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ANTIDEPRESSANT-LIKE ACTIVITY OF CANNABINOID TYPE-1 RECEPTOR ANTAGONIST, RIMONABANT: BEHAVIOURAL INVESTIGATION IN ANIMAL MODEL OF DEPRESSION

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ABSTRACT

Recent findings support the hypothesis that CB receptor blockade might be associated with antidepressant and anti-stress effects. In the current study, the anti-depressant-like effects of rimonabant were studied in validated models of depression. Rimonabant (4-8mg/kg, i.p.) significantly decreased the duration of immobility in a dose dependent manner in mice forced swim test (FST) and in tail suspension test (TST) without affecting the baseline locomotion. Rimonabant potentiated the 5-HTP induced head twitches. Rimonabant (4-8mg/kg) rimonabant significantly reversed the reserpine induced hypothermia. Interactions studies revealed that, rimonabant potentiated the antidepressant activity of standard drugs in FST and TST respectively. Further, the behaviour anomalies exhibited by olfactory bulbectomized rats (OBX) were attenuated by chronic rimonabant treatment as observed in open field test (OFT). In conclusion, this behavioral study depicts the anti-depressant-like effect of rimonabant in acute and chronic model of depression which can be useful as a powerful anti-depressant agent.

KEYWORDS

Rimonabant; Reserpine; Forced swim test; Olfactory bulbectomy and Anti-depressant.

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INTRODUCTION

Rimonabant is the first selective CB1 receptor blocker which was commended. Recent data flaunts the salubrious effects of rimonabant in obesity, smoking cessation, and metabolic syndrome. Rimonabant is a selective cannabinoid receptor antagonist. It is believed that in the CNS, endocanabinoids (ECs) activate the CB1 receptor and regulate the synaptic transmission of excitatory and inhibitory circuits by modulating the release of several monoamine neurotransmitters [1,] which help in treating depression. The EC (endocanabinoids) system consists of endogenous cannabinoid CB-receptor agonists (ECs), CB receptors and proteins that are intricate for the regulation and metabolism of ECs. ECs are a recently discovered class of lipid mediators that includes amides, esters and ethers of long-chain polyunsaturated fatty acids [2]. The cannabinoid receptors are a class of receptors under the G-protein coupled receptor super family. They are found abundantly in the cerebral cortex, basal ganglia and limbic structures, and exert their effects mainly through the CB receptors [3]. Two CB-receptors are known uptil now, CB1 and CB2. Prime location of CB1-receptor is in the CNS, whereas CB2 receptors located in peripheral region and mainly associated with the immune system. CB1 receptor contains 472 amino acids and is a G-protein-coupled receptor (GPCR). CB1 receptors are neuromodulatory GPCR and are highly expressed in the cortex, hippocampus, cerebellum and basal ganglia[4]. Evidence of the role of the endocannabinoid (EC) system in the neurobiology of neuropsychiatric disorders is beginning to emerge. Though some studies have already been done but the present study is more authoritative and exhibit significant evidences for anti-depressant-like activity of rimonabant which it can be proved as efficacious remedy for depression. Animal models of depression have been utilized vigorously to screen novel compounds[5] and were originally designed as screening tests to assess the efficacy of antidepressant drugs. These tests neglect the aspect of face validity but have a strong predictive validity to aid in the identification of efficient antidepressant substances. Hence a battery of behavioural tests were used namely – forced swim test (FST) [6], tail suspension test (TST)[7], effects on 5-hydroxytryptophan (5-HTP) induced head twitch responses (HTR) and olfactory bulbectomized (OBX) rats – to provide significant information on anti-depressant like activity of Rimonabant.

MATERIALS AND METHODS

Animals

Experiments on animals were approved by the Institutional Animal Ethics Committee of Birla Institute of Technology & Science, Pilani, India (Protocol No. IAEC/RES/4/1). Male Swiss Albino mice (18–25g) and Male Wistar rats (200–250 g)

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were obtained from Hisar Agricultural University, Haryana, India and were maintained in standard laboratory conditions with food (standard pellet chow feed) and filtered water *ad libitum*. The animals were employed once for each experiment.

