



## Doubt about antidepressant-like effect

Received 24 May 2012, Revised 02 July 2012, Accepted 07 July 2012, Epub 13 September 2012

### Dear Editor:

Extensive studies have measured antidepressant-like effects of chemical compounds to discover new drugs for depression treatment or to clarify the molecular mechanisms of depression. Most useful antidepressants including tricyclics, selective serotonin reuptake inhibitors (SSRIs), noradrenaline reuptake inhibitors (NRIs), serotonin and noradrenaline reuptake inhibitors (SNRIs), and monoamine oxidase inhibitors (MAOIs) exert antidepressant-like effects in forced swimming test (FST) in mice and rats<sup>[1]</sup>. However, it remains unanswered whether the observed antidepressant-like effects are real antidepressant effects as seen in those by antidepressant drugs used in clinic. Two questions emerge from this topic: the first question is whether the molecular signaling pathway of antidepressant-like effect is the same as that of antidepressant effect; the second question is whether all compounds having antidepressant-like effects can exert antidepressant effect in animal tests and in clinic.

Major depression is a mental illness influenced by genetic and environmental factors. The pathophysiology of depression includes decreased concentration of monoaminergic transmitters, low levels of nerve growth factors, hyperactivation of the hypothalamic-pituitary-adrenal axis, impaired neuronal plasticity and reduced adult neurogenesis. The disease is chronic and mainly caused by long-term, severe life stress. Moreover, current antidepressant drugs need at least 3 to 4 weeks to correct these changes and improve depressive symptoms<sup>[2]</sup>. Although it may be an impossible quest to mimic major depressive disorders

completely in rodents, many models have been established to reproduce the pathophysiology of depression in animals, among which the chronic mild stress (CMS) model has been widely used. The model can induce most of the neurobiological alterations of depression referred above and cause main symptoms of depression, including decreased responsiveness to rewards, anhedonia, decreased appetite and weight loss, which can be reversed by treatment with a wide spectrum of antidepressants for 2 to 4 weeks<sup>[3]</sup>. In fact, it was demonstrated in our experiment that 3 weeks of CMS procedures (various stimuli including restraint, forced swimming, wet cage, deprivation of food and water, reversal of light/dark cycle and tilted cage, **Fig. 1A**) were sufficient to induce depressive behaviors in tail suspension test (TST), FST, sucrose preference test (SPT) as well as novelty suppressed feeding test (NSFT) (**Fig. 1B-E**)<sup>[4-6]</sup> and induced physical impairment in mice. It required at least two weeks to reverse behavioral despair after the end of two-week treatment with fluoxetine (**Fig. 1F-G**). In our experiment, fluoxetine cannot ameliorate depressive symptoms acutely and antidepressant potential of 7-NI under CMS condition cannot induce antidepressant-like effect in normal mice<sup>[4]</sup>. These findings indicated that animal models of depression are indispensable in studying depression.

