

Original Article

Differential involvement of 5-HT_{1A} and 5-HT_{1B/1D} receptor in human interferon α -induced immobility

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Abstract: Although Interferon-alpha (IFN- α) is a powerful drug in treating several viral infections and certain tumors, a considerable amount of neuropsychiatry side-effects such as depression and anxiety are unavoidable consequence. Combination with selective serotonin (5-HT) reuptake inhibitor (SSRI) fluoxetine significantly improved the situation. However, the potential 5-HT_{1A} receptor- and 5-HT_{1B} receptor-signals, involved in the antidepressant effects are still unclear. Here we analyzed the effects of 5-HT_{1A} receptor- and 5-HT_{1B} receptor-signals by using mouse forced swimming test (FST), a predictive test of antidepressant-like action. The present results indicate that: (1) fluoxetine (administered intragastrically, 30 mg/kg; not subactive dose: 15 mg/kg) significantly reduced IFN- α -induced increase of the immobility time in the forced swimming test; (2) 5-HT_{1A} receptor- and 5-HT_{1B} receptor-ligands along or combination have no effects on IFN- α -induced increase of the immobility time in the FST; (3) surprisingly, WAY 100635 (5-HT_{1A} receptor antagonist) and 8-OH DPAT (5-HT_{1A} receptor agonists) markedly enhanced the antidepressant effect of fluoxetine at subactive dose (15 mg/kg, i.g.) on the IFN- α -treated mice in the FST respectively; Further investigations showed that fluoxetine combined with WAY 100635 and 8-OH DPAT failed to produce antidepressant effects in the FST. (4) Co-application of CGS 12066A or GR 127935 with fluoxetine has no synergistic effects on the IFN- α induced increase of immobility time in FST. (5) Interestingly, co-administration of GR 127935, WAY 100635 and fluoxetine significantly reduced the IFN- α induced increase in immobility time of FST, which is more effective than that produced by the co-administration of WAY 100635 and fluoxetine. All results suggest that: (1) compared to 5-HT_{1B} receptor, 5-HT_{1A} receptor signal plays the dominant role in improving the anti-immobility effect of fluoxetine in the IFN- α -induced depression; (2) synergistic effect of 5-HT_{1B} receptor with 5-HT_{1A} receptor depends on fluoxetine-elevated basal level of serotonin in IFN- α -treated mice.

Key words: Depression, interferon-alpha, 5-HT_{1A} receptor, 5-HT_{1B} receptor, forced swimming test

Introduction

Interferon-alpha (IFN- α) is an innate immune-modulator, which is released chiefly by plasmacytoid dendritic cells for both human [1, 2] and mice [3, 4], partly by neurons and glia in central nervous system [5-7]. As a potent multifunctional cytokine IFN- α was widely used in clinical therapy in treating viral infections and cancers [8, 9]. Regrettably, application of the immune signal molecule also induces significant neuropsychiatric disorders, which include symptoms such as depression, irritability, impaired memory, insomnia, loss of appetite and asthenia [10]. Among which, the incidence of depressive

symptoms increased to the range from 10 % to 50 % [11-16]. Seriously, there are increasing reports of suicide attempt and completed suicide during interferon therapy [15, 17, 18]. These issues highlighted the urgency to elucidate the underlying mechanisms of IFN- α induced depression and to establish the effective precautionary measures.

