

# Felbamate reduces hormone release and locomotor hypoactivity induced by repeated stress of social defeat in mice

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## Abstract

Glutamatergic neurotransmission plays a role in stress hormone release and the development of mood diseases. The aim of these studies was to verify the hypothesis that repeated treatment with felbamate, an antiepileptic drug modulating glutamatergic neurotransmission, affects hormone release in response to chronic stress. A mouse model of repeated social defeat (nonaggressive male mouse repeatedly defeated by aggressive counterparts) was used. The results showed that acute treatment with felbamate reduced hypolocomotion in an open field induced by repeated social conflict. The same stress procedure resulted in increased release of corticosterone and dopamine. Felbamate decreased noradrenaline concentrations and inhibited stress-induced rise in corticosterone and dopamine. It is suggested that modulation of stress hormone release may be induced by the action of felbamate on glutamate neurotransmission, and neuroendocrine changes could contribute to behavioural effects of the drug. Antidepressant action of this mood-stabilizing drug suggested by clinicians needs further verification.

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## 1. Introduction

In recent years, a lot of attention has been paid to the role of psychosocial factors in the development of affective disorders. Activation of the stress system leads to behavioural and peripheral changes that adjust homeostasis and improve coping with stress situations. On the other hand, a lack of adaptation to excessive demands can lead to the development of pathological syndromes, such as depression (Smelik, 1987; Nesse, 1999; De Kloet, 2003). Accordingly, antidepressant drugs used in the treatment of affective disorders were shown to interfere with the stress system (Delbende et al., 1994; Jezova and Duncko, 2002; Strohle and Holsboer, 2003; Schule et al., 2004). While various anticonvulsant drugs are increasingly advocated as mood stabilizers (Ernst and Goldberg, 2003), information on their modulatory influence on stress hormone release is nearly

lacking. With the exception of rare human studies in volunteers (Makatsori et al., 2004), no reports on changes in stress hormone levels following the treatment with novel anticonvulsant drugs seem to be available.

Exposure to chronic stress can exacerbate diseases such as depression and affective disorders. Both antidepressant and antistress action of drugs can be tested in animal models. The models vary from short stress tests (e.g., forced swimming test, Porsolt et al., 1977; Lucki, 1997; Shearman et al., 2003) to prolonged stress procedures, such as chronic mild stress model of depression (Willner, 1984; Duncko et al., 2001a,b). An animal model, which is based on conflict social stress situations, is repetitively exposed to agonistic interactions, in which group-housed mice are repeatedly defeated by aggressive singly housed opponents (Miczek and Krsiak, 1979; Mitchell and Fletcher, 1993; Uhlirva et al., 2004).

Glutamatergic neurotransmission is also affected by stressors (Moghaddam, 2002; Blank et al., 2004), it plays a role in stress hormone release (Jezova et al., 1995a), and it is related to the development of mood diseases in humans

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(Paul and Skolnick, 2003). Anticonvulsants that act through modulation of glutamate release are already in use in the treatment of bipolar disorder. Felbamate belongs to this group of drugs. Despite the fact that felbamate is used only for treatment-resistant of epilepsy due to its adverse effects (Besag, 2004), its study is of conceptual interest for psychiatrists. At present, felbamate is under clinical investigation in a double-blind randomized placebo-controlled trial in the treatment of resistant bipolar depression (Number: 02-M-0176, US NIH Clinical Trials, Bethesda, <http://www.clinicaltrials.gov>).

The aim of the present study was to test the hypothesis that repeated treatment with felbamate, an antiepileptic drug known to modulate glutamatergic neurotransmission, modulates hormone release in response to chronic stress. In addition, the effect of acute administration of the drug on social stress-induced suppression of locomotor activity was investigated.

