

Acute Stress-induced Changes in Hippocampal/Prefrontal Circuits in Rats: Effects of Antidepressants

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Acute stress inhibits long-term potentiation (LTP) at synapses from the hippocampus to prefrontal cortex in the rat, a model of the dysfunction in the anterior cingulate/orbitofrontal cortices which has been observed in human depression. We demonstrate that the antidepressants tianeptine and, to a lesser extent, fluoxetine, are able to reverse the impairment in LTP, a measure of frontal synaptic plasticity, caused by stress on an elevated platform. LTP was induced by stimulation of hippocampal outflow. Beneficial effects on neuronal plasticity, defined as a reversal of the effects of stress in this paradigm, can be considered as a new animal model for the impact of stress on hippocampal/frontal circuits, a key target in psychiatric diseases.

Keywords: depression, fluoxetine, long-term potentiation, synaptic plasticity, tianeptine

Introduction

Marked changes in metabolism or blood flow, structural abnormalities and subsequent chronic morphological alterations have been described in depression and these changes are consistently reported in the specific brain areas which are susceptible to stress. In major depressive disorder, decreased blood flow and metabolism have been regularly described in multiple areas of the prefrontal cortex (PFC) with occasional changes in the hippocampal region (Drevets, 1998; for a review, see Harrison, 2002). Conversely, a beneficial response to antidepressants has been associated with reduced blood flow in the hippocampus (Mayberg *et al.*, 2000; Kennedy *et al.*, 2001) and a return to baseline metabolism level or increase in blood flow in the anterior cingulate cortex (Kennedy *et al.*, 2001). Prolonged and repeated depression is also associated with atrophy in cortex and hippocampus. Cortical atrophy has been reported in post-mortem studies, in the anterior cingulate cortex (Ongur *et al.*, 1998) (subgenual part of area 24), the orbital and dorsolateral PFC (Rajkowska *et al.*, 1999). A reduced volume of the orbitofrontal cortex has also been recently observed in depressed patients (Bremner *et al.*, 2002) and hippocampal volume loss associated with repeated depression and with stress (Sheline *et al.*, 1996; Duman and Charney, 1999; Frodl *et al.*, 2002). If subtle tests are used, depression is also associated with significant impairment in working memory, a function subserved by the frontal lobes (Merriam *et al.*, 1999). Thus, the convergence of neuroimaging and neuropathological data has provided support for a model of limbic-cortical dysregulation for depression proposed by Mayberg (1997) and this model would be highly sensitive to stress.

There is a clear direct relationship between the hippocampus and frontal cortex in rats, monkeys and humans.

Although the PFC shows considerable variations across species, as reported by Ongur and Price (2000) and others (Uylings and van Eden, 1990; Petrides and Pandya, 1994), similarities in the position and connections of orbital and medial areas of the PFC indicate that these PFC networks are relatively comparable in rats, monkeys and humans. In rats and monkeys, the orbital and medial PFC networks are intimately connected with the hippocampus and a similar topography of the hippocampal–prefrontal network has been described (Carmichael and Price, 1995). In rats, the prelimbic (the apparent homologue of the medial primate subgenual PFC) cortex is the PFC region where most of the hippocampal terminal fields are localized (Jay and Witter, 1991). Plasticity at hippocampal to PFC synapses can be regulated up and down, as assessed by long-term potentiation (LTP) and long-term depression (LTD), depending on specific patterns of afferent activation (Jay *et al.*, 1995; Takita *et al.*, 1999) and this circuit contributes to working memory processes (Floresco *et al.*, 1997). Exposure to acute stress is known to impair hippocampal LTP in rats (Diamond *et al.*, 1999; Shakesby *et al.*, 2002) and to produce working memory impairment in rats and monkeys (Murphy *et al.*, 1996).

Few valid models of depression exist. Simple models of behavioural despair in rats or mice do not respond to all antidepressants. Models of learned helplessness, where animals continue to escape from an inevitable electrical shock, do not show reproducible effects of fluoxetine or other serotonergic reuptake inhibitors (SSRIs). However, these are pharmacological models, based on the effectiveness of tricyclic antidepressants. Chronic psychosocial stress in tree shrews (Gould *et al.*, 1997), or chronic mild stress in rats (Willner *et al.*, 1992) have clearly been shown to be valid models of depression, but these models are unwieldy and of long duration.