Therapeutic studies found that the selective serotonin re-uptake inhibitors (SSRIs), such as sertraline, fluoxetine, paroxetine and citalopram, are effective in the treatment of IFN- α -induced depression [19, 20]. Thus, adaptive changes in the serotonergic system are believed to underlie the IFN- α induced

depression and the therapeutic efficacy of these antidepressant drugs. Although antidepressant mechanisms of the elevated 5-HT level are still unclear, involvement of synaptic 5-HT receptors is evident. Clinical investigations found that pindolol, the antagonist of 5-HT_{1A} / 5-HT_{1B} receptor, shortened the latency to onset of clinical antidepressant action of SSRIs [21]. Pretreatment with pindolol significantly enhanced the anti-immobility effects of subactive doses of selective serotonin reuptake inhibitors fluoxetine, citalopram or paroxetine in the mice forced swimming test [22]. Several studies evaluated the interaction between 5-HT_{1A} or 5-HT_{1B/1D} receptor antagonists and antidepressant drugs in certain animal models of depression [23-25], but the synergistic coupling of 5-HT_{1A} receptor and 5-HT_{1B} receptor in IFN- α -induced depression is largely unknown.

The forced swimming test (FST) is an effective animal model to screen the antidepressant drugs and study the neurobiological mechanisms of the drug. In order to illustrate the coupling effects of 5-HT_{1A} receptor and 5-HT_{1B} receptor, we first evaluated the role of 5-HT_{1A} or 5-HT_{1B/1D} receptor agonist and antagonist on IFN- α -induced depression using FST. Then, we examined the potential value of combination therapy for effective precautionary control, 5-HT_{1A} or 5-HT_{1B/1D} receptor ligands with fluoxetine, on the latency to onset of clinical action of fluoxetine on the IFN- α -induced depression.

Materials and methods

Animals

Male ICR strain mice (Experimental animal center, China Pharmaceutical University), weighing 18-32 g, were used in the forced swimming test (FST) and open field test (OFT). Animals were housed 5 per cage (40×30×20 cm) under a normal 12 h light/dark cycle (light between 8:00 A.M. and 8:00 P.M.) and had free access to tap water and food pellets. Ambient temperature and relative humidity were maintained at 23 ± 2 °C and at 55 ± 10%, respectively. Mice were habituated to their new environment for 1 week before experimental use. Animals were introduced to the testing room 1 h before being tested and all behavioral tests were performed in the light phase between 9:00 A.M. and 2:00 P.M.. All

the experimental procedures were performed in accordance with the Institutional Animal Care Committee and the China Council on Animal Care at China Pharmaceutical University.

Drug and treatments

The following drugs were used: N-[2-[4-(2-Methoxyphenyl)-1-piperazinyl]ethyl]-N-2-pyridinylcyclohexanecarboxamide maleate salt (WAY 100635, 634908-75-1), (+/-)-8-Hydroxy-2-dipropylaminotetralinehydrobromide (8-OH DPAT, 78950-78-4), N-[4-Methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2-methyl-4-(5-methyl-1,2,4-oxadiazol-3-yl)-1,1-biphenyl-4-carboxamide hydrate hydrochloride (GR 127935, 148642-42-6) and 7-Trifluoromethyl-4-(4-methyl-1-piperazinyl)pyrrolo-[1,2-a]quinoxaline maleate salt (CGS 12066A, 109028-09-3). These four drugs were purchased from Aldrich and Sigma chemicals (Milwaukee, WI, USA). Fluoxetine hydrochloride((±)-N-methyl- γ -[4-(trifluoromethyl)phenoxy]-benzenepropanamine, 56296-78-7) were purchased from Eli Lilly and Company (Suzhou, Jiangsu, P.R.China), buspirone hydrochloride were purchased from Jiangsu Nhwa Pharmaceutical Company (Xuzhou, Jiangsu, P.R.China). IFN- α (Interferon Alpha Human 2a Recombinant) was from ProSpec-Tany TechnoGene Ltd (Rehovot Science Park, Israel). WAY 100635, 8-OH DPAT, CGS 12066A, Buspirone, Fluoxetine were dissolved in distilled water. GR127935 was dissolved in distilled water with gentle (70 °C) heating. IFN- α was diluted with 0.9 % physiological saline (Nanjing Xiaoying Pharmaceutical Company Limited, Jiangsu, China). All the compounds were administered in a volume of 10 ml/kg. 8-OH-DPAT and GR127935 were injected intraperitoneally (i.p.), WAY100635 and CGS-12066A subcutaneously (s.c.), Fluoxetine intragastrically (i.g.) and IFN- α intravenously (i.v.). WAY100635, CGS-12066A, 8-OH-DPAT and GR127935 were given 30 min before TST and OFT, Fluoxetine 3 hours before and IFN- α 15 min before. Control mice received a vehicle according to the same schedule.

