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A N I N T E R N A T I O N A L J O U R N A L

Administration of venlafaxine after chronic methadone detoxification blocks post-depression relapse in rats

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ABSTRACT

Relapse is highly prevalent after detoxification and depression. Due to the advantages of venlafaxine compared with other antidepressants, it is expected that venlafaxine administration may reduce relapse after detoxification and depression. This study aimed to evaluate the effects of venlafaxine on depression-induced relapse to morphine dependence after methadone detoxification. Eighty Sprague-Dawley rats were habituated and conditioned with morphine (10 mg/kg, S.C., for 4 days). After that, primary forced swimming and conditioned place preference (CPP) were tested. They were followed by methadone (70 mg/kg/day, P.O., for 7 days) administration, extinguishing, forced swimming stress (FSS) and administration of venlafaxine (80 mg/kg/day, I.P., for 7 days). Finally same tests were performed. Administration of venlafaxine resulted in a decrement in final preference scores associated with a prime morphine injection (PMI) compared to the primary scores in methadone treated (MTD+) animals. In a swimming test, venlafaxine increased the amount of final floating and decreased final activity scores compared with the primary scores after administration of methadone. Venlafaxine reduced locomotor activity in MTD+ animals in the final test with PMI. There was a positive correlation between the final activity and preference scores after PMI. In conclusion, venlafaxine improved anxiety and depression-induced relapse on methadone detoxified rats.

Key words: Morphine, Methadone, Depression, Relapse, Venlafaxine, Rat

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INTRODUCTION

High prevalence of relapse after abstinence is the most disturbing after effect of opiate dependence treatment [1]. In the case of opiate addiction, there are effective treatments (such as buprenorphine therapy). However, even with these treatments, opiate-use relapse probability remains high [2].

Some neurobiological targets in addiction treatment included: Dopamine receptor partial agonists, modulators of γ-aminobutyric acid signalling, Corticotropin releasing factor (CRF) antagonists, non-CRF targets and Glutamate modulators [3].

Different types of drugs have been shown to be effective in treatment of addiction relapse such as Naltrexone [4,5] (for opioids and alcohol relapse), Modafinil [6] and Carbetocin [7] (for opiate relapse), Aripiprazole [5], Acamprosate [8] and Disulfiram [9] (for alcohol relapse).

Methadone therapy is usually used in licensed opioid-treatment. It has been a standard treatment for illegal opioid addicts in the past 40 years [10]. Methadone is a full agonist at the mu receptor [11].

Fifty percent of those on methadone maintenance therapy were found to be suffering from depression [12]. It may be a driving force in motivating opiate-dependent individuals seek treatment [13], particularly as depression is one of the prime causes of drug addiction relapse [14].

Some antidepressants like Sertraline [15] and Venlafaxine [16] and substances with antidepressant activity such as Berberine [17] and Saffron extract [18] are effective in delaying or reducing addiction relapse irrespective of methadone administration.

Venlafaxine shows an attribute of selective inhibition for reuptake of norepinephrine and serotonin [19]. In severe depression, venlafaxine administration is an effective treatment. Also in resistant depression following treatment with a selective serotonin reuptake inhibitor (SSRI) it is a better choice than turning to another SSRI [20].

Animal models are used for the study of special drug related behaviors, such as initial sensitivity measured by drug-induced locomotor behavior [21].

Despite successful results for blocking opiate seeking activities [6,7,16], the effect of administration of venlafaxine on post-depression relapse, depression and locomotion after chronic methadone detoxification and behavioral extinction have not been shown simultaneously. Relapse-inducing outcomes of drug-primes and acute administration of drugs are not easy to interpret. It is one of the shortcomings of a CPP version of the relapse model [14].

This study aimed to determine the effects of venlafaxine on morphine relapse, depression-like behavior and locomotion post-depression (which occurred after chronic methadone administration and abstinence). Effects of morphine prime, chronic methadone (7 days) and venlafaxine (7 days) administrations were evaluated in this study too.