## 2. Experimental procedures

### 2.1. Animals

Experimentally, naive adult male mice (albino out-bred strain ICR, VELAZ s.r.o., Prague, Czech Republic, 30–37g) were used in this study. Food and water were available ad libitum. Mice were housed either singly without any handling in self-cleaning cages with a grid floor (8×6×13 cm) or in groups of 17–20 in standard plastic cages (38×22×14 cm) with the floors covered with wooden shavings. After 3 weeks of this housing, each singly housed mouse was allowed 30 min adaptation in a Plexiglas neutral observation cage (20×20×30 cm) with clean wooden shavings before it was coupled with a group-housed male partner for 4 min/day. As experimental subjects in Experiments 1 and 2 served the group-housed mice with or without defeat in four conflict dyadic interactions, the singly housed mice exhibiting aggressive behavioural activities were received 1 week apart (Sulcova and Krsiak, 1989). Numbers of attacks, tail rattling and threats exhibited by singly housed mice were recorded and evaluated by the hardware/software Observer 3.1, Noldus Technology, Holland. Animals were housed, and behavioural testing was performed in a different room during the light phase of the constant light–dark cycle with lights on at 6:00 and off at 18:00 h. Temperature was maintained at  $21\pm 3$  °C, and relative humidity was 50%. The mice were not handled except on the experimental days. The study protocol was approved by the Animal Care Committee of the Masaryk University Brno, Faculty of Medicine, Czech Republic.

### 2.2. Experiment 1

Group-housed males ( $n=33$ ) were used for the experiment. In the first part of the study, mice were given water (10 ml/kg)

or acute doses of felbamate (Taloxa<sup>®</sup>, Suspension for Oral Use, Schering-Plough Labo N.V., Belgium; 15 or 60 or 240 mg/kg) orally via a syringe, in a randomized order, 30 min prior to the open field observations performed in the identical animal house but a different room from that used for the social defeat interactions. Each animal was placed singly into the centre of a novel environment (arena 30×30 cm) of the PC-controlled tracking apparatus Acti-track (Panlab, S.L., Spain) with infrared beam sensors. Over a 3-min testing period, the distance travelled, as a marker of locomotor/exploratory behaviour, in the open field was measured. Two days later, each mouse was defeated with a singly housed mouse exhibiting aggressive behaviour in a 4-min agonistic interaction. The procedure was repeated four times, 7 days apart. Immediately after the last (fourth) agonistic interaction, each mouse was administered the same treatment as in the first part of the experiment. Thirty minutes following the drug administration, the animal was placed into the open field arena and distance travelled was measured, as described before. Data of two group-housed mice, which were seriously wounded during the aggressive dyadic encounters, were excluded from the statistical analysis.

### 2.3. Experiment 2

The group-housed male mice were randomly assigned into two treatment groups. The first group ( $n=18$ ) received tap water 10 ml/kg/day orally and the second group ( $n=22$ ) felbamate (Taloxa<sup>®</sup>, Suspension for Oral Use, Schering-Plough Labo N.V.) at the dose of 240 mg/kg/day orally for a period of 3 days. On Day 4, each treatment continued, but both groups were allocated into two subgroups because only a half of each experimental group was exposed to 4-min dyadic aversive social interactions with their non-treated singly housed aggressive male mouse opponents, always performed 30 min after the water or drug administration. The same procedure was repeated until Day 7. Altogether, the group-housed mice received four agonistic interactions (always with the same partner, one per day). Immediately after the last (fourth) agonistic interaction, blood samples were collected. Blood ( $1.8\pm 0.2$  ml) was withdrawn from the retro-orbital plexus under short ether anaesthesia in an adjacent room. In the control groups (without aversive behavioural experience of aggressive interactions), blood samples were collected after the drug or water administration in the comparable interval of 34 min (in the other group, it was 30 min before exposition to aggressive partner +4 min of agonistic interaction).

### 2.4. Plasma hormone measurements

Blood was collected in polyethylene tubes containing EDTA or heparin as anticoagulant and centrifuged immediately at 4 °C to separate plasma, which was stored at –20 °C until analysed. Plasma corticosterone levels were

