *5HT-2AR* $^{-/-}$ mice (Figure 1e).

These findings are in line with previous data showing that the effects of antidepressants grow with the passage of time,[8] and suggest that an acute antidepressant administration may represent a new and safe tool for hindering persistent memories; in addition, they suggest that pharmacotherapies that activate 5-HT2A receptors in the hippocampus represent potentially useful new strategies to treat these disorders by manipulating the persistence of fear memories.

Conflict of interest

The authors declare no conflict of interest.

L Slipczuk[1,2], M Tomaiuolo[1], F Garagoli[1], N Weisstaub[3], C Katche[1], P Bekinschtein[4] and JH Medina[1,5]

[1]*Institute of Cellular Biology and Neuroscience, School of Medicine, University of Buenos Aires, Buenos Aires, Argentina;* [2]*Department of Internal Medicine, Albert Einstein Medical Center, Philadelphia, PA, USA;* [3]*Systems Neuroscience*

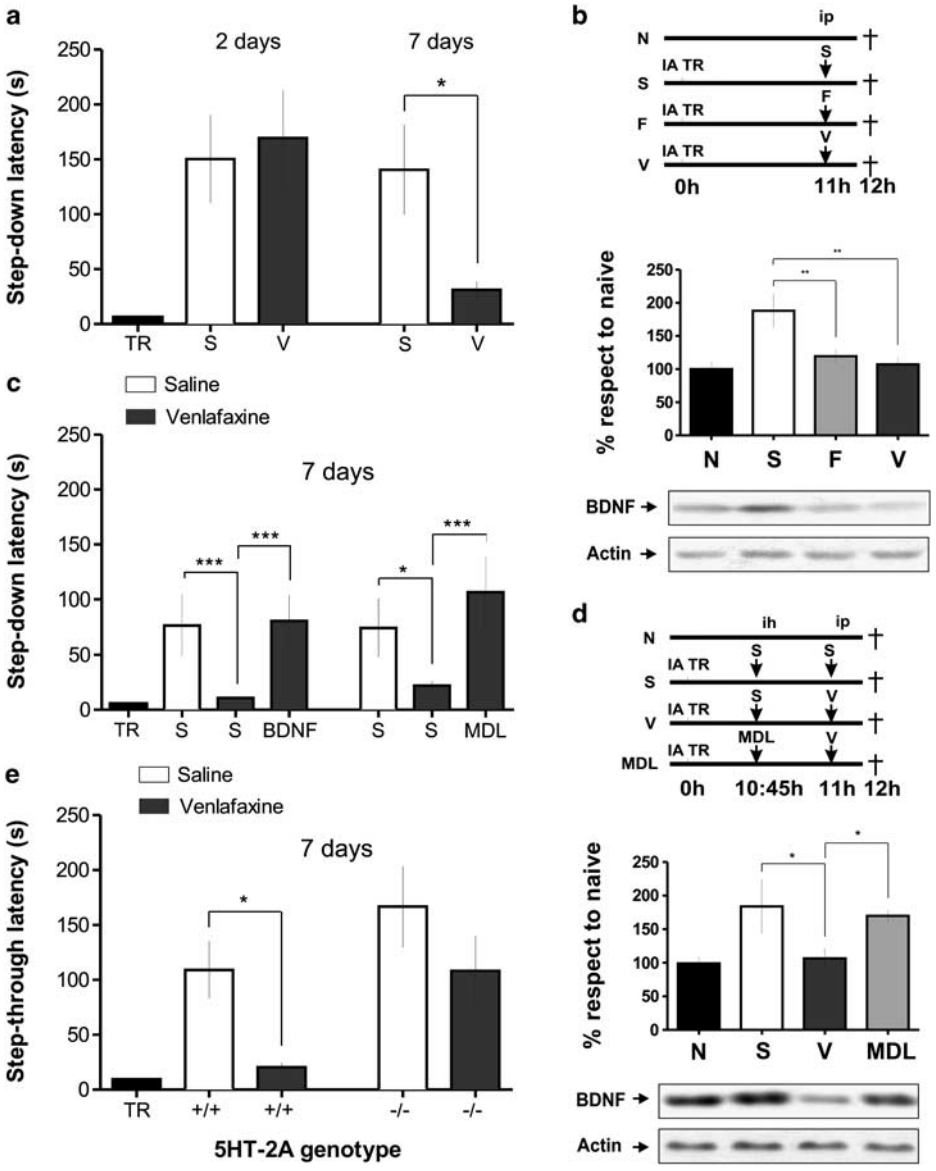

Figure 1 (**a**) Attenuation of memory persistence by systemic administration of venlafaxine (V) 11 h after inhibitory avoidance (IA) training; saline (S) injection. Memory was assessed either 2 or 7 days after training. $n = 10$ animals per group. $^{*}P < 0.05$, student *t*-test. (**b**) Same as (**a**), but here we used immunoblotting to determine the levels of brain-derived neurotrophic factor (BDNF) in the dorsal hippocampus 12 h after training. BDNF/actin ratios were calculated and data are expressed as percentage of control. $n = 6$ animals per group. $^{**}P < 0.01$, Newman–Keuls test after analysis of variance (ANOVA). (**c**) Systemic administration of S or V 11 h after IA training. Intrahippocampal infusions of S or MDL11939, a 5-hydroxytryptamine (5-HT)2A receptor antagonist, were given around 11 h after training and infusion of S or human recombinant BDNF were given 12 h after training. Memory was tested 7 days after training $n = 10$; $^{*}P < 0.05$; $^{***}P < 0.001$, Newman–Keuls after ANOVA. (**d**) The same as panel **c**, but here we assessed BDNF/actin ratios in the dorsal hippocampus 12 h after training. $n = 6$ animals per group. $^{*}P < 0.05$. (**e**) V impaired persistence of IA memory storage 7 days after training in *5HT-2AR*$^{+/+}$ mice but not in *5HT-2AR*$^{-/-}$ mice. $n = 7$–10 animals per group. $^{*}P < 0.05$; Newman–Keuls test after ANOVA. Data are expressed as mean ± s.e.m. of training lantency (TR) or test step-down latency.

Section, Department of Physiology, School of Medicine, University of Buenos Aires, Buenos Aires, Argentina; [4]*Department of Experimental Psychology and Welcome Trust Behavioural and Clinical Neuroscience Institute, University of Cambridge, Cambridge, UK and* [5]*Department of Physiology, School of Medicine, University of Buenos Aires, Buenos Aires, Argentina*
E-mail: jmedina@fmed.uba.ar

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Supplementary Information accompanies the paper on the Molecular Psychiatry website (http://www.nature.com/mp)