Drugs

Rimonabant and Bupropion (BUP) were procured as a legacy from Ranbaxy Research laboratory (Delhi, India). Fluoxetine (FLX) was procured from IPCA Labs, India. Reserpine was purchased from Sisco Research Laboratories Pvt. Limited (India). Pargyline and 5-hydroxy tryptophan (5-HTP) were purchased from Sigma chemical (USA). The drugs for anesthesia namely, ketamine and xylazine were purchased from Reidel Neon Labs, Indian Immunologicals (Mumbai, India). mCPP was purchased from Lancaster chemicals, USA. The drugs were freshly prepared in distilled water and administered per oral (p.o.) or intraperitoneally (i.p.) (as specified) in a constant volume of 10 ml/kg as applicable. For interaction studies, the antidepressants/ligands like mCPP/ fluoxetine / bupropion were administered i.p., 45 and 30 min respectively before testing in forced swim or tail suspension tests as per the protocol adopted earlier in our laboratory [8,11]. In the chronic treatment schedule, the drugs were administered p.o. once a day for 14 days. All the drug administrations were carried out between 10:00 and 15:00 h.

Spontaneous locomotor activity

The spontaneous locomotor activity was assessed using an actophotometer [9]. The animals were individually placed in a square arena (30 cm × 30cm), with walls painted black and after an initial 2 min familiarization period, the digital locomotor scores were recorded for the next 10 min in a dimly lit room. The arena was cleaned with dilute alcohol and dried between trails.

Forced swim test

The forced swim test was carried out as depicted elsewhere [6] with slight modifications. Mice were dropped individually into a plexi-glass cylinder (height: 30 cm, diameter: 22.5 cm) filled with water to a depth of 15 cm and maintained at 23–25 °C. In this test, after an initial vigorous activity (2 min), the mice acquire an immobile posture which was characterized by motionless floating in the water, making only those movements necessary to keep the head above the water. The duration of immobility which reflects the state of depression was recorded during the last 4 min of the 6 min test. The mice were subjected to 15 minute training session under similar conditions, 24 h before the test.

Tail suspension test

The mice were individually suspended by the tail to a horizontal bar (distance from floor was 50 cm) using scotch tape (distance from tip of tail was

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approximately 1 cm). Typically, mice exhibited several escape-oriented behaviour interspersed with temporary increasing bouts of immobility [10]. The duration of immobility (in seconds) during the 6-min test session was recorded.

Interaction studies

The interaction studies with merchandised antidepressants were carried out in mice using the FST. Mice were treated individually with a single dose (p.o.) of vehicle, fluoxetine (20 mg kg^{-1}) and bupropion (20 mg kg^{-1}) post 15 min of rimonabant administration. The doses of standard antidepressants were obtained from pilot studies or from previous studies carried out in our laboratory [8]. Thirty minutes after the antidepressant injection, mice were subjected to FST/TST. All the equipment employed to valuate the rodent's behaviour was sprayed with alcohol to banish thoroughly between trials to eliminate the residual odour.

5-Hydroxytryptophan-induced head twitch response

The method mentioned elsewhere [12] was adopted with slight modifications. Fifteen minutes after 5-HTP (5 mg kg-1) administration, the number of head twitches exhibited by the mice (vehicle or drug treated) during the next 15 min was recorded as head twitch scores. The head twitch response was characterized by abrupt lateral movements, which may be accompanied by body twitches and hind limb retraction.

Reserpine induced hypothermia test

The rats were gently hand-restrained, and the lubricated digital thermometer probe was inserted into the rectum. The rectal temperature of the rats treated with reserpine (1 mg/kg, i.p)/ MP (10-20 mg/kg, i.p.)/ ESC (10 mg/kg, i.p) was recorded at 30, 60, 90 and 120 min after the drug administration. Reserpine was injected 15 min post drug administration. The difference in the rectal temperature between the baseline and 120th min values were tabulated. On the day preceding the experiments, the rectal temperature of the rats were assessed in a similar manner in order to habituate the animals to the experimental procedures.