MATERIAL AND METHODS

Animals

Eighty young Male Sprague-Dawley rats (180-220 g; obtained from the Animal House of Ahvaz Jundishapur University of Medical Sciences) were housed (3-4 rats/cage) on a 12 h light-dark cycle (lights on at 7 a.m. to 7 p.m.). Water and standard feeding pellets were available for the rats at all times in the cage. The rats were kept in a temperature-controlled room (23±2 ºc). Animals were tested and conditioned during the light phase. They were handled 5 min/day for 7 days in the laboratory before the onset of experiments and were returned to their cages after undergoing each experimental protocol. All experiments were conducted in

conformity with national standards and Ahvaz Jundishapur University of Medical Sciences (AJUMS) Guide for the Care and Use of Laboratory Animals. They were also approved by the local Institutional Ethics Committee (Ethics Code: AJUMS.REC.1392.327, 14 March 2012). All measures were undertaken to minimize animal suffering and the number of animals used.

Drugs

Morphine Sulfate Pentahydrate and Methadone Hydrochloride (racemic mixture, 99% purity) were obtained from Temad Pharmaceutical Company (Tehran, Iran). Venlafaxine Hydrochloride (99.5% purity) was obtained from Tehran Chemie and Purcina Pharmaceutical Companies (Tehran, Iran). All drugs were in the powder form.

Fresh stocks of morphine, methadone and venlafaxine were prepared daily according to the weight of animals in the experimental design. Morphine Sulfate Pentahydrate or Venlafaxine Hydrochloride was dissolved in the normal saline (NaCl 0.9 %) so that the animals received the appropriate dose in a volume of 1 ml. Morphine (10 mg/kg) was injected subcutaneously (S.C.) for 4 days [6]. Methadone Hydrochloride (70 mg/kg) was dissolved in sucrose solution 3% (w/v) (to reduce the bitter taste of methadone) in the concentration of 0.5 mg/ml. It was administered orally (in drinking water) for 7 days [22]. Venlafaxine Hydrochloride (80 mg/kg) was dissolved in the normal saline (NaCl 0.9 %) and injected intraperitoneal (I.P.) for 7 days [23]. The route of administrations was based on the volume of drug and vehicle.

Measures

Conditioned Place Preference Apparatus and Paradigm

Two rectangular Plexiglas test apparatuses (Borj Sanat Co., Tehran, Iran), each consisting of three distinct chambers [6,16,24] were used with some modifications. Conditioning chambers differed in paint (wall color) and texture (size and shape of pores in bottom sheet) cues. The inner walls of one side chamber (30 cm length×30 cm width×35 cm height) were white with a fine pored rough grid floor. The other side chamber (30 cm length×30 cm width×35 cm height) had vertical black and white striped walls with a quadrangular pored (each pore 1 cm^2) floor. Medial chamber (30 cm length×15 cm width×35 cm height) had gray inner walls and a black iron floor. All the walls and 3 floors were washable. Side chambers were separated from the medial one via guillotine-like doors. A dim illumination (40 Lux, by Luxmeter, TES1336, Taiwan) was used on the CPP boxes.

Conditioning was performed in silence. Time spent in each chamber was recorded via offline observation using a digital camera (Sony, DSC-W570, Japan, 2011) set up overhead on the CPP box and two chronometers (Fox40, China). An animal was considered in a chamber whenever all its four limbs were in the chamber.

A preconditioning test was used in order to determine the unconditioned place preference. The two guillotine-like doors were removed so that the animal could access all chambers. When an animal showed an innate preference to each side chamber in the 15 min preconditioning test, the animal was excluded from the study.

Eight conditioning sessions were held on 4 consecutive days. Morphine sulfate (10 mg/kg) or normal saline (in equivalent volume as the vehicle) were injected subcutaneously (S.C.) to the rats. Animals were allocated separately in a specific side chamber (while the guillotine-like doors were closed) in the CPP box for 30 min after each injection. A 5 h interval existed between morning and afternoon injections. The drug-paired chamber and order of injection of the drug and the vehicle were counterbalanced across animals. Morphine and saline injection sessions

were alternatively changed in the morning and afternoon. Animals that had received morphine in the morning, receive saline in the afternoon (on 1st conditioning day). They received saline in the morning and morphine in the afternoon (on 2nd conditioning day). Half of the animals received morphine in the black and white chamber, and the other half received it in the white chamber. One day without injection was necessary for induction of sensitization [25].