Forced swimming test (FST)

The studies were carried out on mice according to the method of Porsolt et al. (1978). Mice underwent two swim sessions: conditioning interval on day one and test interval on day two. Mice were placed in glass

5HT receptors and IFN α -induced immobility

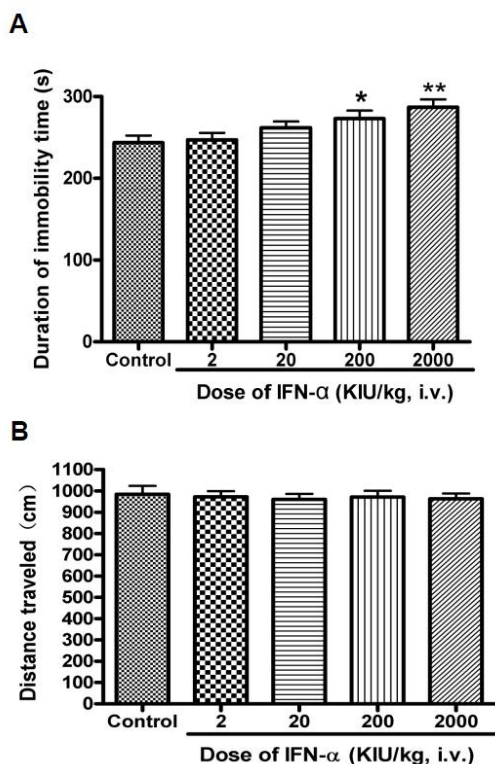


Figure 1. Effect of IFN- α treatment on the immobility time in the forced swimming test (A) and locomotor activity in the open field test (B). Saline (control) or IFN- α (2-2000 KIU/kg, i.v.) is administered 15 min before test. Data are expressed as means \pm S.E.M.; n=10 for each group. **P<0.01, *P<0.05 compared with the saline control group.

cylinder (30 cm in height, 15 cm in diameter) filled 10cm high with water (25 ± 2 °C). A video camera facing the container and linked to a computer equipped with a video tracking system (Yishu, Shanghai, China) registered each mouse's activity within the course of the 6 min test period and calculated the time spent in immobility. Each mouse was judged immobile when it ceased struggling and remained floating motionless in the water, making only those movements necessary to keep its head above water.

Locomotor activity in the open field test

The procedure developed by Janssen et al. (1960) was employed. Locomotion was evaluated in Infra Red panels (1 m Long, 1 m wide). The panels has white floor composed with Infra red lamps and was divide to four

open fields (4* 50x50 cm). A video-tracking camera (placed 200cm above the center of the floor) monitored the activity of mice and the video signal was transmitted to a computer and analyzed using VIDEOTRACK system (Viewpoint Ltd, Lyon, France). Individual control or drug-injected animals were gently placed in the centre of the arena and were allowed to explore freely. Locomotor activity in the open field chamber was recorded for 5 min using a computer. Floor surfaces were thoroughly cleaned with 70% ethanol between tests.

Statistical analysis

The obtained data were present as the mean \pm S.E.M. Comparisons between experimental and control groups were performed by one-way analysis of variance (ANOVA) in the FST and open-field test followed by intergroup comparisons using Tukey's HSD test. P < 0.05 was considered significant.