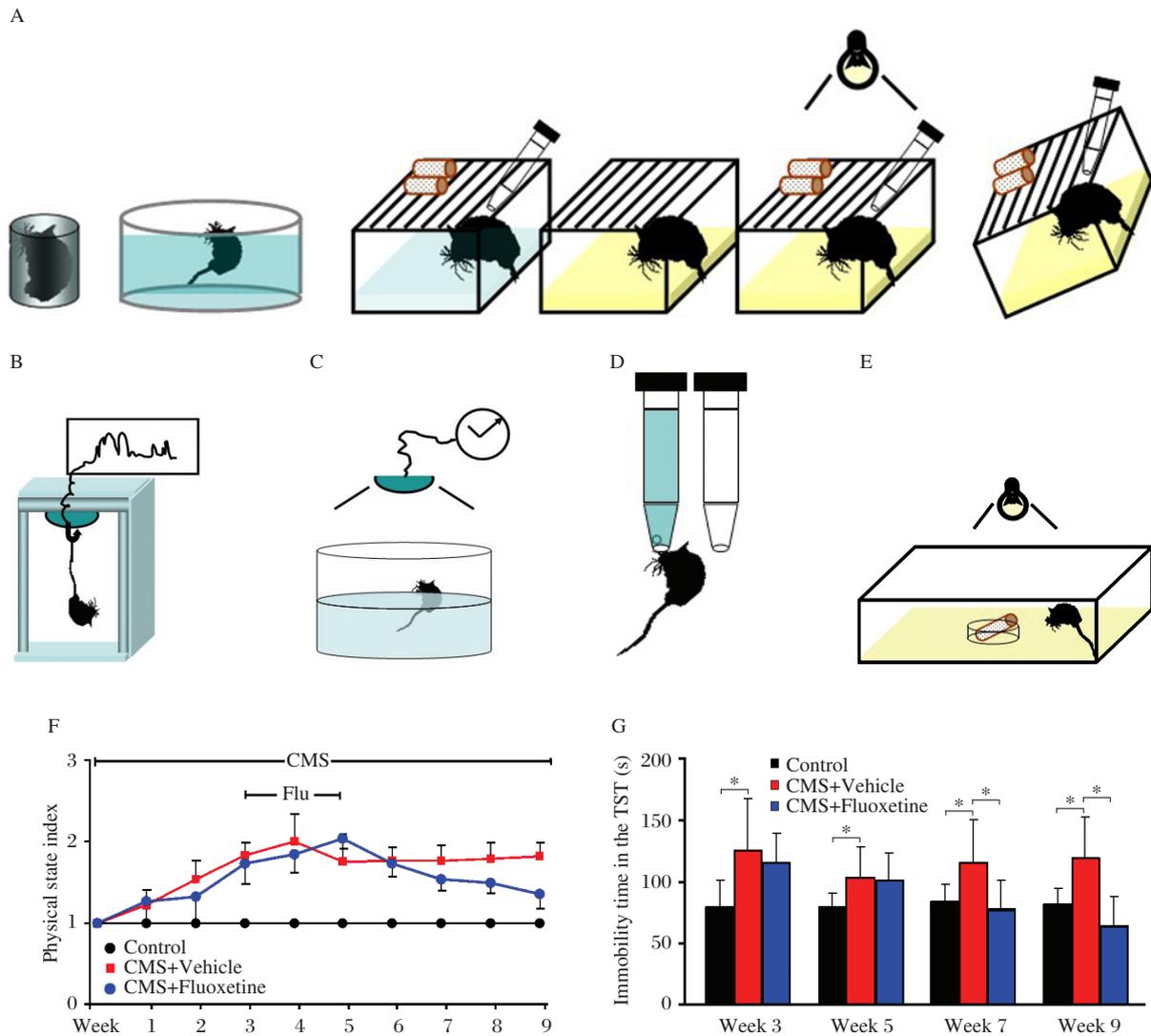
The biggest caveat of antidepressant-like effect is that medications are tested in normal animals after acute administration, which is inconsistent with the pathological development of depression. As antidepressant drugs do not exert antidepressant effect in

This work was supported by grants from the Science and Technology Foundation of Nanjing Medical University (No. 09NJMUZ15) and from the Natural Science Foundation of Jiangsu Province (No. 10KJB31008).

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The authors reported no conflict of interests.



**Fig. 1** Fluoxetine exerts antidepressant effects in a delayed manner in mice exposed to CMS. A: Three weeks of CMS procedures (various stimuli including restraint, forced swimming, wet cage, deprivation of food and water, reversal of light/dark cycle and tilted cage) caused prolonged immobility in TST (B) and FST (C), a low percentage of sucrose preference in SPT (D) and longer latency to feed in NSFT (E). F and G: Adult mice were exposed to CMS for 9 weeks and administered with fluoxetine (10 mg/kg, i.p.) for 14 d from d 22 to d 35 of CMS exposure, and their behaviors were examined 24 h, 2 and 4 weeks after the end of treatment. Fluoxetine reversed CMS-induced PS impairment and immobility time prolongation in TST 2 and 4 weeks but not 24 h after the end of treatment.  $n = 17-20$ ;  $*P < 0.05$ . Kruskal-Wallis ranks test for PS, one-way ANOVA for TST. CMS: chronic mild stress; NSFT: novelty suppressed feeding test; PS: physical state; SPT: sucrose preference test; TST: tail suspension test.