Conditioned Place Preference Test (CPP Test): Animals may receive or not receive a morphine prime injection (10 mg/kg, S.C.) for the final CPP tests. They were placed separately in the middle gray chamber and guillotine-like doors were removed. Presence of animal in each chamber was videotaped by the digital camera. All 3 chambers were freely accessible to them for 30 min. Then the animals were returned to their cages. The box (its floor and walls) was washed by camphorated ethanol (70 %) and then with wet cotton. The CPP score (%) was computed by the formula [26] as follows: CPP Score (%) = (Time spent in morphine-paired side/Total time spent in morphine and saline-paired sides) ×100.

Eight to ten CPP sessions (1 session/day, each session lasted for 15 min) without any injection were used for to extinguish the behavior. The guillotine-like doors were removed so that animals could freely roam in the chambers. Then the amount of time spent by each rat in each chamber was recorded. The sessions were continued until: 1) Rats spent less than 55% of the total time in the morphine-paired chamber during two consecutive days [27]. 2) The preference for the morphine-paired side decreased to less than 75 Sec differences for 2 consecutive sessions [6].

Locomotor Activity

The number of transitions into the side chambers in 30 min CPP tests was counted via offline observation as an indicator of locomotor activity [25,28] or decision making behavior [29].

Forced Swimming Training, Test and Stress

The rats were individually forced to swim for 10 min in a Plexiglas cylinder (46 cm height and 20 cm diameter, Borj Sanat Co., Tehran, Iran) 24 h before forced swimming test [30]. The cylinder was filled with water (30 cm depth). Water temperature maintained at 25±2 ºc. Then the rats were taken from the water, towel-dried and transferred to a warm place and then returned to their cages.

On the test day, the rats were exposed to the cylinder for 6 min. The behaviors in the six min forced swimming test were videotaped. Video files were coded and later scored only by an observer blind to the animal's individual treatment. The time sampling method (every 5 Sec, using a reverse timer, QC pass, 2012, China) was used for scoring animal's behaviors. Behaviors were scored as floating when the rats stopped struggling and moved only to keep their nose above the water surface. They were judged as active when the animals exhibited limb movement (climbing, swimming or diving). Every video was observed 3 times. Average scores of each behavior were entered into the statistical software. Seven days forced swimming stress (5 min/day) was used for induction of depressive-like behavior [31].

Experimental Design

Experiments took 47-49 days per group and all experiments lasted 3 months due to inter and intra group time lag to avoid many overlaps in injections and experiments (Fig. 1). Animals were handled 5 min/day for 7 days in the laboratory. After preconditioning (8th day) and conditioning protocols, one day without injection (13th day, sensitization) was used. Animals were exposed to the primary tests at day 15. Forced swimming and CPP tests were done in an hour apart (time needed to keep rats in a warm place). Then they were treated differently from the 16th day.

Administration of methadone (or its vehicle), the forced swimming stress (or without stress) and administration of venlafaxine (or its vehicle) were 3 distinct interventions. All rats underwent the extinguishing protocol (23-30/ 32nd days). Forced swimming and venlafaxine interventions were performed after methadone intervention and extinguishing in order to remodel the clinical problem. Finally CPP tests were performed in 2 consecutive days in order to show the effect of the morphine prime injection. Final forced swimming test were performed in 2 consecutive days in order to equate acute effects of forced swimming tests on the CPP tests. Experimental groups are shown in the Table 1.