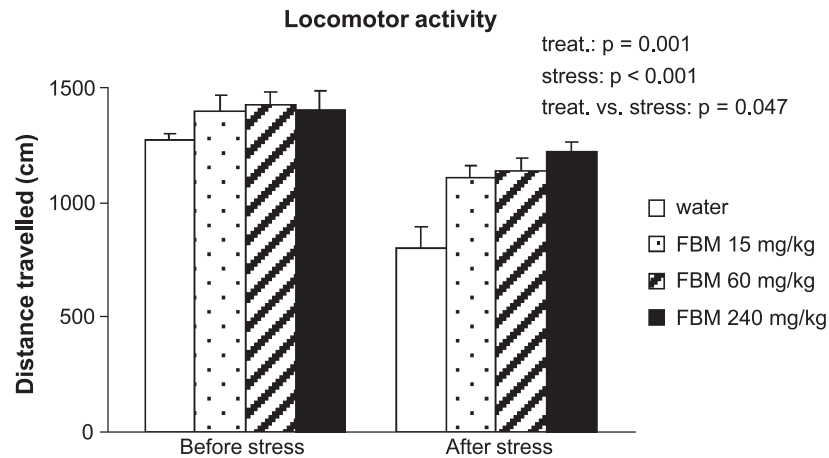


Fig. 1. Effect of felbamate (FBM) administration (15, 60, 240 mg/kg, orally) on locomotor activity in mice before and after repeated social stress. Values represent means±S.E.M.

analysed by RIA after dichloromethane extraction of the steroids from 10 µl aliquots of plasma, as described previously (Jezova et al., 1994). Antibodies were kindly provided by Prof. C. Oliver (Marseille). Plasma adrenaline, noradrenaline and dopamine were measured by the radioenzymatic assay, as described by Peuler and Johnson (1977).

2.5. Statistical evaluation

Behavioural data were subjected to a two-way mixed design analysis of variance (ANOVA), followed by Tukey test for pairwise comparisons, and calculations were made using STATISTICA (Stat Soft 1999 Edition). Statistical significance for hormonal results was determined by two-way ANOVA, followed by Tukey test for pairwise comparisons, as appropriate. The probability level was set to 95% as a limit to reject the null hypothesis. Data were expressed as means±S.E.M.

3. Results

In the first experiment with the group-housed mice repeatedly defeated on the agonistic interactions (stress) with the aggressive singly housed mice (the median values with an interquartile range of Q1–Q3 of aggressive activities exhibited by singly housed mice towards defeated experimental animals in each of the four paired interactions: attacks with a bite, 11, Q1=7, Q2=21; tail rattles, 65, Q1=46, Q2=84; threats, 67, Q1=51, Q2=83), an inhibition of locomotion (the total distance travelled) in the open field arena was observed when compared to their performance before repeated aversive experience of agonistic interactions. Two-way mixed design ANOVA revealed significance for factor stress:  $F(1,27)=55.36, p<0.001$ , factor treatment:  $F(3,27)=7.14, p=0.001$  and treatment vs. stress interaction:  $F(1,27)=3.01, p=0.047$ . Thus, felbamate in the

dose range of 15–240 mg/kg increased the locomotor activity in the stressed group of mice (Fig. 1).

In the second experiment, a significant elevation of dopamine levels in plasma was observed in the water-treated mice stressed by repeated exposure to agonistic interaction with aggressive partners (the median values with an interquartile range Q1–Q3 of aggressive activities exhibited by singly housed mice towards defeated experimental

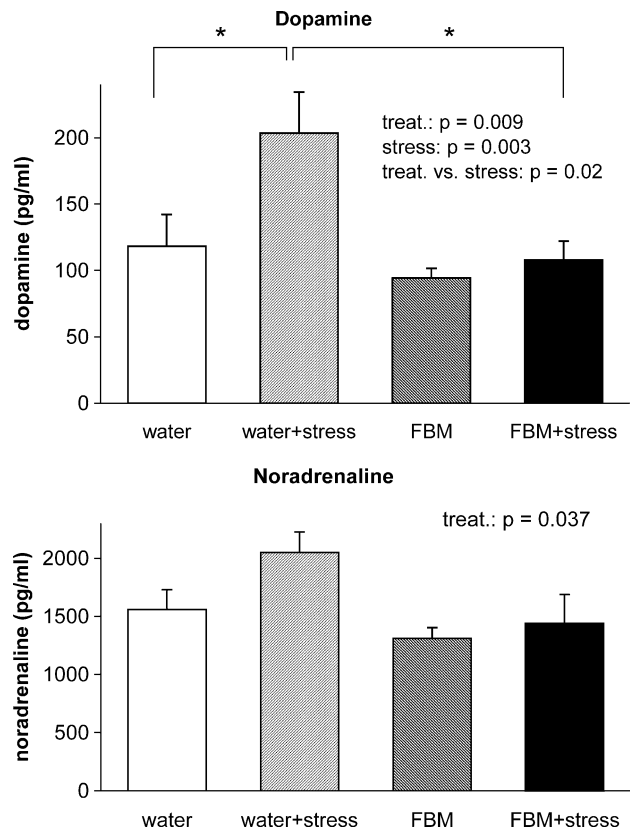


Fig. 2. Effect of felbamate (FBM) treatment (240 mg/kg, orally) on plasma dopamine and noradrenaline levels in mice with and without social stress. Values represent means±S.E.M. \* $p<0.05$ .