Results

The effect of IFN- α treatment in mouse forced swimming test and open field test

Intravenous administration of IFN- α (i.v.) dose-dependently increased the immobility time in FST (control: 243.6 ± 27.62 ; 200 group: 273.1 ± 30.61 , P=0.04; 2000 group: 287.1 ± 30.39 , P =0.004, **Figure 1A**). Meanwhile, over the dose range applied, IFN- α (2-2000 KIU/kg) showed no statistically significant effect on the distance traveled of the mice in open field test (971.85 ± 85.13 , P =0.80; 959.8 ± 81.03 , P =0.61; 971.55 ± 91.65 , P =0.80; 962.5 ± 80.70 , P =0.65, **Figure 1B**).

Effects of fluoxetine on the IFN- α -increased immobility in FST

Pre-treatment the selective serotonin reuptake inhibitors fluoxetine was inactive at the dose of 15 mg/kg (242.8 ± 28.50 , P =0.6, **Figure 2**); but when given at 30 mg/kg, it significantly reduced the immobility time compared with control group (219.4 ± 19.90 , P =0.04, **Figure 2**). Therefore, the inactive dose of fluoxetine (15 mg/kg) was chosen for the interaction studies.

Effects of 8-OH DPAT, WAY 100635, CGS 12066A, GR 127935 and buspirone in FST

5HT receptors and IFN α -induced immobility

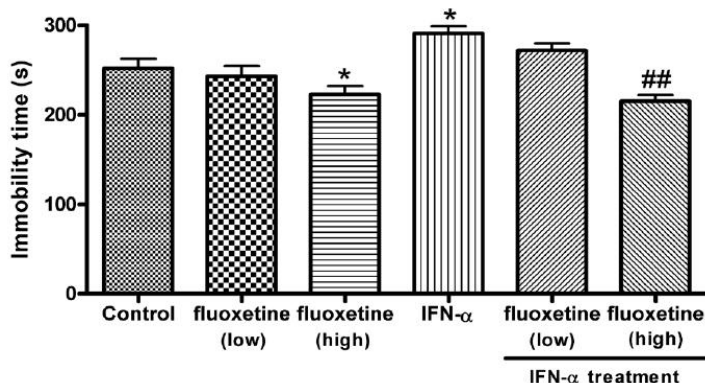


Figure 2. Effects of fluoxetine on the effect of IFN- α in the forced swimming test in mice. Saline (control) or IFN- α (2000 KIU/kg, i.v.) was administered 15 min before measurement of immobility time. Fluoxetine (15 mg/kg and 30 mg/kg, i.g.) was administered 3 hours before the test. All values are mean \pm S.E.M.; n= 8 for each group. *P<0.05 vs control group. ## P<0.01 vs IFN- α group.

Application of 5-HT_{1A} receptor agonist 8-OH DPAT (1 mg/kg, i.p.), 5-HT_{1A} receptor antagonist WAY 100635 (0.3 mg/kg, s.c.), 5-HT_{1B} receptor agonist CGS 12066A (2 mg/kg, s.c.), 5-HT_{1B/1D} receptor antagonist GR 127935 (3 mg/kg, i.p.) and 5-HT_{1A} receptor agonist buspirone (20 mg/kg, i.g.), separately, showed no statistically significant effect on the duration of immobility in FST. (255.0 \pm 25.64, P =0.83; 267.6 \pm 34.71, P =0.40; 259.3 \pm 30.13, P =0.65; 261.3 \pm 29.32, P =0.56; 258.5 \pm 34.45, P =0.71, **Figure 3A**). Furthermore, combined administration with 8-OH DPAT and WAY 100635 also have no effect on the IFN- α induced increase in the immobility time (268.4 \pm 22.25, P = 0.10; 285.8 \pm 20.19, P =0.68; 284.7 \pm 18.0, P =0.60, **Figure 3B**).

GR 127935 and CGS 12066A also had no statistical difference of immobility time in the same animal model (277.6 \pm 30.77, P =0.40, **Figure 5A**).

Compared to 5-HT_{1A} receptor ligands, coadministration of GR 127935 (3 mg/kg, i.p.)