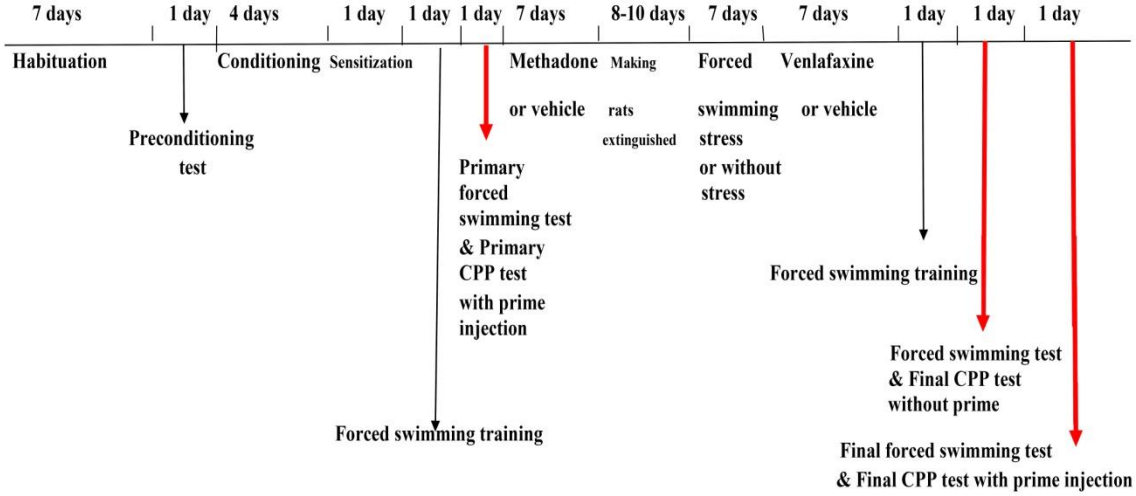

Figure 1 - Experimental design. The conditioned place preference paradigm, forced swimming test, steps of experiments and protocols has been demonstrated. The number of morphine and saline injections was equal in all animals either in conditioning or in the final CPP tests. Morphine administration was not an intervention between groups.

Table 1 – Experimental Groups

Groups	**Interventions**		
	Methadone	Forced swimming stress	Venlafaxine
MTD-FSS-VLX-	-	-	-
MTD-FSS+VLX-	-	+	-
MTD-FSS-VLX+	-	-	+
MTD-FSS+VLX+	-	+	+
MTD+FSS-VLX-	+	-	-
MTD+FSS+VLX-	+	+	-
MTD+FSS-VLX+	+	-	+
MTD+FSS+VLX+	+	+	+

MTD=Methadone (70 mg/kg/day, p.o., for 7 days), FSS=Forced swimming stress (5 min/day, for 7 days), VLX=Venlafaxine (80 mg/kg/day, i.p., for 7 days). The sign of + or - is representative of received or not received the treatment. Morphine administration was not an intervention between groups.

Statistical Analysis

The "Statistical Package for Social Sciences" (IBM SPSS 15.00, Chicago, IL, USA) was used for data analysis. GraphPad Prism 4.00 Software (San Diego California, USA) was used to draw histograms and linear regressions. Data were represented as means ± SEM. Normalization of the data was determined using Kolmogrov-Smirnov test. Parametric data were analyzed by one-way Analysis of Variance (ANOVA). It

was followed by post hoc tests (Tukey or LSD) whenever necessary. Significance was assumed at the $p<0.05$ level. Percentage changes of values were used whenever the raw test values were not significantly different among groups. Percentage changes of CPP scores in different test days (Fig. 2) were calculated for each group using the formula as follows: Percentage change of CPP scores= ((CPP score $_{\text{next test}}$-CPP score $_{\text{previous test}}$)/CPP score $_{\text{previous test}}$) ×100. Percentage changes of floating or activity values in the forced swimming tests were computed using this formula: ((Final value-Primary value)/Primary value) ×100.

Pearson (when the variable distribution was normal) or Spearman (when the variable distribution was not normal) correlations were used to determine the possible relationships among the final CPP scores, transitions, activity and immobility in animals.

