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P.2.d.009 Changes in glutamatergic transmission in rat frontal cortex induced by chronic imipramine treatment

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The past years of depression research have focused on the role of the monoamines in the pathophysiology and treatment. The monoamine theory has implicated abnormalities in serotonin and noradrenalin in the pathophysiology of major depression and bipolar depression. Tricyclic antidepressants, which inhibit serotonin (5-HT) and noradrenaline (NA) uptake are widely used to treat depressive disorders. To produce significant therapeutic effect, repetitive administration of the drug for at least two – three weeks is necessary. This has been linked to development of adaptive changes in the brain monoamine receptors as well as other neurotransmitter systems. Depressive disorders are associated with both structural and functional abnormalities in a number of human brain structures including frontal cortex. It has been shown that drugs used for treatment of depression modulate glutamatergic transmission and modify density of ionotropic glutamate receptors in animals, however, functional implications of these effects are not fully understood. We have previously shown that treatment of rats with imipramine or citalopram for 14 days results in a reduction of glutamatergic cortical field potentials in rat ex vivo brain slices (Bobula 2003). In the present study we aimed at finding the effect of repetitive administration of imipramine on the release of glutamate in the frontal cortex.

Male Wistar rats received imipramine (10 mg/kg twice daily) for 7, 14 or 21 days. Brain slices were prepared 48 hours after last drug administration. Field potentials were evoked by electrical stimuli applied to layer V and recorded in layer II/III. To isolate AMPA/kainate receptor-dependent component of the field potential, slices were incubated in CGP 37849 (2 μM). To isolate NMDA receptor-dependent component, slices were incubated in NBQX (5 μM). To estimate a changes in glutamate release after antidepressant therapy the time necessary to blockade NMDA component by MK-801, which blocks NMDA receptors in an activity-dependent manner, was measured.

Treatment with imipramine resulted in an average decrease of the initial slope of the AMPA/kainate component by 0%, 40% and 45% for 7, 14 and 21 days of drug administration, respectively. In the case of the NMDA component of the field potential its initial slope was reduced by 0%, 45% and 40%, respectively.

Moreover, 14 days of treatment with imipramine prolonged the time to reach 50% of the initial amplitude of the NMDA component by about 30% comparing to control animals (from 160 s to 210 s) in MK-801 containing incubation medium. Calculations, based on double exponential fits, indicated that the probability of glutamate release was reduced from 0.69 to 0.49.

These results indicate that treatment with a tricyclic antidepressant induces adaptive modifications of glutamatergic synaptic transmission in rat cortex, which depends on the duration of treatment. and persists for at least 2 days after the last drug administration. This effect is consistent with existing neurochemical, molecular, behavioral and electrophysiological data supporting the "glutamatergic hypothesis" of the action of antidepressants.

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P.2.d.010 In vivo effect of venlafaxine on locus coeruleus neurons: role of opioid, alpha2-adrenergic and 5-HT1A receptors

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Venlafaxine is a dual 5-HT/NA re-uptake inhibitor antidepressant. Similarly to tricyclic antidepressants, the new dual antidepressants have evidenced analgesic properties. It has been shown that, both the antidepressant and analgesic effects of antidepressants are regulated by opioid, α2-adrenergic and 5-HT1A receptors. In fact, opioid system activation has been involved in the analgesic effect of tricyclics and it has been shown that the antidepressant and antinociceptive effects of venlafaxine were blocked by an inhibitor of NA synthesis and a noradrenergic neurotoxin respectively. In addition, the activation of 5-HT1A receptors blocked the analgesic and enhanced the antidepressant effect of venlafaxine.

Locus coeruleus (LC) is implicated in several neural pathways responsible for some somatic and emotional processes, such as pain and depression and its activity is regulated by several receptors, such as opioid, α2-adrenergic and 5-HT1A receptors. Therefore, considering that LC activity is subject to the action of these receptors, the first aim of our study will be to explore the role of α2-adrenergic, opioid, and 5-HT1A receptors in the in vivo acute effect of venlafaxine on LC neurons. This will be achieved using electrophysiological techniques in vivo, after both acute and long-term treatment and will help us to further understand both the antidepressant and analgesic effects of venlafaxine, and the relationship between them.