There is thus a clear need for new animal models which take into account the abnormal brain activation patterns seen in psychiatric diseases. We thus wished to use the acute deleterious effects of stress on hippocampal–PFC plasticity in the rat as a model of depression, based on the brain circuitry shown to be impaired in depression.

Materials and Methods

Electrophysiology and Surgery

All animal experiments were performed in accordance with our institution guidelines (Centre National de la Recherche Scientifique) and the prerogatives from the French Agriculture and Forestry Ministry (decree 874848, license A91429). Adult (300–400 g) male Sprague–Dawley rats, housed in pairs, were used for the study. They were maintained under standard laboratory conditions on a 12 h light/

dark cycle with lights on from 8 a.m. and *ad libitum* access to food and water. During surgery, the rats were anaesthetized with sodium pentobarbital (60 mg/kg, i.p.) and placed in a stereotaxic frame with body temperature maintained at 37°C by a homeothermic warming blanket. The procedures for implantation and recording extracellular field potentials in the prelimbic area of the PFC are described elsewhere (Jay *et al.*, 1995). Briefly, recording electrodes (64 µm diameter, two nickel chrome wires) were positioned in the prelimbic cortex (coordinates: 3.3 mm anterior to bregma, 0.8 mm lateral to the midline) and a bipolar concentric stainless steel stimulating electrode (150 µm outer diameter with a 300 µm tip separation) was lowered into the ipsilateral CA1/subicular region of the ventral hippocampus (coordinates: 6.5 mm posterior to bregma, 0.5 mm lateral to the midline). Stimulation of the CA1/subicular region evokes a characteristic monosynaptic negativegoing field excitatory postsynaptic potential (PSP) in the PFC with a peak latency of 18–22 ms. The final placement of the recording and stimulating electrodes (3.0–3.8 mm and 4.6–6.0 mm below the cortical surface, respectively) were optimized using electrophysiological criteria (maximum amplitude of the field potential). Test pulses (100 µs) were delivered every 30 s at an intensity that evoked a response of 70% of its maximum (range: 250–400 µA). At this intensity, the field potential is most likely to reflect summated PSPs. High-frequency stimulation (HFS) to induce LTP consisted of two series of 10 trains (250 Hz, 200 ms) at 0.1 Hz, 6 min apart, delivered at test intensity. Postsynaptic potential amplitudes were analysed using A/Dvance software, expressed as a percentage change of the mean response over a 30 min baseline period and presented in figures as the mean ± SEM for 2 min epochs. Statistical comparisons were carried out using analysis of variance (ANOVA).

Stress Protocol

Behavioural stress protocol was adapted from Xu *et al.* (1998). Rats were placed on an elevated and unsteady platform (21 × 20 cm², 1 m above ground level) for 30 min. The animal showed behavioural ‘freezing’ – i.e. piloerection, immobility for up to 10 min, defecation and sometimes urination – while on the platform. At the end of stress, rats were anaesthetized (sodium pentobarbital, 60 mg/kg i.p.) on the platform and immediately after, placed in the stereotaxic frame. LTP was induced within 180 min after the end of stress. Control nonstressed rats were anaesthetized immediately after transfer from the animal house.

Corticosterone Assay

Rats were decapitated immediately after the 30 min exposure to stress (stressed rats) or after removal from their paired-housed home cage (control rats) and blood was collected. Blood samples were centrifuged at 4°C and 3000 r.p.m. for 15 min and serum stored at –20°C. Plasma corticosterone was assessed by radioimmunoassay (RIA; DSL 80100; Texas) and data were analysed with ANOVA.

Drugs

All drugs were dissolved in NaCl (0.9%), injected at 10 mg/kg and administered by an i.p. route. Tianeptine sodium salt was provided by Servier (Courbevoie, France). Fluoxetine hydrochloride was purchased from Sigma (Saint Quentin Fallavier, France). The doses were chosen as the antidepressant dose which did not induce secondary effects. All the drugs or saline solution (NaCl 0.9%) were acutely administered 40 min prior to induction of LTP.