Rat olfactory bulbectomy

Bilateral olfactory bulbectomy was performed as described [11,8] with slight modification as mentioned below. Briefly, the rats were anaesthetized with xylazine (5 mg kg-1) and ketamine (75 mg kg-1, i.p.). The head of the rat was fixed in a stereotaxic frame and the skull was exposed by a midline sagittal incision. Burr holes (2 mm in diameter) were drilled 8 mm anterior to bregma and 2 mm on either side of the midline at a point corresponding to the posterior margin of the orbit of the eye. The olfactory bulbs were removed by suction, the holes were then filled with

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haemostatic sponge to control excessive bleeding and the scalp was sutured. To prevent post-surgical infection, the rats were given Sulprim injection (each mL containing 200 mg of sulfadiazine and 40 mg of trimethoprim) intramuscularly (0.2 mL/300 g) once a day for 3 days, post-surgery. Sham-operated rats were treated in the same way, including piercing of the dura mater, but their bulbs were left intact.

Open field exploration

The OBX and sham rats were subjected to an open field test on the 29th day post surgery and the 15th day of chronic drug/vehicle administration. The open field exploration was conducted as described by [13] with slight modifications. The apparatus consisted of a circular (90 cm diameter) arena with 75-cm-high aluminium walls and a floor equally divided into 10-cm squares. A 60 W light bulb was positioned 90 cm above the base of the arena, which was the only source of illumination in the testing room. Each rat was individually placed in the centre of the open field apparatus and the ambulation scores (number of squares crossed) was noted for 5 min.

STATISTICAL ANALYSIS

All the data were expressed as mean ± S.E.M and analysed using one-way analysis of variance (ANOVA) followed by post hoc Dunnett's test. The level of statistical significance was fixed at $P<0.05$.

RESULTS

Locomotor scores

Fig.1A displays the effects of rimonabant on locomotor activity in mice. Rimonabant (2-8 mg/kg i.p) treatment had no influence on the mice locomotor activity when compared to control group.

Fig. 1A

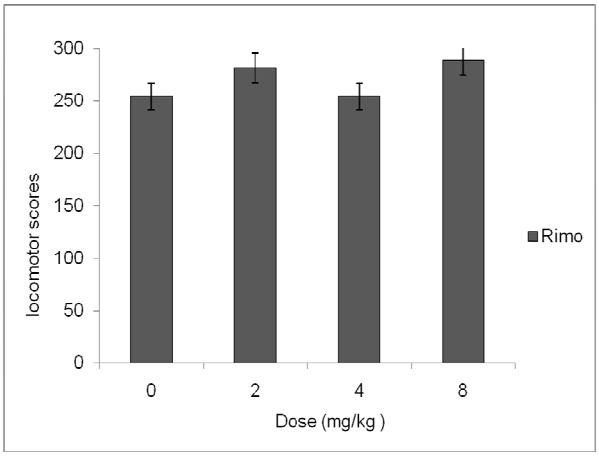

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Fig 1 B

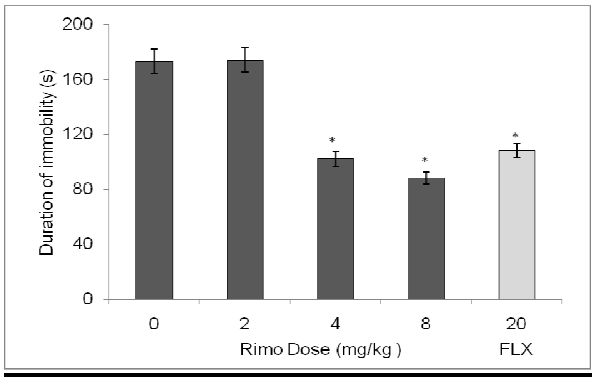
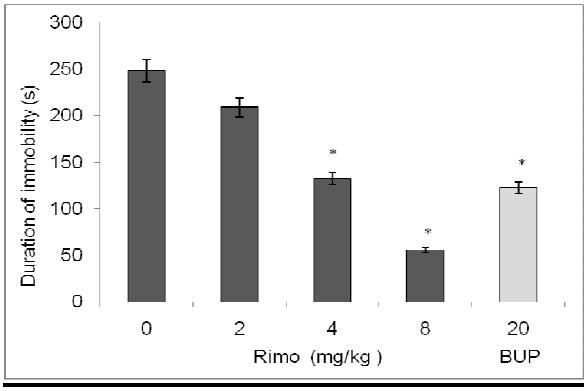