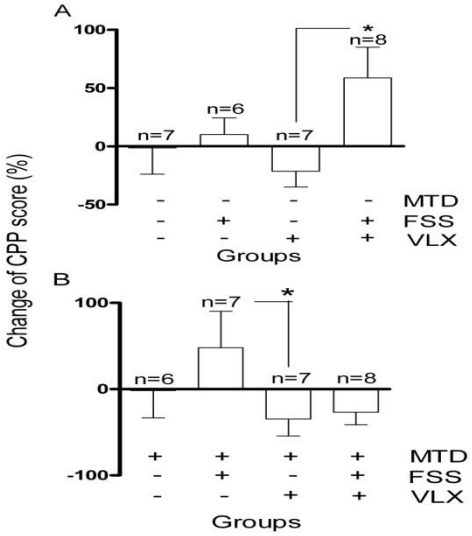

Figure 2 - Effects of forced swimming stress and venlafaxine on percentage changes of CPP score. MTD=Methadone, FSS=Forced swimming stress, VLX=Venlafaxine. The sign of + or - is representative of received or not received the treatment. A. Between final test with prime injection and final test without prime injection, *$p<0.05$, -80.204±27.774% difference, 1-way ANOVA, Tukey HSD post-hoc test. B. Between final test with prime injection and primary test with prime injection, *$p<0.05$, -82.599±39.54% difference, 1-way ANOVA, LSD post-hoc test. The difference between percentage changes of CPP scores between MTD+FSS+VLX+ and MTD+FSS+VLX- values did not reach to the significant level ($p>0.05$, -74.709±39.544% difference), 1-way ANOVA, LSD post-hoc test. The number of morphine and saline injections was equal in all animals either in conditioning or in the final CPP tests. Morphine administration was not an intervention between groups.

RESULTS

Effects of forced swimming stress and Venlafaxine on percentage changes of conditioned place preference scores

Significant differences were observed in percentage changes of CPP scores in the primary and 2 final tests. Change of CPP scores between the final test with prime injection and the final test without prime injection differed significantly between MTD-FSS-VLX+ and MTD-FSS+VLX+ animals. No significant difference between the final test with prime injection and the final test without prime injection was observed among MTD-FSS-VLX-, MTD-FSS+VLX- and MTD-FSS+VLX+ animals (Fig. 2 A). Change in CPP scores between the final test with prime injection and the primary test with prime injection was significant merely between MTD+FSS+VLX- and MTD+FSS-VLX+ animals (Fig. 2 B). The effects of forced swimming stress and venlafaxine on crossing number and percentage changes of CPP, floating and activity scores are shown in Table 2.

Table 2. Effects of forced swimming stress and venlafaxine on crossing number and percentage changes of CPP, floating and activity scores in methadone treated animals.

Groups	% Changes of CPP Score FA-FW/FW	% Changes of CPP Score FA-PA/PA	% Changes of floating Score F-P/P	% Changes of activity Score F-P/P	Crossing number FW	Crossing number FA
MTD+FSS-VLX-	30.31±46.78	-1.65±31.71	-66.02±3.33	58.04±6.82	10.78±1.87	10.00±4.45
MTD+FSS+VLX-	11.21±35.59	47.95±42.34	-82.10±5.12	*18.26±12.10$^{a\#\#}$	16.00±2.74	18.23±4.04
MTD+FSS-VLX+	-11.53±9.70	*-34.65±19.55$^{b\#}$	***6.25±10.60$^{a,b,d\#\#}$	**7.01±9.46$^{a\#\#}$	19.86±6.08	12.18±3.84
MTD+FSS+VLX+	-10.32±19.80	-26.76±14.60	-71.30±8.45	*16.78±3.58$^{a\#\#}$	11.25±2.80	*8.10±2.51$^{b\#}$

Values are means ± S.E.M (n=6-8/group). *P<0.05, **P<0.01, ***P<0.001**,** a=compared to MTD+FSS-VLX- group, b= compared to MTD+FSS+VLX- group, c= compared to MTD+FSS-VLX+ group, d= compared to MTD+FSS+VLX+ group, FA=Final test after prime injection, FW=Final test without prime injection, F=Final, P=Primary, MTD=Methadone (70 mg/kg/day, p.o., for 7 days), FSS=Forced swimming stress (5 min/day, for 7 days), VLX=Venlafaxine (80 mg/kg/day, i.p., for 7 days). The sign of + or - is representative of received or not received the treatment. #1-way ANOVA, LSD post-hoc test, ##1-way ANOVA followed by Tukey-Kramer as post ANOVA test.