Interactions of fluoxetine with WAY 100635, 8-OH DPAT on the effect of IFN- α in FST

Either 8-OH DPAT (1 mg/kg, i.p.) or WAY 100635 (0.3 mg/kg, s.c.) co-administered with a subactive dose of fluoxetine (15 mg/kg, i.g.) significantly reduced the immobility time in FST, respectively (241.7 \pm 14.13, P=0.001; 232.4 \pm 24.8, P =0.001. **Figure 4**). Additionally, coapplication of fluoxetine (15 mg/kg, i.g.), 8-OH DPAT (1 mg/kg, i.p.) and WAY 100635 (0.3 mg/kg, s.c.) did not produce significant change of the immobility time in FST (268.0 \pm 19.26, P =0.07, **Figure 4**).

Interaction of fluoxetine with GR127935, CGS 12066A on the effects of IFN- α in FST

Pre-treatment with GR 127935 (3 mg/kg, i.p.) or CGS 12066A (2 mg/kg, s.c.) had no statistically significant effect on the IFN- α induced increase of immobility time (277.2 \pm 33.60, P =0.42; 270.5 \pm 33.68, P =0.24, **Figure 5A**). Combined administration of

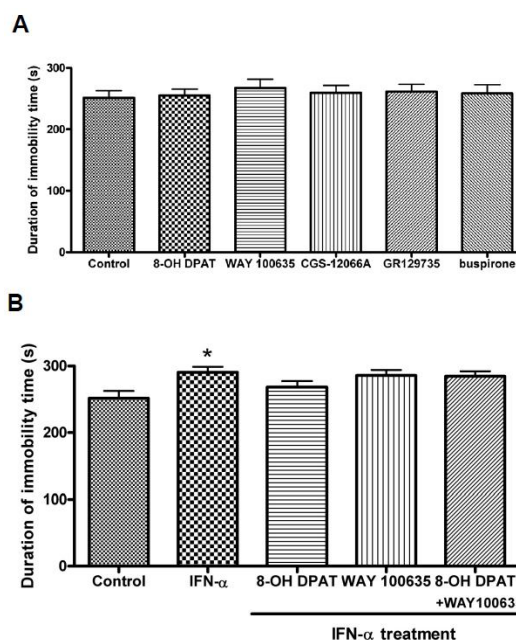


Figure 3. Effects of 8-OH-DPAT, WAY100635, CGS-12066A, GR127935 and buspirone on the immobility time in the forced swimming test in mice (A); co-administration with 8-OH DPAT and WAY 100635 (B) or GR 127935 and CGS 12066A (C) on the IFN- α induced increase in the immobility time. WAY 100635 (0.3 mg/kg, s.c.), 8-OH DPAT (1 mg/kg, i.p.), GR 127935 (3 mg/kg, i.p.), CGS 12066A (2 mg/kg, s.c.) were administered 60 min before test. Buspirone (20 mg/kg, i.g.) was administered 3 hours before the test. All values are mean \pm S.E.M.; n= 8 for each group. *P<0.05 vs control group.