healthy humans, the phenomenon that antidepressant drugs produce antidepressant-like effects in rodents is confusing. SSRIs can increase the concentration of 5-HT in the synaptic cleft within minutes and improve depressive symptoms after at least two weeks, indicating that the antidepressant effect of SSRIs is not directly dependent on the concentration of 5-HT, but on the long-term changes induced by 5-HT. Inversely, depletion of endogenous serotonin completely blocks the antidepressant-like effects, implying that the concentration of 5-HT control the depressive symptom immediately<sup>[7]</sup>. A great number of studies indicated

that the underlying molecular signaling pathway of antidepressant-like effect is not the same as that of antidepressant effect. Although some tests, particularly FST, are effective in predicting the antidepressant efficacy of drugs, the conflicting onset time and underlying mechanism should not be ignored. In conclusion, based on the distinctive pathophysiology of depression, antidepressant-like effect may be a misrepresentation of depression.

Although a large range of antidepressants caused a reduction in the immobility of mice and rats in FST within hours, which are the so called antidepressant-

like effects, the underlying mechanism is hard to understand. First, why cannot antidepressant-like effects be observed in other indexes of depression, including TST, SPT, NSF and body weight? Second, since antidepressants exert antidepressant-like effects in animals within hours observed in FST, why cannot these drugs induce antidepressant effects acutely in humans? Third, since it needs a very long time to cause changes in a variety of molecules in multiple tissues underlying the etiology of depression, why do antidepressants induce antidepressant-like behavior in animals in physical condition within so short time? What is the molecular basis? Fourth, the validity of FST for measuring depression-related behaviors in physical condition is questionable.

Currently, most antidepressant-like effects are based on behavioral changes of rodents in FST. In FST, the motor stimulant properties may result in a false positive in screening procedures. Additionally, the test environment of FST is an acute stressor for animals, so immobility may be seen as an adaptive response to an inescapable situation. Precisely, the reduction of immobility in FST of animals with no depression (under physical condition) may reflect excitement or a failure to adapt to an acute stressor rather than the antidepressant mood. Moreover, although about 83%-94% of chronic antidepressants treatments decrease the immobility time of mice in FST, acute or subchronic treatment of many antidepressants are ineffective. Many compounds exert antidepressant-like effect in animal experiments but not in clinic. For instance, amisulpride, an atypical antipsychotic which is ineffective in treating depression in clinic, also displays antidepressant-like property in FST but not in TST in mice<sup>[8]</sup>. In addition, TC-5214, a form of mecamlamine, failed to significantly relieve major depression in phase III trial even though it induced robust antidepressant-like effect in animal test<sup>[9]</sup>. Many psychostimulants have antidepressant-like potency, but the clinical significance is still unclear<sup>[10]</sup>. On the other hand, several well-known antidepressants such as gepirone, buspirone and chlorimipramine, have no antidepressant-like effect in FST<sup>[11]</sup>. Accordingly, the behavior pattern of rodents in FST is just a potential predictor of antidepressants response, but not the antidepressant effect.

Considering the questions described above, it may be reasonable that studies on the pathology of depression and the mechanisms of antidepressant, and screening of new potential antidepressant should be based on animal models of depression. It is worth celebrating that scientists currently have found that a single sub-psychomimetic dose of ketamine, a NMDAR

(*N*-methyl-*D*-aspartate receptor) antagonist, generates fast onset antidepressant responses in patients with major depression. In a study of the underlying mechanism published in *Nature*<sup>[12]</sup>, FST was performed after chronic mild stress. Additionally, the fast-acting antidepressant effect of ketamine was measured not only in FST but also in learned helplessness and NSFT, indicating that ketamine, unlike former compounds which display antidepressant-like effect only in FST, was effective indeed in curing depression acutely<sup>[12,13]</sup>. Accordingly, antidepressant-like effect can be measured as a rough predictor of antidepressant effect of antidepressants and it may be time to emphasize the importance of animal models of depression in studying depression.

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