Effects of forced swimming stress and venlafaxine on percentage changes of floating and activity scores between the final and primary forced swimming tests

Percent changes of activity scores in MTD-FSS+VLX+ animals were significantly less than other MTD-FSS+VLX- animals. There were significant differences in percentage changes of floating and activity scores in methadone treated groups. Percentage changes of floating scores in the MTD+FSS-VLX+ animals were significantly higher than other methadone treated animals. On the other hand, percentage changes of activity scores in the MTD+FSS-VLX- animals were significantly higher than other methadone treated animals (Fig. 3).

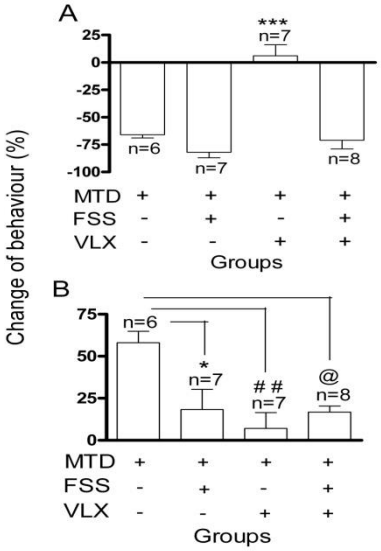

Figure 3 - Effects of of forced swimming stress (for 7 days, 6 min/day) and venlafaxine (80 mg/kg, for 7 days, s.c.) on percentage changes of floating and activity scores between the final and primary forced swimming tests. MTD=Methadone, FSS=Forced Swimming Stress, VLX=Venlafaxine. The sign of + or - is representative of received or not received the treatment. A. Change of floating scores. ***p<0.001, significantly more than values of MTD+FSS-VLX- (72±9 % difference), MTD+FSS+VLX- (88±11 % difference) and MTD+FSS+VLX+ (77±10 % difference) groups, 1-way ANOVA, Tukey post hoc test. B. Change of activity scores. *p<0.05, versus MTD+FSS-VLX- (40±4 % difference). ##p<0.01 versus MTD+FSS-VLX- (51±6 % difference). @ p<0.05 versus MTD+FSS-VLX- (41±4 % difference), 1-way ANOVA, Tukey post-hoc test. The number of morphine and saline injections was equal in all animals either in conditioning or in the final CPP tests. Morphine administration was not an intervention between groups.

Effects of forced swimming stress and venlafaxine on locomotor activity in the final conditioned place preference tests

The numbers of crossings (entries) into the side chambers in 2 final CPP tests (without and then with morphine prime injection) were compared between the methadone controlled and methadone treated animals. Therefore four different states of locomotor activity have been shown in the Figure 4. Differences in the number of crossings did not reach to the significant level only in the final test without prime injection in methadone treated animals.

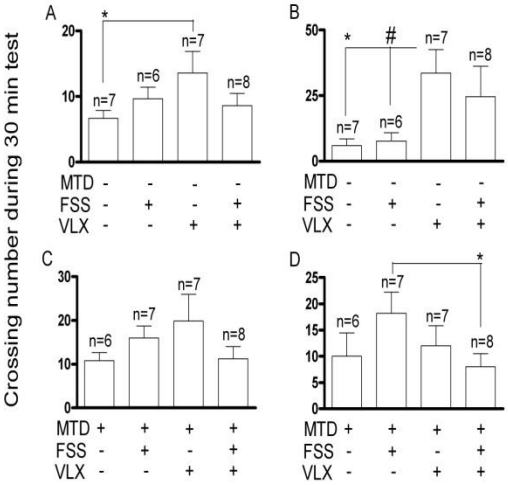

Figure 4 - Effects of venlafaxine (80 mg/kg, i.p., 7 days) on crossing number in 2 final CPP tests. MTD=Methadone, FSS=Forced swimming stress, VLX=Venlafaxine. The sign of + or - is representative of received or not received the treatment. A. Crossing number in the final CPP test without morphine prime injection in methadone controlled rats. *p<0.05, difference =