Fig 1C



*A. Effect of rimonabant (2, 4,8mg/kg/10ml) on spontaneous locomotor activity of mice. The columns represent mean locomotor scores recorded in a 6 min observation period. The error bars indicate s.e.m., n = 6 per group. B. Effect of rimonabant on duration of immobility of mice in FST. The columns represent mean duration of immobility in seconds (s) and error bars indicate s.e.m., n = 6 per group. *p < 0.05 compared with vehicle treated group C. Effect of rimonabant on duration of immobility of mice in TST. The columns represent mean duration of immobility (s) and error bars indicate s.e.m., n = 6 per group. *p < 0.05 compared with vehicle-treated group.*

Forced swim and tail suspension tests

These tests for depressive-like behaviour quantitates the duration of immobility which reflect the behavioural despair. *Post-hoc* analysis revealed that, rimonabant (2-8 mg/kg) induced a significant (p<0.05) reduction of immobility time as compared to control group in mice FST (Fig. 1B). The positive control FLX (10 mg/kg) also induced a significant change in immobility. In TST, rimonabant and BUP treatment significantly (p <0.05) decreased the duration of immobility as compared to control group

Interaction studies

The peak dose of rimonabant (4-8 mg/kg) showed significant (p < 0.05) decrease in the duration of immobility which was selected for the interaction studies. The anti-depressant-like effects of rimonabant were weaker than that of fluoxetine (FLX 10 mg/kg i.p). Pre-treatment with rimonabant significantly (p < 0.05) enhanced the anti-depressant action of FLX i.e. decreased duration of immobility (p < 0.05) in mice FST (Fig. 2A). Co-administration of rimonabant (4-8mg/kg) and BUP significantly (p <0.05) augmented the anti-depressant activity of BUP in mice TST, when compared to BUP alone

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(Fig.2B). mCPP significantly induced the depressant-like effect characterized by increased duration of immobility (p<0.05) in mice FST. Rimonabant significantly reversed the depressant-like effect of mCPP (Fig.3)

Fig 2A

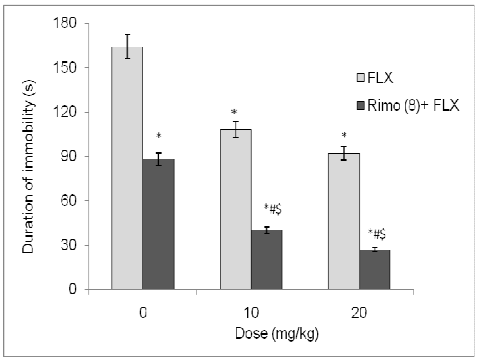


Fig 2B

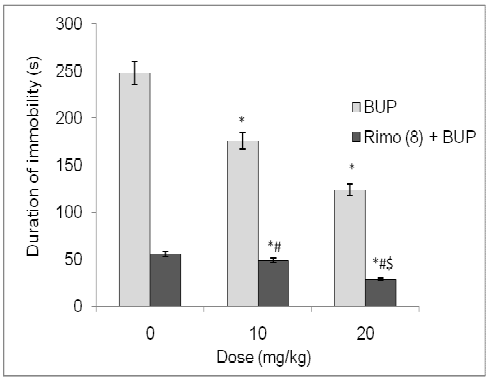
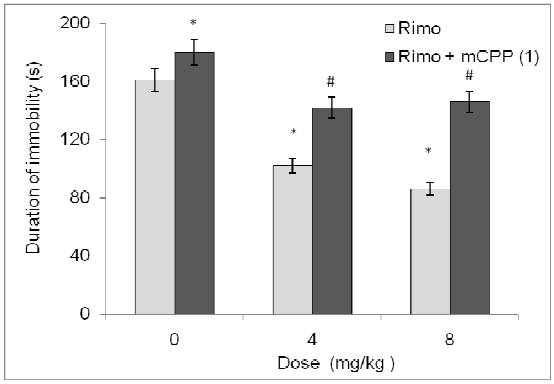


Fig 2C



*A .Effect of pre treated rimonabant on anti-depressant activity of flouxitiene in mice FST. The columns represent mean duration of immobility in seconds (s) and error bars indicate s.e.m., n = 6 per group. *p < 0.05 compared with vehicle treated group, #p<0.05 vs. fluoxetine treatment, $ p<0.05 vs. rimonabant treatment. B. Effect of pretreated rimonabant on anti-depressant activity of bupropion in mice TST. The columns represent mean duration of immobility (s) and error bars indicate s.e.m., n = 6 per group. *p < 0.05 compared with vehicle-treated group. , #p<0.05 vs. bupropion treatment, $ p<0.05 vs. bupropion treatment.*

5- HTP induced head twitches response

The co-administration of pargyline and 5-HTP (75 + 5 mg/kg) induced the characteristic head twitch response. Pre-treatment with rimonabant (4-8 mg/kg) and FLX significantly (p <0.05) potentiated the head twitch response as compared to combination of pargyline and 5-HTP (Fig. 4A).