animals in each of the four paired interactions: attacks with a bite, 18,  $Q1=8.5$ ,  $Q2=35$ ; tail rattles, 75,  $Q1=51.5$ ,  $Q2=103.5$ ; threats, 77.5,  $Q1=51.5$ ,  $Q2=97.5$ ). Two-way ANOVA for dopamine revealed significant treatment ( $F(1,36)=7.70$ ,  $p=0.009$ ), stress ( $F(1,36)=10.23$ ,  $p=0.003$ ) and treatment vs. stress ( $F(1,36)=6.06$ ,  $p=0.019$ ) effects. Post hoc analysis by Tukey test showed that social stress increased plasma dopamine levels in water-treated controls ( $p<0.05$ ). Drug treatment decreased the stress effect on dopamine levels ( $p<0.05$ ). However, it did not significantly modulate dopamine levels in unstressed animals (Fig. 2).

Noradrenaline levels tended to rise following social stress exposure, but the changes failed to be significant (Fig. 2). Nevertheless, the two-way ANOVA revealed significant treatment effect ( $F(1,36)=4.68$ ,  $p=0.037$ ). Tukey test showed that treatment effect was significant when comparing water and felbamate treated groups ( $p<0.05$ ). No significant changes were found in plasma adrenaline levels (Fig. 3).

In the group of mice after agonistic interaction experience with aggressive isolates, we detected a significant increase in corticosterone levels. Two-way ANOVA revealed significant treatment ( $F(1,36)=6.86$ ,  $p=0.013$ ) and treatment vs. stress ( $F(1,36)=11.91$ ,  $p=0.001$ ) effects. Post hoc Tukey test comparison for factor stress within felbamate-treated mice revealed significance between stress

and nonstressed animals ( $p<0.05$ ). In the water-treated groups, the comparison for factor stress showed significant increase in stressed mice ( $p<0.05$ ). Felbamate treatment caused a significant increase in plasma corticosterone levels in the nonstressed group of mice ( $p<0.05$ ), while it significantly ( $p<0.05$ ) reduced stress induced hormone concentrations (Fig. 3).

#### 4. Discussion

The present study shows that repeated social conflict procedure resulted in increased release of corticosterone and dopamine. Hormone responses were blunted by repeated treatment with a glutamate release inhibiting drug felbamate. Acute treatment of mice with felbamate reduced hypolocomotion in an open field induced by agonistic interactions in mice.

The hypolocomotion has been described in some, though not all models of social stress and depression (Pare, 1989; Pal and Dandiya, 1994; Palanza, 2001; Will et al., 2003), and it has been confirmed in our model of repeated social defeat (Sulcova, 2000; the present study). It may be argued that in our experimental design, the mice were used as their own controls when subjected to open field tests, and some interference with the data obtained cannot be excluded. However, a significant interference is not very likely because the open field tests were performed 1 month apart, and habituation to the procedure is of low probability, as is the effect of 1-month age difference (Sulcova, 1999, 2000). Moreover, 1 month should be a sufficient washout period for eliminating unwanted side effects of felbamate and its impact on mouse locomotor activity. As the paired agonistic interactions with aggressive partner obviously include physical components, our findings are in agreement with previous reports that physical stress induces long-term reduction of locomotor activity (Pijlman et al., 2003). On the other hand, we failed to observe a significant rise in noradrenaline, which is known to respond predominantly to somatic stressors. However, we found a significant enhancement of dopamine and corticosterone release, as measured shortly after the last agonistic interaction. The rise of corticosterone levels in response to social defeat has been repeatedly reported (Koolhaas et al., 1995; Rodgers et al., 1997; Haller et al., 1999). It should be noted that hormone levels measured in present experiments were higher than usual basal values as the blood was taken under short ether anaesthesia known to enhance catecholamine and corticosterone release (Michalikova et al., 1990).