-7±3. The difference between MTD-FSS+VLX+ and MTD-FSS-VLX+ values was not significant (p>0.05, difference= -5±3). B. Crossing number in the final CPP test with morphine prime (10 mg/kg, s.c.) injection in methadone controlled rats. * p<0.05, difference= -28±13. # p<0.05, difference= -26±11. The difference between MTD-FSS-VLX- and MTD-FSS+VLX+ values was not significant (p>0.05, difference= -19±13). C. Crossing number in the final CPP test without prime injection in methadone treated rats. The difference between MTD+FSS-VLX- and MTD+FSS-VLX+ values did not reach (p>0.05, difference= -9±5) to the significant level. D. Crossing number in the final CPP test with prime injection in methadone treated rats. * p<0.05, difference= -10±5. The difference between MTD+FSS-VLX- and MTD+FSS+VLX- values was not significant (p>0.05, difference= -8±6), 1-way ANOVA, LSD post-hoc test.

Correlation between the final activity and CPP scores

CPP scores in the final test with prime injection were positively correlated (37.4% correlation, p<0.05, Pearson, F= 4.312, df = 40) with the final activity scores in forced swimming test (Fig. 5).

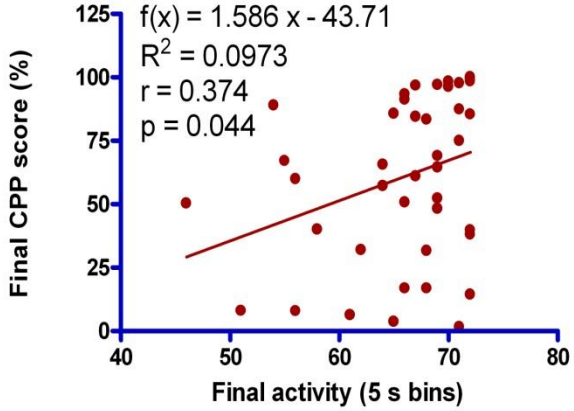

Figure 5 - Plot of CPP scores in the final test with morphine prime (10 mg/kg, s.c.) versus final activity scores in forced swimming test. The line represents linear regression for the values of methadone controlled and treated animals from different groups. N=42.

Correlation between CPP scores in the two final CPP tests

The CPP scores in the final test with prime injection were positively correlated (72.3 % correlation, p<0.001, Pearson, F= 43.78, df = 40) with CPP scores in the final test without prime injection (Fig. 6).

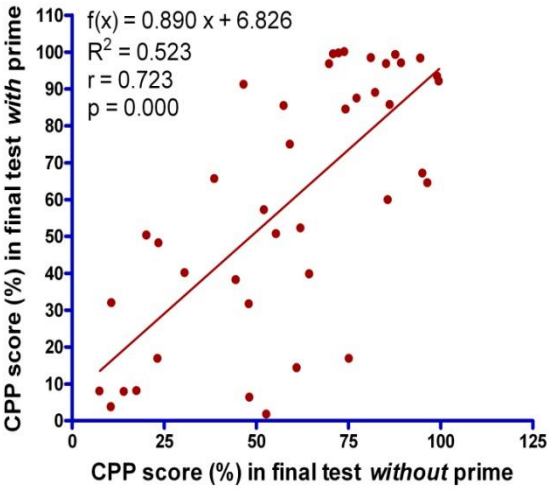

Figure 6 - Plot of the CPP scores in the final test with morphine prime (10 mg/kg, s.c.) versus CPP scores in the final test without prime injection. The line represents linear regression for the values of methadone controlled and treated animals from different groups. N=42.

DISCUSSION

The current study evaluates the relapse risk, depression status and possible relationships between them simultaneously after methadone detoxification. Decreases of CPP scores between the final and primary CPP tests with prime injection in MTD+FSS-VLX+ animals differed significantly from increases of CPP scores in MTD+FSS+VLX- ones; therefore administration of venlafaxine (80 mg/kg/day, 7 days, i.p.) is helpful for decreasing post-depression reinstatement risk after chronic methadone detoxification. This effect was not significant between the final CPP test without prime injection and primary CPP test with prime injection; thus the effectiveness of venlafaxine in blocking forced swimming induced-morphine primed reinstatement is more than morphine primed-reinstatement alone. It also suggests that administration of venlafaxine after chronic methadone detoxification could shift animal's tendency to decrease depression induced-morphine primed relapse. This shift could be closely related to reward pathways. An advantage of this result is that venlafaxine administration could be effective in blocking relapse after chronic methadone administration especially in non-depressed rats. The present finding agrees with previous [16] findings and may be useful after methadone detoxification programs.