5HT receptors and IFN α -induced immobility

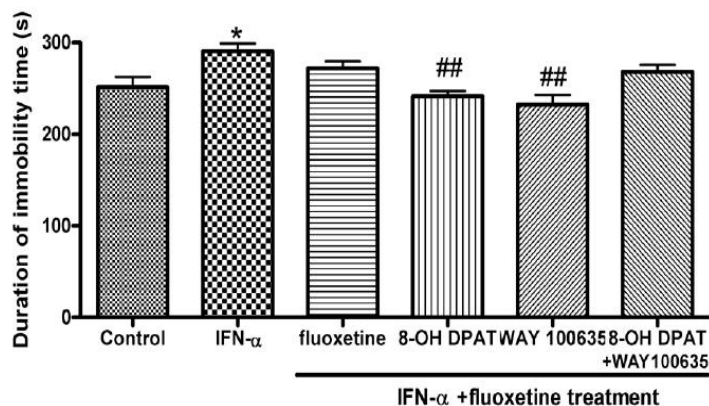


Figure 4. Interaction of fluoxetine with WAY00635, 8-OH-DPAT on the effect of IFN- α in the forced swimming test in mice. 8-OH DPAT (1 mg/kg, i.p.) or WAY 100635 (0.3 mg/kg, s.c.) was administered 60 min before measurement of immobility time. Fluoxetine (15 mg/kg, i.g.) was administered 3 hours before the test. Saline (control) or IFN- α (2-2000 KIU/kg, i.v.) is administered 15 min before test. All values are mean \pm S.E.M.; n= 8 for each group. *P<0.05 vs control group. ##P<0.01 vs IFN- α group.

and/or CGS 12066A (2 mg/kg, s.c.) with fluoxetine (15 mg/kg) has no effect on the IFN- α induced increase of the immobility time (267.8 \pm 17.13, P =0.06; 273.1 \pm 20.75, P =0.17; 262.6 \pm 24.28, P =0.05, **Figure 5B**).

GR 127935 potentiates effect of WAY 100635 co-administered with fluoxetine in the IFN- α -induced immobility in the FST

GR 127935 further significantly reduced the immobility time in WAY 100635 and fluoxetine treated IFN- α -induced depressive mice in FST (226.6 \pm 14.63, P = 0.00008, **Figure 6**).

Discussion

Besides the effectiveness in treating viral infections and cancers, Interferon-alpha (IFN- α) also induces significant neuropsychiatric disorders, especially depression. Hence, we do need to clarify the underlying mechanisms of IFN- α -induced depression and to establish the effective treatments. In this regard, one of the most powerful antidepressants and the potential serotonergic signaling involved in the process was investigated.

Commonly used pegylated IFN- α -2a and 2b are bound covalently to polyethylene glycol and have much longer half-lives which is 4 to 16 hours in human [26]. IFN- α can penetrate the blood brain barrier (BBB) in the area of deficient, such as the area postrema, median eminence and infundibular recess [27]. Moreover, the concentration of IFN- α in serum and cerebrospinal fluid after systemic administration is detectable and can reach at 35-110 units (U)/ml in the cerebrospinal fluid (CSF) [28, 29]. Makino et al. evidenced that central administration of IFN- α (50 IU per mouse, i.cist.) significantly increased the

immobility in the mouse forced swimming test [30]. These results are in line with the findings that human IFN- α can induce depressive symptoms both central and peripheral administration [31-33]. Most of the basic and clinical literatures points to the notion that 5-HT1AR and 5-HT1BR have the potential anxiolytic and antidepressant activity [34, 35]. Therefore, we aimed to explore the