The results of this study demonstrate that felbamate can disinhibit suppressed locomotor activity in repeatedly defeated group-housed mice. Although this finding is not sufficient to judge its potential antidepressant effects, several other data support such a possibility. Defeat is a major stressor for male rodents (Martinez et al., 1998; Haller et al., 1999), and its behavioural consequences may serve as

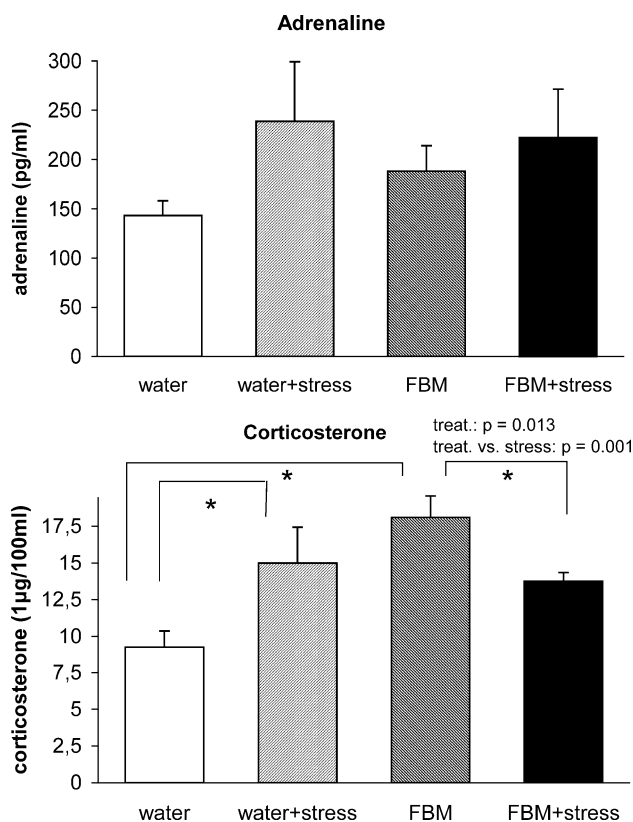


Fig. 3. Effect of felbamate (FBM) treatment (240 mg/kg, orally) on plasma adrenaline and corticosterone levels in mice with and without social stress. Values represent means  $\pm$  S.E.M. \* $p<0.05$ .

an animal model of depression (Keeney and Hogg, 1999). It has been shown that antidepressants were effective in reversal of inescapable stress-induced hypolocomotion in an open field (Pal and Dandiya, 1994), and a decreased locomotor activity has been described in other models of experimental depression (Pare, 1989). Changes in both central and peripheral synthesis of catecholamines have been observed in animal models of depression (Duncko et al., 2001a,b). Also, results of our pilot studies indicate that the model of agonistic interactions is suitable for screening antidepressant drug activities (Sulcova, 1999). Thus, it is possible that observed action of felbamate on the locomotion as well as on stress hormone release could be a sign of its antidepressant action. This possibility, however, needs further verification in additional studies.

The presented data verified the hypothesis that repeated treatment with felbamate, an antiepileptic drug known to modulate glutamatergic neurotransmission, modulates hormone release in response to chronic stress. Noradrenaline levels decreased in felbamate-pretreated mice irrespective of the presence of stress exposure, while the release of adrenaline failed to be modified by the drug pretreatment. These results demonstrate that felbamate affects the sympathetic nervous system rather than the adrenomedullary function in mice. However, the only catecholamine, which showed a clear response to repeated social conflict, was dopamine, and this response was prevented by felbamate administration. Dopamine is of both sympathetic nerve and adrenomedullary origin. Administration of felbamate reduced also the rise in corticosterone levels in stressed animals. In the control group, felbamate elicited an elevation of plasma corticosterone levels. It is not surprising, as several antidepressant drugs have been shown to increase plasma corticosterone after single administration (Jezova et al., 1984; Moncek et al., 2003; Hendrie et al., 2003).