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Reserpine induced hypothermia

Administration of reserpine (1m/kg i.p) elicited a pronounced decrease (p <0.05) in core body temperature of rats. This effect was significantly (p <0.05) attenuated by rimonabant. Similarly, FLX reversed the hypothermic effect of reserpine [Fig. 4B].

Fig 4A

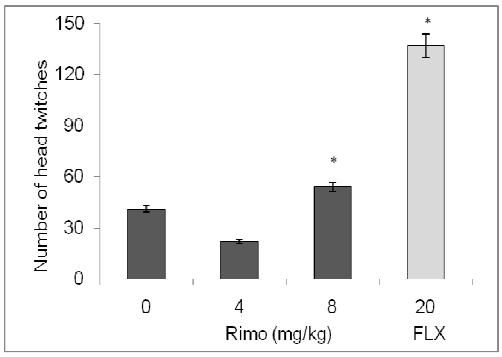
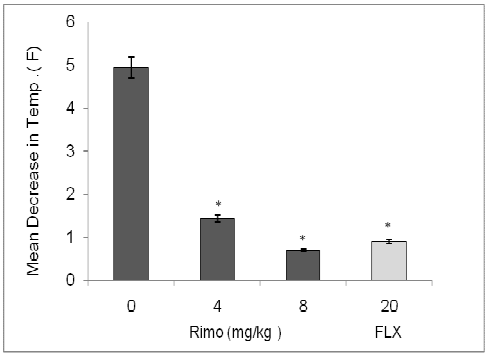


Fig 4 B



*A. Effect of rimonabant on 5-hydroxytryptophan and pargyline - induced head twitch response in mice. The columns represent mean number of head twitches and error bars indicate s.e.m., n=6 per group. *p < 0.05 compared with vehicle-treated group. B. Effect of rimonabant on reserpine induced hypothermia in rats. The columns represent mean decrease in temperature and error bars indicate s.e.m,, n=6 per group.*p<0.05 compared with vehicle treated group.*

Olfactory bulbectomy in Rats

Open field test

The effects of rimonabant on the behaviour of OBX/sham rats were analyzed in different circumstances as shown in Table-1. Removal of the olfactory bulbs produced a characteristic hyperactivity in the OBX rats when compared to sham rats in the open field test. Chronic (14 days) treatment with rimonabant significantly (p< 0.05) reduced the ambulation, rearing and fecal pellets (p <0.05) in OBX rats as compared to the vehicle treated OBX rats. Rimonabant (4 mg/kg) exhibited anti-depressant-like effects and escitalopram was the most effective among all treatments.

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Table1

Effect of rimonabant and escitalopram on the behaviour of OBX rats in modified open field

Treatments	Dose (mg/kg)	Ambulation	Rearing	Pellets
Sham Control	0	83.9±1.7	8.7±1.7	1.1±0.3
OBX	0	179.66±4.17 *	20.66±0.80 *	4.5±0.43*
Rimonabant	4	65±6.42#	9.2±2.64#	3±0.82#
Rimonabant	8	103.75±19.7#	9.25±2.5#	4.5±0.24#
Escitalopram	10	112.2±10.3 #	11.3±4.1 #	2.2±0.12 #

*Values represent mean±S.E.M. n = 6 in each group. Escitalopram/vehicle was administered (p.o.) once day for 14 days. *P < 0.05 compared with vehicle treated sham rats, #P < 0.05 compared with vehicle treated OBX rats.*