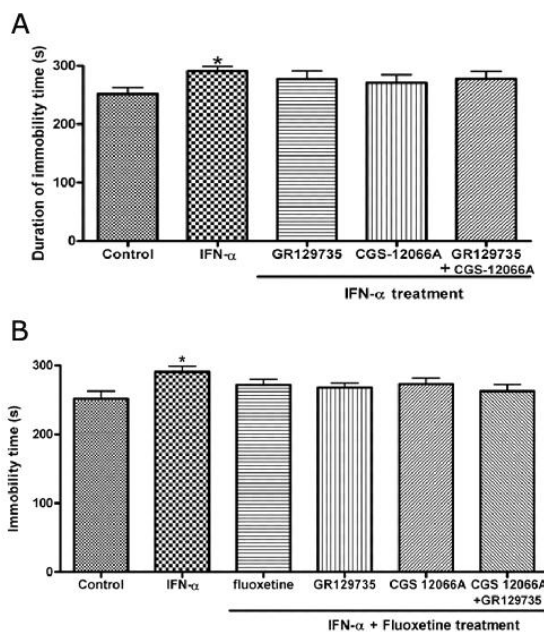


Figure 5. Effects of GR 127935 and CGS 12066A on the effect of IFN- α in the forced swimming test (A), Interaction of fluoxetine with GR 127935, CGS 12066A on the effect of IFN- α in the forced swimming test (B). Saline (control) or IFN- α (2000 KIU/kg, i.v.) was administered 15 min before measurement of immobility time. GR 127935 (3 mg/kg, i.p.) or CGS 12066A (2 mg/kg, s.c.) was administered 60 min before measurement of immobility time. All values are mean \pm S.E.M.; n= 8 for each group. *P<0.05 vs control group.

5HT receptors and IFN α -induced immobility

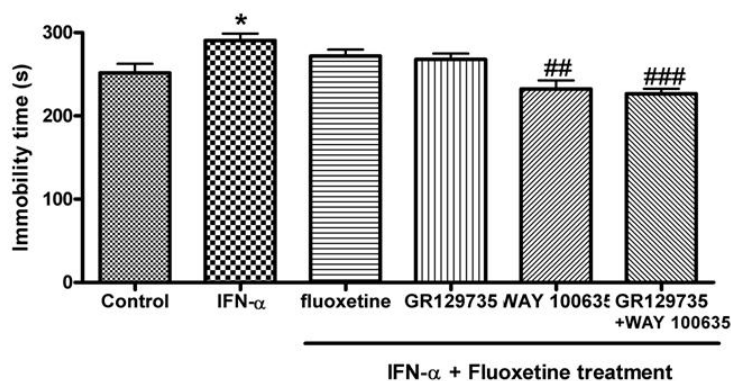


Figure 6. GR 127935 potentializes effect of WAY 100635 co-administered with fluoxetine in immobility time of FST in mice. GR 127935 (3 mg/kg, i.p.) was administered 75 min before measurement of immobility time. WAY 100635 (0.3 mg/kg, s.c.) was administered 60 min before measurement Fluoxetine (15 mg/kg, i.g.) was administered 3 hours before the test. Saline (control) or IFN- α (2-2000 KIU/kg, i.v.) is administered 15 min before test. All values are mean \pm S.E.M.; n= 8 for each group. *P<0.05 vs control group. ##P<0.01 vs IFN- α group. ###P<0.001 vs IFN- α group.

involvement of 5-HT1A/1BR and fluoxetine in mice forced swimming test.

Although forced swimming test has some drawbacks represented by the possibility of obtaining some false positives or negatives, it's still one of the most powerful tools in screening antidepressant drugs and studying the neurobiological mechanisms of depression. In order to exclude the potential 'false' positive effect of enhancing motor activity and the 'false' negative result of decreasing locomotion, we analyzed the possible influence of these drugs by open field test [36]. The results that IFN- α (i.v.) had no effect on the locomotor activity indicate that the IFN- α -induced increase of the immobility time in the forced swimming test was not due to motor dysfunction. The depressive behavior of IFN- α in FST is somewhat in accordance with clinical studies about IFN- α -induced significant side-effect of major depressive disorders [12, 20].

The monoamine theory is one of the major hypotheses explaining the biological etiology of major depressive disorders, which proposes that the mood disorder is caused by metabolic disruption of amino compounds in the brain [37]. Recent clinical research found that serotonergic system is involved in the development of IFN- α -induced depressive

symptoms [38]. Consistently, the level of 5-hydroxytryptamine (5-HT) is significantly reduced in the rat frontal cortex in a dose-dependent manner after single intracerebroventricular (i.c.v.) injection of IFN- α [39]. Although fluoxetine elevated 5-HT level and show unambiguous antidepressive effects in patients and different animal models, the mechanism of serotonergic signaling underlying IFN- α -induced depressive-like effects is largely unknown. Previous studies have shown that 5-HT1A and 5-HT1B/D receptors play important roles in mediating the antidepressive effects of fluoxetine [40]. However, our data clearly show that application of a low concentration of 5-HT1A and/or 5-HT1B/D receptor agonist and/or antagonist, including WAY 100635, 8 OH DPAT, CGS 12066A and GR 127935, alone fails to alter the immobility time in the FST (Figure3A). These behavior results indicate that low level of 5-HT1A and/or 5-HT1B/D receptor blockade is not sufficient to trigger the serotonergic antidepressive signaling. The finding that WAY 100635 and GR 127935 produced no significant changes in extracellular 5-HT levels in the rat brain [41, 42] further explained the lack of antidepressant effects of these autoreceptor ligands given alone.