Factors responsible for felbamate effects on locomotor/exploratory behaviour and stress hormone release are unclear. The mechanism of action of felbamate involves several processes, such as blockage of voltage-gated sodium channels (Stefani et al., 1997), attenuation of glutamate excitatory neurotransmission (Rho et al., 1994; Subramaniam et al., 1995; Stefani et al., 1997; Brown and Aiken, 1998; Kleckner et al., 1999), enhancement of GABA-evoked chloride currents (Rho et al., 1994; Brown and Aiken, 1998) and a blockage of L-type calcium channels (Meldrum, 1996). In relation to the present study, particularly interesting is the action of felbamate on glutamatergic neurotransmission. Glutamate is a neurotransmitter considered to be involved in both stress response and depression (Jezova et al., 1995a; Paul and Skolnick, 2003). Glutamate receptor antagonists can interfere with stress-induced neuroendocrine (Jezova et al., 1995b; Zelena et al., 1999), as well as behavioural alterations (Papp and Moryl, 1994). Glutamate acts via different types of ionotropic and metabotropic receptors. Felbamate is referred to modulate especially

ionotropic receptors of NMDA subtype. Blockade of NMDA receptors by a selective antagonist resulted in an inhibition of corticosterone release during immobilization stress (Jezova et al., 1995b). It is therefore possible that felbamate induces its inhibitory effect on corticosterone release in the present model of social stress via glutamatergic mechanisms.

In conclusion, presented effects of low doses of felbamate observed in the social stress model used, which is close to real life events and emulates human psychiatric disorders, suggest possible antidepressant-like properties of felbamate, which need further verification. Accompanying neuroendocrine changes observed in this study may be induced by the action of felbamate on glutamate neurotransmission and may play a role in the mechanisms involved.

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### References

- Besag, F.M., 2004. Behavioural effects of the newer antiepileptic drugs: an update. *Expert Opin. Drug Saf.* 3, 1–8.
- Blank, T., Nijholt, I., Spiess, J., 2004. Molecular determinants mediating effects of acute stress on hippocampus-dependent synaptic plasticity and learning. *Mol. Neurobiol.* 29, 131–138.
- Brown, W.M., Aiken, S.P., 1998. Felbamate: clinical and molecular aspects of a unique antiepileptic drug (Review). *Crit. Rev. Neurobiol.* 12, 205–222.
- De Kloet, E.R., 2003. Hormones, brain and stress (Review). *Endocr. Regul.* 37, 51–68.
- Delbende, C., Tranchand Bunel, D., Tarozzo, G., Grino, M., Oliver, C., Mocaer, E., Vaudry, H., 1994. Effect of chronic treatment with the antidepressant tianeptine on the hypothalamo-pituitary-adrenal axis. *Eur. J. Pharmacol.* 251, 245–251.
- Duncko, R., Brtko, J., Kvetnansky, R., Jezova, D., 2001a. Altered function of peripheral organ systems in rats exposed to chronic mild stress model of depression. *Cell. Mol. Neurobiol.* 21, 403–411.
- Duncko, R., Kiss, A., Skultetyova, I., Rusnak, M., Jezova, D., 2001b. Corticotropin-releasing hormone mRNA levels in response to chronic mild stress rise in male but not in female rats while tyrosine hydroxylase mRNA levels decrease in both sexes. *Psychoneuroendocrinology* 26, 77–89.
- Ernst, C.L., Goldberg, J.F., 2003. Antidepressant properties of anticonvulsant drugs for bipolar disorder. *J. Clin. Psychopharmacol.* 23, 182–192.
- Haller, J., Fuchs, E., Halasz, J., Makara, G., 1999. Defeat is a major stressor in males while social instability is stressful mainly in females: towards development of a social stress model in female rats. *Brain Res. Bull.* 50, 33–39.
- Hendrie, C.A., Pickles, A.R., Duxon, M.S., Riley, G., Hagan, J.J., 2003. Effects of fluoxetine on social behaviour and plasma corticosteroid levels in female Mongolian gerbils. *Behav. Pharmacol.* 14, 545–550.