The results show that acute administration of venlafaxine produced a dose-dependent, complete inhibition of LC activity (ED50 = 1.8±0.2 mg/kg). This inhibitory effect was not reversed by the opioid receptor antagonist naloxone (5 mg/kg, i.v.), but subsequent administration of idazoxan (1 mg/kg, i.v.), an α2-adrenoceptor antagonist, did reverse this inhibitory effect. The pre-administration of the 5-HT1A receptor agonist, 8-OH-DPAT (1 and 40 μg/kg), significantly enhanced the venlafaxine inhibitory effect, decreasing the ED50 by 56% and 44% respectively (one-way ANOVA followed by Newman-Keuls test). A 14-day treatment with venlafaxine (40 mg/kg/day) induced a suppression of the firing activity of LC neurons (basal firing rate of the non-treated group (2.2±0.1 Hz, unpaired Student's t-test) compared to the basal firing rate of the treated group (1.1±0.1 Hz), $p < 0.0001$, paired Student's t-test). In these treated animals, venlafaxine produced a similar inhibitory effect to in non-treated animals (ED50 = 2.0±0.5 mg/kg). This inhibitory effect was not reversed by naloxone (5 mg/kg, i.v.), but was reversed by idazoxan (1 mg/kg, i.v.). In addition, the pre-administration of 8-OH-DPAT (40 μg/kg) significantly enhanced the venlafaxine effect, decreasing the ED50 by 60% (one-way ANOVA followed by Newman-Keuls test).

In summary, the present results indicate that venlafaxine inhibits LC firing through a mechanism independent of opioid receptors

and dependent on α2-adrenoceptors. In addition, the activation of 5-HT1A receptors potentiates the inhibitory effect of venlafaxine in LC neurons in non-treated and long-term venlafaxine treated animals. This data could contribute to understanding the effect of venlafaxine in LC neurons and elucidating its mechanism of action in depression and analgesia. Supported by: FIS-PI031430 and PAI/CTS510.

P.2.d.011 Behavioral response to clomipramine after application of different stressors in ovariectomized female rats

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Statement on the purpose of the study: It is widely accepted that stress may be involved in the clinical manifestation of depression (Mazure, 1995). Also, it is well documented that women are more susceptible to depression than men (Goodwin, Gotlib, 2004). However, it is not known whether and in which extent stressors of different strength might influence the response of female animals with imbalance of estrogen and the effect of antidepressant drugs in experimental models of depression.

The aim of present work was to evaluate the influence of strength stressors on clomipramine effect assessed in forced swim test using ovariectomized (OVX) rats and OVX-estrogen treated female rats and its possible correlation with corticosterone response.

Methods: The intact cycling females, OVX females and OVX-estrogen treated females were injected with clomipramine (50.0 mg/kg, i.p.) or saline. These groups of animals were received electric shocks of different intensity and duration (mild – 5 ms, 0.1 mA, moderate – 5 ms, 1.0 mA and severe – 10 ms, 1.0 mA) 24 h and 1 h before being subjected to forced swim test. At the end of behavioral procedures all rats were decapitated and corticosterone plasma levels were measured by ELISA kit. Statistical processing of the received data was carried out using two-way ANOVA test and post-hoc Dunnett's test for multiple comparisons at $p < 0.05$.