How does 5-HT1A and/or 5-HT1B/D receptor involved in antidepressive signaling? Considering the clinical side-effects of antidepressants and its treatment, one possible mechanism is through the combinational adjustment of certain antidepressive signals. Fortunately, we found that combination of subactive dose of fluoxetine (15 mg/kg) with WAY 100635 or 8-OH DPAT significantly reduced the immobility time in FST in IFN- α -treated mice. Previous studies demonstrated that acute application of WAY 100635 further elevated the 5-HT level produced by serotonergic antidepressants in various brain regions of rats [43-47]. Moreover, repeated or single administration of IFN- α reduced the extracellular 5-HT level in serum and brain [38, 39]. These findings suggest that 5-HT1AR antagonist is an

effective partner with selective serotonin reuptake inhibitor (SSRI) fluoxetine in treating depression through the blockade of presynaptic 5-HT_{1A} autoreceptors. In order to elucidate the puzzling results of 5-HT_{1A} agonist and antagonist, we evaluated the antidepressant effects of coadministration of fluoxetine, WAY 100635 and 8-OH DPAT in the FST. The antidepressant effects were not found. The reasons are as follows: Firstly, it is likely that WAY 100635 and 8-OH DPAT block the synergistic effect of each other. Secondly, 8-OH DPAT have a preferential effect at postsynaptic 5-HT_{1A} receptors [48]. Thirdly, IFN- α may differentially affect presynaptic and postsynaptic 5-HT_{1A} receptors. Moreover, the results further exclude the possibility that WAY 100635 acts as partial agonist at postsynaptic 5-HT_{1A}.

On the other hand, administration of CGS 12066A or GR 127935 with fluoxetine has no synergistic effect in the IFN- α -induced increase in immobility time of FST. The result is consistent with previous finding that blockade of 5-HT_{1B} receptors with GR 127935 could evoke the anti-immobility effect of paroxetine, but not fluoxetine [49]. Interestingly, co-administration of GR 127935, WAY 100635 and fluoxetine significantly reduced the IFN- α -induced increase in immobility time of FST, which is more effective than that produced by the co-administration of WAY 100635 and fluoxetine (Figure 6). Accordingly, the 5-HT_{1B} receptors located on neuronal terminals act not only as autoreceptors on 5-HT neurons, but also as heteroreceptors on non-serotonergic neurons where they control the release of other neurotransmitters including noradrenaline and dopamine [50]. Therefore, it is speculated that the noradrenaline-mediated neurotransmission may be involved in the anti-immobility effects observed after combined administration of 5-HT_{1B} receptor antagonists and WAY 100635 co-administered with fluoxetine.

In conclusion, all the positive interactions described seem to be specific, since these drugs (given alone or combined) do not affect the locomotor activity of the mice in the open field test. Findings presented here indicate that synergistic effect of 5-HT_{1B} receptor with 5-HT_{1A} receptor depends on fluoxetine-elevated basal level of serotonin in IFN- α -treated mice. Moreover, 5-HT_{1A} receptor signaling plays the dominant role in improving

the anti-immobility effect of fluoxetine in the IFN- α -induced depression. Additionally, our results suggest that combination of 5-HT_{1A} antagonist with subactive fluoxetine can be helpful in IFN- α -induced depression treatment.

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5HT receptors and IFN α -induced immobility

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