Since a significant difference was observed between the percentage changes of CPP scores of MTD-FSS-VLX+ and MTD-FSS+VLX+ animals merely in the two final tests, it may confirm that forced swimming stress augments morphine-primed reinstatement via affecting reward pathways too. This may be due to “the role of cAMP Response Element Binding Protein (CREB), Brain Derived Neurotrophic Factor (BDNF), Dynorphin and Corticotropin-Releasing Factor (CRF) in mediating the cross-talk between stress and drugs of abuse” [32].

Both stress and venlafaxine interventions in methadone treated animals could reduce the final activity as compared with the primary activity. Another surprising finding was that unlike force swimming stress, venlafaxine could increase the final floating compared with the primary one after administration of methadone. Venlafaxine could reduce final activity compared with the primary one in methadone-controlled animals that underwent forced swimming stress (MTD-FSS+). Swimming and climbing behaviors are functions of blockade of serotonin and norepinephrine transporters respectively [33]. It has been demonstrated that "expression of norepinephrine or serotonin transporters was not affected by chronic treatment with venlafaxine (70 mg/kg/day, 14 days), but immobility time in the forced swimming test was reduced" [34]. "Administration of venlafaxine (32 mg/kg/day for 10 weeks) reduced floating time in rats" [35]. It has been reported that "methadone increases desensitization of 5-hydroxytryptamine (5-HT_3) receptor subtypes" [36]. Thus the increment of final floating in methadone treated animals might be attributed to this desensitization. It was previously established that floating time could be affected by anxiety [37], bilateral lesion of the lateral septum [38], serotonin and norepinephrine [39], expression of brain derived neurotrophic factor mRNA in the hippocampus and micro RNA-16 [40], 5-Hydroxytryptamine transporter genotype [41], adrenocorticotropin and corticosterone levels [42]. Decrease of preference, increase of floating and it's possible relation with a decrease in anxiety are also supported with a previous study [37]. Therefore, evaluation of the role of these factors in specific regions could be helpful for determination of possible mechanisms involved in these observations.

Evaluation of the crossing number in the two final CPP tests demonstrated that administration of venlafaxine could enhance locomotor activity in methadone controlled animals. Unlike in methadone controlled animals, venlafaxine administration could reduce locomotor activity in methadone treated ones in the final test with prime injection. These results might be consistent with the involvement of

mesolimbic dopamine release in drug seeking, reward and locomotion [43]. This also agrees with significant reductions observed in the final CPP scores and locomotor activity after prime injection in methadone and venlafaxine treated animals (MTD+FSS-VLX+ and MTD+FSS+VLX+). Another interpretation is that the more transition indicates more decision making behavior [29]. Therefore, it might be concluded that administration of venlafaxine could enhance decision making behavior in methadone controlled animals while it could reduce it in methadone treated animals. Further molecular evaluation of frontal cortex may provide more evidence for this possibility.

There was a significant positive correlation between the final activity in the forced swimming test and final CPP scores after prime injection. On the contrary, such a correlation was not observed between the final activity and final CPP scores without prime injection. It might be concluded that the less reinstatement risk, the less activity in the final forced swimming test. This idea might be supported at least by MTD+FSS-VLX+ and MTD+FSS+VLX+ animals. "Transgenic rats overexpressed human adenosine A_{2A} receptor in hippocampus, striatum and forebrain spend less time swimming and climbing" [44]; therefore the adenosine A_{2A} receptor might be one of the candidates involved in this correlation.

The high positive correlation between the two final CPP scores might represent a strong correlation between «stress»-induced reinstatement and «stress+prime»-induced reinstatement.

CONCLUSION

In conclusion, administration of venlafaxine could block relapse after chronic methadone detoxification. Venlafaxine improved anxiety and depression on methadone detoxified rats. The exact mechanisms involved in these observations are still not clear and further neurobiological and behavioral studies should open up new understandings of mechanisms to prevent opiate relapse.

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