DISCUSSION

In the present study, the anti-depressant like effects of rimonabant were graded in animal model of depression. The practice of using whole animal assay is considered to be a swift method to testimony neuro-psychopharmacological effect of prose compounds. This investigation encompassed acute (forced swim and tail suspension tests) and mechanistic test (reserpine induced hypothermia in rats) and 5-HTP induced head twitches in mice and chronic animal model of depression, Olfactory bulbectomy was employed to examine the effects of rimonabant. The prognostic assertions of the aforementioned anti-depressant assays are already reported to be adequate. While interpreting the anti-depressant-like effect of any test substance based on swimming and exploratory behaviour of rodents, the influence of the test substance in baseline locomotion in animal is of prime concern[9]. In the present study rimonabant (4-8mg/kg i.p) significantly decreased the duration of immobility in mice FST and TST. Reduction in duration of immobility reflects the anti-depressant properties of drugs. The anti-depressant-like effect of rimonabant seems not to be associated with any motor effects,

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since it did not show significant change in locomotion of mice. Interactions with SSRIs are necessary for conclusive assessment of ADs potential[14]. Rimonabant (4-8mg/kg) significantly enhanced the AD-like action of FLX. Due to species dependent variation, BUP failed to exhibit anti-depressant effects in FST with swiss Albino mice[7]. Hence, interaction study in TST was expected to throw some light on the influence on dopaminergic system. In the present study, rimonabant pre-treatment was found to augment the anti-depressant effects of BUP (10 and 20mg/kg) in TST indicating the influence on dopaminergic system. Rimonabant significantly reversed the depressant-like effect of mCPP, possibly by affecting the serotonin transporter system.

One of the pharmacological mechanisms of ADs is the enhancement of synaptic concentrations of monoamine, particularly serotonin. 5-HTP being the immediate precursor of 5-HT, its administration was reported to increase the serotonergic transmission inducing a characteristic head twitch response in mice[8, 15, 16.] The present study, the PRG and 5-HTP induced head twitch responses were significantly potentiated by FLX and rimonabant pre-treatment. In this regard, the anti-depressant-like effect of rimonabant appears to be modulated by an increase in 5-HT concentrations in the synapse [8].

Depletion of biogenic amines (NE, 5-HT, DA) in the brain has been examined to induce catalepsy, ptosis and the most recorded parameter, hypothermia. The decrease of body temperature induced by reserpine is proved to be antagonized by anti-depressants that act by increasing the amount of biogenic amines at the synaptic cleft[17]. In the prevailing study, rimonabant (4-8mg/kg body weight) and Fluoxetine (10mg/kg body weight) prevented the decrease in rectal temperature at 120th minute after reserpine challenge indicating anti-depressant effect in this sensitive model.

Olfactory bulbectomy was proposed as an agitated hypo-serotonergic model of depression [18] and used to explore the novel agents for their anti-depressant potential [5]. OBX rats exhibited a specific abnormal behavioural pattern in the open field test[19] characterized by increased ambulation, rearing and fecal pellets[20] and this abnormal behaviour were reversed by anti-depressants [21]. In the open field test, rimonabant (4-8mg/kg p.o.) and escitalopram consequentially reversed the hyperactivity exhibited by OBX rats.

The present neuro-behavioural studies showed anti-depressant- like effects of rimonabant in animal models of depression. The stringent mechanism by which rimonabant produced anti-depressant-like effect is not understood. However, it could be due to the regulation the synaptic transmission of excitatory and inhibitory circuits by modulating the release of several monoamine neurotransmitters[1] and the results obtained in FST ,

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TST , potentiation of head twitch responses and reversal of reserpine induced hypothermia suggests that, rimonabant produced anti-depressant-like effect by increasing the concentration of neurotransmitter in synapse.

In conclusion, antidepressant-like effects of rimonabant are comparable to conventional antidepressants have been reported with CB1 receptor antagonists in rodent models with high predictive validity. Although these data are just emerging, a strong foundation for a CB1 receptor mechanism is already in place. Regardless of the strengths of the preclinical information, clinical investigation in patients with major depressive disorders will be required to ultimately test the hypothesis that blockade of CB1 receptors will affect depression. Rimonabant has already demonstrated efficacy in the treatment of obesity and tobacco smoking, two disease-related conditions that share features and comorbid signs with major depressive disorders The convergence of these findings connotes that rimonabant may be useful as a powerful anti-depressant agent.

