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The Antidepressant Fluoxetine Restores Plasticity in the Adult Visual Cortex

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We investigated whether fluoxetine, a widely prescribed medication for treatment of depression, restores neuronal plasticity in the adult visual system of the rat. We found that chronic administration of fluoxetine reinstates ocular dominance plasticity in adulthood and promotes the recovery of visual functions in adult amblyopic animals, as tested electrophysiologically and behaviorally. These effects were accompanied by reduced intracortical inhibition and increased expression of brain-derived neurotrophic factor in the visual cortex. Cortical administration of diazepam prevented the effects induced by fluoxetine, indicating that the reduction of intracortical inhibition promotes visual cortical plasticity in the adult. Our results suggest a potential clinical application for fluoxetine in amblyopia as well as new mechanisms for the therapeutic effects of antidepressants and for the pathophysiology of mood disorders.

Clinically used antidepressant drugs (ADs) increase extracellular serotonin and/or noradrenaline levels, but the relationship between acute increases in these neurotransmitters and the clinical antidepressant effect, which develops with a time delay of several weeks, has remained unclear (1, 2). Chronic antidepressant administration promotes neurogenesis and synaptogenesis in the adult hippocampus (3, 4) as well as increased expression of the neurotrophin brain-derived neurotrophic factor (BDNF) and its primary receptor, TrkB (5, 6). These cellular and molecular events seem to be necessary to mediate the therapeutic effects of ADs. The behavioral response to ADs is blocked if the induced neurogenesis is disrupted (7), whereas direct infusion of BDNF into the hippocampus or the overexpression of its receptor in transgenic mice induces an antidepressant effect (8, 9). Although neurogenesis, synaptogenesis, and BDNF signaling are events that correlate with neuronal plasticity, it remains to be demonstrated whether ADs induce functional modifications of neuronal circuitry in the brain.

We investigated whether chronic treatment with fluoxetine, a selective serotonin reuptake inhibitor (SSRI), restores plasticity in the adult visual system of the rat. We used two classical models of plasticity: (i) the ocular dominance (OD) shift of visual cortical neurons after monocular deprivation (MD) and (ii) the recovery of visual functions in the adult after long-term MD (amblyopia). These two plastic phenomena in the rat are restricted to a critical period during postnatal development and are absent in the adult because of a decline of plasticity that occurs in the visual cortex where recording is performed. The C/I VEP ratio is around 2.5 in adult animals, reflecting the predominance of crossed fibers in rat retinal projections. MD in control adult animals (P100) did not change binocularity in the visual cortex contralateral to the deprived eye (C/I VEP ratio 2.73 ± 0.2, n = 5 animals) (Fig. 1A). In contrast, fluoxetine-treated adult rats showed a marked OD shift in favor of the nondeprived eye after MD (C/I VEP ratio 1.0 ± 0.08, t test P < 0.001, n = 5), thus displaying a plastic modification normally restricted to the early stages of brain development.

Changes of binocularity after MD may be due to an initial depression of the response to stimulation of the deprived eye, followed by an increased open-eye response (15), or only to an increase in the open eye’s strength (16). To analyze which of these two components contributes to the reinstatement of OD plasticity induced by chronic antidepressant treatment in the adult rat, we compared VEP amplitudes in response to stimulation of either eye, respectively, in fluoxetine-treated and control animals. A reduction of the response to stimulation of the deprived eye after 1 week of MD (t test P < 0.05, n = 7) (fig. S1) was evident in fluoxetine-treated rats. No difference in the open eye’s strength was observed after antidepressant treatment.

To exclude the possibility that pharmacological treatment per se affects binocularity in normal (not deprived) adult animals, we next assessed OD in rats with binocular vision after chronic treatment with fluoxetine. The C/I VEP ratio in adult animals after chronic antidepressant treatment did not differ from that observed in non-drug-treated rats (t test P = 0.703, n = 4) (fig. S2). To ensure that basic response properties of visual cortical neurons were not altered after chronic administration of fluoxetine, we analyzed orientation selectivity and cell responsiveness by recording single units in a subset (n = 2) of the same animals (n = 39 cells for fluoxetine; n = 55 cells for controls). Orientation selectivity of cortical neurons (the percentage of orientation-biased cells: 36%) was in the range of normal adult rats. No difference in cell responsiveness (t test P = 0.677) (fig. S3) was found between fluoxetine-treated and control animals.