Results: Application of mild or moderate shocks caused profoundly decreased time immobility ($p < 0.05$) in OVX rats injected with clomipramine as compared to clomipramine-injected non-shocked OVX rats. On the contrary, severe shock had no effect on time immobility in OVX rats injected with clomipramine as compared to clomipramine-injected non-shocked OVX rats ($p > 0.05$). Application of mild or moderate shocks significantly decreased time immobility ($p < 0.05$) in E2-treated OVX rats as compared to E2-treated non-shocked OVX rats. Severe shock had no effect on time immobility in E2-treated OVX rats as compared to E2-treated non-shocked OVX rats ($p > 0.05$). Application of moderate shock significantly increased corticosterone level ($p < 0.05$) in E2-treated OVX rats injected with clomipramine as compared to clomipramine-injected non-shocked E2-treated OVX rats. Nevertheless, application of mild or severe shock had no effect on corticosterone level in E2-treated OVX rats injected with clomipramine as compared to clomipramine-injected non-shocked E2-treated OVX rats ($p > 0.05$).

Conclusions: Thus, these results suggest that duration and intensity of stressors profoundly affect the behavioral response of female rats with imbalance of estrogen to clomipramine in forced swim test. Plasma corticosterone levels correlate with the behavioral response to clomipramine indicating that reactivity of hypothalamus–pituitary–adrenal axis to stress may be involved in the mechanisms of depression in female rats.

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P.2.d.012 Vagus nerve stimulation: effects on noradrenergic neuronal firing and serotonin transmission in the rat brain

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Introduction: Vagus nerve stimulation (VNS) is an efficacious intervention in treatment-resistant depression [1]. Electrophysiological recordings in the rat brain showed that VNS increases the firing rate of noradrenaline (NE) neurons after only one day of stimulation, an effect which increases over 3 months. In contrast, serotonin (5-HT) neuronal firing is increased only after 14 days of VNS, but it also increases over 3 months [2]. Additional studies were carried to further characterize these effects.

Methods: Rats were implanted a VNS electrode around the left carotid artery and vagus nerve and a stimulator subcutaneously in the back area under chloral hydrate/sodium pentobarbital anesthesia. The stimulator was turned on 48 h later using various parameters (30 seconds on every 5 minutes; current: 0.25–1 mA; frequency: 1–145 Hz; pulse width: 130–750 ms). The selective noradrenergic toxin DSP-4 was used to lesion NE neurons of the locus coeruleus. Rat dorsal raphe 5-HT neurons were recorded under choral hydrate anesthesia with the stimulator being turned off immediately before the experiments. Hippocampus CA_3 pyramidal neurons were recorded using five-barrelled iontophoretic pipette.

Results: Analysis of a previously published data set [2] revealed that not only spontaneous firing rates of NE and 5-HT neurons are increased by VNS, but as well the percentages of neurons firing in bursts: 41% of NE neurons fired in bursts in shams and 88% and 85% in 14- and 90-day stimulated rats. The percentage of 5-HT neurons T Hdischarging in bursts was significantly increased only after 90 days of VNS (control: 17%, 14 days: 21%, 90 days: 32%). The following VNS parameters produced the largest increases in 5-HT neuronal firing: 0.25 mA, 20 Hz, 500 ms pulse width and were used for the next series of experiments. The enhancement of the firing rate of 5-HT neurons after 14 days of VNS was abolished by the DSP-4 lesion. Direct application of 5-HT on CA3 pyramidal neurons showed that the responsiveness of their 5-HT_{1A} receptors was unaltered after 14 days of VNS. In contrast, their tonic activation by endogenous 5-HTwas significantly increased, as revealed by the robust disinhibitory effect of the 5-HT_{1A} antagonist WAY-100,635 on firing rate in comparison to controls.

Discussion: VNS initially increases only the firing activity and pattern of NE neurons, and subsequently those of 5-HT neurons, presumably as a cascade effect. The VNS parameters used clinically correspond to the optimal ones that best activate 5-HT neurons in the rat brain. Finally, VNS has the capacity to increase postsynaptic 5-HT_{1A} transmission in the rat hippocampus, as do other antidepressant treatments, albeitby a different mechanism. The antidepressant response to VNS seen clinically correlates well with changes observed in the 5-HT and NE system documented in