- Jezova, D., Duncko, R., 2002. Enhancement of stress-induced pituitary hormone release and cardiovascular activation by antidepressant treatment in healthy men. *J. Psychopharmacol.* 16, 235–240.
- Jezova, D., Jurcovicova, J., Vigas, M., Labrie, F., 1984. Possible mechanisms involved in naloxone-, morphine- and stress-induced ACTH release in rats. In: Usdin, E., Kvetnansky, R., Axelrod, J. (Eds.), *Stress: The Role of Catecholamines and Other Neurotransmitters*. Gordon and Breach Science Publishers, New York, pp. 263–273.
- Jezova, D., Guillaume, V., Jurankova, E., Carayon, P., Oliver, C., 1994. Studies on the physiological role of ANF in ACTH regulation. *Endocr. Regul.* 28, 163–169.
- Jezova, D., Jurankova, E., Vigas, M., 1995a. Glutamate neurotransmission, stress and hormone secretion. *Bratisl. Lek. L.* 96, 588–596.
- Jezova, D., Tokarev, D., Rusnak, M., 1995b. Endogenous excitatory amino acids are involved in stress-induced adrenocorticotropin and catecholamine release. *Neuroendocrinology* 62, 326–332.
- Keeney, A.J., Hogg, S., 1999. Behavioral consequences of repeated social defeat in the mouse: preliminary evaluation of potential animal model of depression. *Behav. Pharmacol.* 10, 753–764.
- Kleckner, N.W., Glazewski, J.C., Chen, C.C., Moscrip, T.D., 1999. Subtype-selective antagonism of *N*-methyl-D-aspartate receptors by felbamate: insights into the mechanism of action. *J. Pharmacol. Exp. Ther.* 289, 886–894.
- Koolhaas, J.M., Meerlo, P., De Boer, S.F., Strubbe, J.H., Bolhuis, B., 1995. Social stress in rats: an animal model of depression? *Acta Neuropsychiatr.* 7, 27–29.
- Lucki, I., 1997. The forced swimming test as a model for core and component behavioral effects of antidepressant drugs. *Behav. Pharmacol.* 8, 523–532.
- Makatsori, A., Duncko, R., Moncek, F., Loder, I., Katina, S., Jezova, D., 2004. Modulation of neuroendocrine response and non-verbal behavior during psychosocial stress in healthy volunteers by the glutamate release-inhibiting drug lamotrigine. *Neuroendocrinology* 79, 34–42.
- Martinez, M., Calvo-Torrent, A., Pico-Alfonso, A., 1998. Social defeat and subordination as models of social stress in laboratory rodents: a review. *Aggress. Behav.* 24, 241–256.
- Meldrum, B.S., 1996. Update on the mechanism of action of antiepileptic drugs (Review). *Epilepsia* 37, 4–11.
- Michalikova, S., Balazova, H., Jezova, D., Kvetnansky, R., 1990. Changes in circulating catecholamine levels in old rats under basal conditions and during stress. *Bratisl. Lek. L.* 91, 689–693.
- Miczek, K.A., Krsiak, M., 1979. Drug effects on agonistic behavior. In: Thompson, T., Dews, P. (Eds.), *Advances in Behavioral Pharmacology*. Academic Press, New York, pp. 87–161.
- Mitchell, P.J., Fletcher, A., 1993. Venlafaxine exhibits pre-clinical antidepressant activity in the resident–intruder social interaction paradigm. *Neuropharmacology* 32, 1001–1009.
- Moghaddam, B., 2002. Stress activation of glutamate neurotransmission in the prefrontal cortex: implications for dopamine-associated psychiatric disorders (Review). *Biol. Psychiatry* 15, 775–787.
- Moncek, F., Duncko, R., Jezova, D., 2003. Repeated citalopram treatment but not stress exposure attenuates hypothalamic–pituitary–adrenocortical axis response to acute citalopram injection. *Life Sci.* 72, 1353–1365.
- Nesse, R.M., 1999. Proximate and evolutionary studies of anxiety, stress and depression: synergy at the interface. *Neurosci. Biobehav. Rev.* 23, 895–903.
- Pal, S.N., Dandiya, P.C., 1994. Glutathione as a cerebral substrate in depressive behavior. *Pharmacol. Biochem. Behav.* 48, 845–851.