We next evaluated the recovery of visual functions in adult amblyopic animals. Rats that were rendered amblyopic by long-term MD were
chronically treated with fluoxetine, and the previously closed eye was opened while the open eye was closed (by reverse suture) during the last 2 weeks of antidepressant treatment (17). We measured VA by recording VEPs from the visual cortex contralateral to the long-term-deprived eye. In control animals, VA of the formerly deprived eye did not show any sign of recovery (0.62 ± 0.06 cycle/deg) as compared with the fellow eye (1.06 ± 0.01 cycle/deg) (Fig. 1B). In contrast, fluoxetine-treated adult rats showed a complete rescue of VA (0.97 ± 0.04 cycle/deg). A behavioral measure of VA (17), performed in the same animals before VEP recordings, confirmed the electrophysiological data: Complete recovery of VA (0.88 ± 0.02 cycle/deg) was evident in fluoxetine-treated long-term-deprived rats but not in controls (Fig. 1C). In the same animals in which VA was assessed, we also evaluated OD. In control animals, there was no rescue of binocularity in the visual cortex contralateral to the formerly deprived eye (C/I VEP ratio 1.11 ± 0.20, n = 5) (Fig. 1D), whereas fluoxetine-treated adult rats showed a full recovery of binocularity with a C/I ratio of 2.25 ± 0.17.

Because there is evidence that the maturation of intracortical inhibitory circuitries causes the end of plasticity in the visual system (18), we used in vivo brain microdialysis to investigate whether the visual cortical plasticity induced by fluoxetine was accompanied by decreased γ-aminobutyric acid–mediated (GABAergic) transmission. Extracellular basal levels of GABA were substantially reduced in the visual cortex of fluoxetine-treated adult rats (Fig. 2A) as compared with controls (two-way analysis of variance (ANOVA) repeated measures P = 0.02, post hoc Holm-Sidak test P < 0.02, n = 5). No difference in extracellular glutamate levels was detected between fluoxetine-treated and control animals (two-way ANOVA repeated measures P = 0.494, n = 5) (fig. S4). The reduced levels of GABA in fluoxetine-treated animals did not affect spontaneous activity (t test P = 1.0) (fig. S5), which was assessed in the same animals in which basic response properties of cortical neurons were examined.

To assess the reduction of intracortical inhibition at the functional level, we next examined long-term potentiation (LTP) of layer II-III field potentials induced by θ-burst stimulation (TBS) of the white matter (WM-LTP) in the visual cortex, a form of synaptic plasticity that is absent in the adult because of the maturation of intracortical inhibitory circuitries (19). WM-LTP was fully restored in fluoxetine-treated adult rats (Fig. 2B). No WM-LTP was present in control animals. We next investigated long-term depression (LTD) of layer II-III field potentials after low-frequency stimulation from the white matter, after chronic antidepressant treatment. We found that LTD was saturated in the visual cortex of MD adult rats chronically treated with fluoxetine as compared with controls [95.4% of pre–low-frequency stimulation baseline amplitude for MD fluoxetine-treated animals and 79.4% for controls].

Because chronic antidepressant administration increases the expression of the neurotrophin BDNF in limbic structures, most notably in the hippocampus (5, 20), we measured BDNF protein levels, using the enzyme-linked immunosorbent assay (ELISA) method, in the adult rat visual cortex after chronic fluoxetine administration. We found increased expression of BDNF in the visual cortex of fluoxetine-treated adult rats (t test P < 0.04, n = 6) (Fig. 2C). BDNF protein expression was similarly enhanced in the hippocampus (t test P < 0.01, n = 6) (fig. S6). To examine whether the increased BDNF expression is causally linked to the reinstatement of plasticity in the adult visual system, we then assessed OD in rats that were intracortic ally infused (via osmotic minipumps) with BDNF (1 ng μl⁻¹) in parallel to MD. Control animals infused with vehicle solution showed no change of binocularity in the visual cortex contralateral to the deprived eye (C/I VEP ratio 2.44 ± 0.1, n = 2). In contrast, adult rats intracortically infused with BDNF showed an OD shift in response to MD (C/I VEP ratio 1.32 ± 0.08 t test P < 0.001, n = 4) (Fig. 2D).

Finally, to directly test whether the reduction of intracortical inhibition underlies the reopening of visual cortical plasticity in adulthood, we evaluated OD in fluoxetine-treated adult rats that were infused intracortically with the benzodiazepine agonist dizapam (Dz) (2 mg ml⁻¹) or vehicle solution during the period of MD (Fig. 3A). Cortical Dz administration in adult rats chronically treated with fluoxetine totally prevented the OD shift induced by MD (Fig. 3B). Control animals intracortically infused with vehicle solution showed an OD shift in favor of the nondeprived eye after MD (C/I VEP ratio 1.07 ± 0.04, t test P = 0.01, n = 3).

Our findings demonstrate that chronic fluoxetine administration reinstates a juvenile-like form of OD plasticity in adulthood, which is indicated by a decrease in the response to stimulation of the deprived eye and promotes a complete recovery of visual functions in adult amblyopic rats. These effects are accompanied by a marked reduction of GABAergic inhibition and increased BDNF protein expression in the visual cortex. Furthermore, we provide evidence that the reduction of intracortical inhibition induced by ADs is a critical cellular mechanism to restore plasticity in the adult, because cortical infusion of Dz in fluoxetine-treated rats prevented the OD shift of cortical neurons after MD.