REFERENCES

1. Wilson, R.I. and Nicoll, R.A. (2002) Endocannabinoid signaling in the brain. Science 296, 678–682
2. Devane, W.A. et al. (1992) Isolation and structure of a brain constituent that binds to the CB receptor. Science 258, 1946–1949
3. Matias, I. et al. (2006) Endogenous cannabinoids in the brain and peripheral tissues: regulation of their levels and control of food intake. Int. J. Obes. (Lond) 30, 7–12
4. Howlett, A.C. (2002) The cannabinoid receptors. Prost. Lipid Mediat 68–69, 619–631
5. Bourin M, Fiocco AJ, Clenet F : How valuable are animal models in defining anti-depressant activity? Hum Psychopharmacol Clin, 2001, 16, 9–21.
6. Porsolt R.D., Bertin, A. Jalfre. M. Behavioural despair in mice: a primary screening test for anti-depressants. Arch. Int. Pharmacodyn. Ther. 1977; 229, 327–336. pp. 170-171
7. Borsini F, Meli A :Is the forced swimming test a suitable model for revealing anti-depressant activity? Psychopharmacology, 1988, (Berl)94, 147–160.
8. Pandey D K , Ramamoorthy R, Mahesh R., Radha R.: Depressant-like effects of Parthenolide in rodent behavioural anti-depressant test battery. Journal of Pharmacy Phamacology, 2008,60,1643-1650
9. Boissier, J.R. Simon. P. .Action of caffeine on the spontaneous motility of the mouse. Arch. Int. Pharmacodyn. Ther. 1965; 158, 212–221.

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10. Steru, L, Chermat, R.. Thierry, B . Simon. P. The tail suspension test: a new method for screening anti-depressant drugs. Psychopharmacolgy (Berl) 1985; 85, 367–370.
11. Mahesh, R., Rajkumar, R., Minasri, B., Venkatesha Perumal, R. (2007) Potential antidepressants: pharmacology of 2 (4-methyl piperazin-1-yl)-1,8-naphthyridine-3-carbonitrile in rodent behavioral models. Pharmazie 62: 919–924
12. Martin, P., Massol, J., Soubrie, P., Puech, A. J. (1989) Effects of triiodothyronine (T3) on the potentiation by antidepressants of L-5-hydroxytryptophan-induced head-twitches in mice. Prog. Neuropsychopharmacol. Biol. Psychiatry 13: 735–748
13. Kelly, J. P., Wyrnn, A. S., Leonard, B. E. (1997) Olfactory bulbectomized rat as a model of depression: an update Pharmacol. Ther. 74: 299–316
14. Cryan J F, Valentino RJ, Lucki I : Assessing substrates underlying the behavioral effects of antidepressants using the modified rat forced swimming test. Neurosci. Biobehav. Rev, 2005, 9, 547-569.
15. Ortmann R, Martin S, Radeke E, Delini Stula A. : Interaction of beta-adrenoreceptor agonists with the serotonergic system in rat brain. A behavioural study using the L-5-HTP syndrome. Naunyn Schmiedeberg's Arch. Pharmacol,1981, 316, 225–230.
16. Schreiber R , Brocco M, Audinot V, Gobert A, Veiga S, Millan MJ : (1-(2,5-dimethoxy-4 iodophenyl)-2-aminopropane)- induced head–twitches in the rat are mediated by 5-hydroxytryptamine (5-HT) 2A receptors: modulation by novel 5-$HT_{2A/2C}$ antagonists, D_1 antagonists and 5-HT_{1A} agonists. J. Pharmacol. Exp. Ther, 1995, 273, 101–112.
17. Englert L F, Ho BT, Taylor D : The effects of (-)-delta9-tetrahydrocannabinol on reserpine-induced hypothermia in rats. Br. J. Pharmacol 1973, 49, 243-252.
18. Lumia AR, Teicher MH, Salchli F, Ayers E, Possidente B :Olfactory bulbectomy as a model for agitated hyposerotonergic depression. Brain Res, 1992, 587: 181–185.
19. Song C, Leonard BE: The olfactory bulbectomised rat as a model of depression. Neurosci Biobehav Rev, 2005, 29: 627–647.
20. Slotkin TA, Miller DB, Fumagali F, Mccook EC, Zhang J, Bissette G, Seidler FJ :Modeling geriatric depression in animals: biochemical and behavioural effects of olfactory bulbectomy in young versus aged rats. J Pharmacol Exp Ther, 1999, 289: 334–345.

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21. Van Reizen H, Leonard BE : Effects of psychotropic drugs on the behaviour and neurochemistry of olfactory Bulbectomised rats. Pharmacol Ther, 1990, 47, 21–34.