- Palanza, P., 2001. Animal models of anxiety and depression: how are females different? *Neurosci. Biobehav. Rev.* 25, 219–233.
- Papp, M., Moryl, E., 1994. Antidepressant activity of non-competitive and competitive NMDA receptor antagonists in a chronic mild stress model of depression. *Eur. J. Pharmacol.* 263, 1–7.
- Pare, W.P., 1989. Stress ulcer susceptibility and depression in Wistar Kyoto (WKY) rats. *Physiol. Behav.* 46, 993–998.
- Paul, I.A., Skolnick, P., 2003. Glutamate and depression: clinical and preclinical studies (Review). *Ann. N.Y. Acad. Sci.* 1003, 250–272.
- Peuler, J.D., Johnson, G.A., 1977. Simultaneous single isotope radioenzymatic assay of plasma norepinephrine, epinephrine and dopamine. *Life Sci.* 21, 625–636.
- Pijlman, F.T., Wolterink, G., Van Ree, J.M., 2003. Physical and emotional stress have differential effects on preference for saccharine and open field behaviour in rats. *Behav. Brain Res.* 17, 131–138.
- Porsolt, R.D., Le Pichon, M., Jalfre, M., 1977. Depression: a new animal model sensitive to antidepressant treatments. *Nature* 266, 730–732.
- Rho, J.M., Donevan, S.D., Rogawski, M.A., 1994. Mechanism of action of the anticonvulsant felbamate: opposing effects on *N*-methyl-D-aspartate and gamma-aminobutyric acid A receptors. *Ann. Neurol.* 35, 229–234.
- Rodgers, R.J., Cao, B.J., Dalvi, A., Holmes, A., 1997. Animal models of anxiety: an ethological perspective (Review). *Braz. J. Med. Biol. Res.* 30, 289–304.
- Shearman, L.P., Rosko, K.M., Fleischer, R., Wang, J., Xu, S., Tong, X.S., Rocha, B.A., 2003. Antidepressant-like and anorectic effects of the cannabinoid CB1 receptor inverse agonist AM251 in mice. *Behav. Pharmacol.* 14, 573–582.
- Schule, C., Baghai, T., Laakmann, G., 2004. Mirtazapine decreases stimulatory effects of reboxetine on cortisol, adrenocorticotropin and prolactin secretion in healthy male subjects. *Neuroendocrinology* 79, 54–62.
- Smelik, P.G., 1987. Adaptation and brain function. *Prog. Brain Res.* 72, 3–9.
- Stefani, A., Spadoni, F., Bernardi, G., 1997. Voltage-activated calcium channels: targets of antiepileptic drug therapy? *Epilepsia* 38, 959–965.
- Strohle, A., Holsboer, F., 2003. Stress responsive neurohormones in depression and anxiety. *Pharmacopsychiatry* 36, 207–214.
- Subramaniam, S., Rho, J.M., Penix, L., Donevan, S.D., Fielding, R.P., Rogawski, M.A., 1995. Felbamate block of the *N*-methyl-D-aspartate receptor. *J. Pharmacol. Exp. Ther.* 273, 878–886.
- Sulcova, A., 1999. Agonistic behavior in mice used as a model for testing of antidepressant drug activity (valproate, citalopram, gabapentin). *Behav. Pharmacol.* 10, 90.
- Sulcova, A., 2000. Do anticonvulsants gabapentin and lamotrigine induce in mice behavioural changes suggesting their potential antidepressant activity? *Psychopharmacology Suppl.* 1, 126.
- Sulcova, A., Krsiak, M., 1989. Differences among nine 1,4-benzodiazepines: an ethopharmacological evaluation in mice. *Psychopharmacology* 97, 157–159.
- Uhlirova, L., Sustkova-Fiserova, M., Krsiak, M., 2004. Behavioral effects of flumazenil in the social conflict test in mice. *Psychopharmacology* 171, 259–269.
- Will, C.C., Aird, F., Redei, E.E., 2003. Selectively bred Wistar-Kyoto rats: an animal model of depression and hyper-responsiveness to antidepressants. *Mol. Psychiatry* 8, 925–932.
- Willner, P., 1984. The validity of animal models of depression. *Psychopharmacology* 83, 1–16.
- Zelena, D., Makara, G.B., Jezova, D., 1999. Simultaneous blockade of two glutamate receptor subtypes (NMDA and AMPA) results in stressor-specific inhibition of prolactin and corticotropin release. *Neuroendocrinology* 69, 316–323.