The effects induced by fluoxetine in adult visual cortical plasticity are surprisingly similar to those caused by environmental enrichment, a
condition characterized by increased exploratory behavior and sensory-motor stimulation, which we recently found to promote amblyopia recovery in adulthood through a reduction of intracortical inhibition (21). Our data suggest that the enhanced serotonergic transmission induced by chronic treatment with fluoxetine promotes functional and/or structural mechanisms that shift the intracortical inhibitory-excitatory balance, triggering plasticity in the adult visual cortex. We propose that the reduced GABAergic inhibition induced by chronic fluoxetine administration and increased BDNF expression open the pathway to the genes that regulate plasticity, thus allowing a functional modification of neuronal circuits that underlies the sensitivity to MD in the adult and recovery from amblyopia. Because previous studies have shown that serotonin enhances neuronal responses to the excitatory amino acid agonist N-methyl-D-aspartate in neocortical slices of adult rats (22), we cannot rule out the possibility that reinstatement of plasticity in the adult visual cortex induced by chronic fluoxetine administration may also involve an increased glutamatergic transmission.

We also observed the occurrence of WM-LTP in the visual cortex of fluoxetine-treated rats, a phenomenon that is usually absent in the adult but can be restored if GABA-mediated inhibition is reduced (23). Chronic administration of ADs in healthy humans increases the amplitude of the P1 and N1 components of VEPs in response to repeated presentation of visual stimuli, which has been suggested to be a form of synaptic plasticity (24). Taken together, these findings indicate that a similar increase of plasticity, which is described here in the rodent visual cortex, may also take place in the human visual cortex.

Fig. 2. Reduced intracortical inhibition and increased expression of BDNF in the adult rat visual cortex after chronic antidepressant treatment. (A) GABAergic neurotransmission in the visual cortex of fluoxetine-treated adult rats. In vivo brain microdialysis revealed that basal extracellular levels of GABA were significantly lower in fluoxetine-treated animals than in control rats (two-way ANOVA repeated measures P = 0.02, post hoc Holm-Sidak test P < 0.02 where indicated, n = 5). (B) LTP of neural transmission in the adult visual cortex. WM-LTP, measured 20 to 30 min after TBS, was significantly higher in the visual cortex of fluoxetine-treated animals than in controls (two-way ANOVA repeated measures P < 0.005, post hoc Student-Newman-Keuls test P < 0.01). Scale bars are 50% of baseline amplitude and 5 ms. (C) BDNF protein levels after antidepressant treatment. BDNF protein expression, quantified by means of ELISA, was significantly higher in the visual cortex (t test P < 0.04, n = 6) of adult rats chronically treated with fluoxetine than in controls. (D) Intracortical administration of BDNF. Adult animals cortically infused with BDNF showed an OD shift in the visual cortex contralateral to the deprived eye as compared with control animals (t test P < 0.001, n = 4). Error bars represent SEM; asterisk indicates statistical significance.

Fig. 3. Cortical administration of Dz prevented the restoration of OD plasticity induced by chronic fluoxetine administration. (A) Schematic diagrams of the experimental procedure followed (top) and of the osmotic minipump implant and recording site of VEPs in the binocular visual cortex contralateral to the deprived eye (bottom). Cortical administration of the benzodiazepine agonist Dz was performed in parallel with MD during the last week of antidepressant treatment. Oc1B, primary visual cortex. (B) Blockade of OD plasticity in fluoxetine-treated rats intracortically infused with Dz. The C/I VEP ratio in the visual cortex contralateral to the deprived eye after MD in fluoxetine-treated adult animals that were cortically infused with the benzodiazepine agonist Dz (Fluox + Dz) was not different from that of control (nondeprived) animals (C/I VEP ratio 2.48 ± 0.29, t test P = 0.483, n = 4), but differed significantly from either that of adult rats chronically treated with fluoxetine (Fluox) (t test P = 0.001, n = 5) or that of animals cortically infused with vehicle solution (Fluox + Veh) (t test P = 0.01, n = 3). Error bars represent SEM; asterisk indicates statistical significance.
visual system during chronic SSRI treatment. Moreover, our results open the possibility that chronic treatment with antidepressants may also have similar effects in other brain areas, such as those involved in mood regulation in depressed patients, and suggest new mechanisms for the therapeutic effects induced by ADs and the pathophysiology of mood disorders.

Our finding that fluoxetine, a widely prescribed AD in humans, restores plasticity in the adult visual system suggests that antidepressants may be used as a complementary treatment to current therapies for human amblyopia. Although amblyopia can be prevented by occlusion treatment during childhood, there are currently no treatment strategies that would restore vision to the amblyopic eye in adults (25). Our data also indicate a potential clinical application for antidepressants in neurological disorders in which synaptic plasticity is compromised because of excessive intracortical inhibition (26–28).

References and Notes
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17. Materials and methods are available as supporting material on Science Online.
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Reports: “The antidepressant fluoxetine restores plasticity in the adult visual cortex” by
J. F. Maya Vetencourt et al. (18 April, p. 385). The list of supporting online material (SOM) was
omitted from the end of the paper. The SOM contains Materials and Methods, figs. S1 to S7,
and References. It is available at www.sciencemag.org/cgi/content/full/320/5874/385/DC1.