Results

Inhibition of Cortical LTP by Acute Stress

The effect of an acute inescapable stress on LTP, recorded *in vivo* in the prelimbic cortex of anaesthetized rats, was assessed using HFS of the ipsilateral CA1/subicular region in the ventral hippocampus (for brain structures see Fig. 1). Rats placed on an elevated platform for 30 min showed behavioural (‘freezing’ behaviour) as well as endocrine signs of

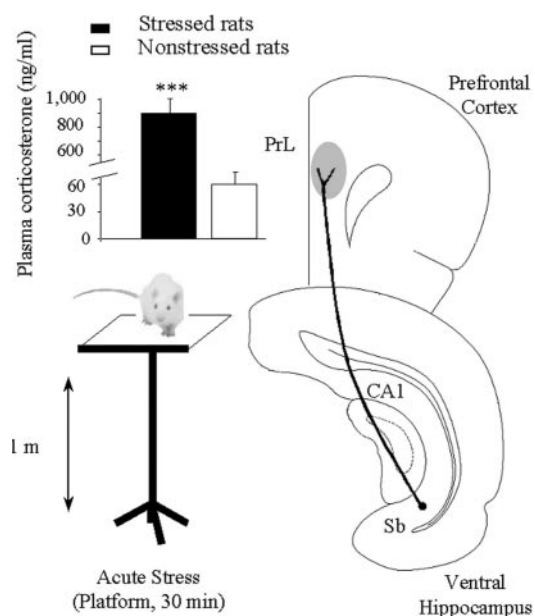


Figure 1. Illustration of the acute stress protocol and schematic representation of the direct hippocampal projection to the PFC in rats. Glutamatergic neurons of the CA1/subicular region in the ventral hippocampus project directly to the prelimbic area (PrL) of the PFC. Sb, subiculum. Inset: increase in plasma corticosterone levels observed in stressed rats immediately after removal from the platform.

stress (for details see Materials and Methods), with a significant and dramatic increase in plasma corticosterone levels at the end of the 30 min period of stress when compared to nonstressed rats ($n = 8$; 901.2 ± 112.2 and 60.1 ± 13.3 ng/ml in stressed and nonstressed rats, respectively; $P < 0.001$; Fig. 1, inset). When tetanic stimulation was applied in the ventral hippocampus within 180 min after the end of the stress period, LTP in the PFC was completely blocked during the 120 min post-tetanus recording ($n = 8$; $108.3 \pm 6.6\%$ and $98.1 \pm 5.1\%$ during the first 30 min after HFS and last 30 min of recording; $P > 0.05$) when compared to pre-HFS baseline (Fig. 2). In nonstressed rats, tetanic stimulation of the hippocampus induced a robust LTP characterized by a significant and long-lasting increase in the amplitude of the cortical PSP ($n = 6$; $138.1 \pm 8.8\%$ and $126.3 \pm 5.5\%$ during the first 30 min after HFS and last 30 min of recording; $P < 0.01$) when compared with pre-HFS baseline (Fig. 2).

Effects of Antidepressants

In stressed rats treated with an acute injection of the antidepressant tianeptine (10 mg/kg i.p.) 40 min prior to hippocampal HFS, a stable and long-lasting LTP was induced in the PFC ($n = 9$; $141.6 \pm 3.1\%$ and $126.0 \pm 3.4\%$ during the first 30 min after HFS and last 30 min of recording; $P < 0.001$) when compared with pre-HFS baseline (Fig. 3a). Tianeptine thus fully prevented the stress-induced suppression of LTP ($P < 0.01$) when compared to stressed rats injected with saline ($n = 8$; $111.1 \pm 7.3\%$ and $102.1 \pm 5.1\%$ during the first 30 min after HFS and last 30 min of recording; Fig. 5). Tianeptine was also active at 1 mg/kg i.p. (Fig. 3a). To assess the selectivity of this effect, tianeptine (10 mg/kg) was tested in another group of stressed animals on hippocampal-PFC synaptic responses

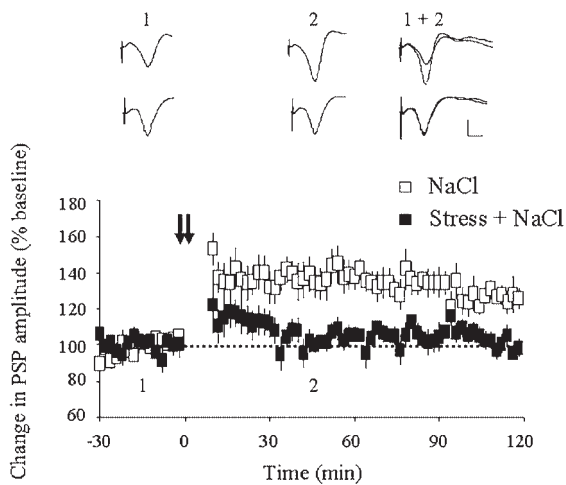


Figure 2. Acute inescapable stress (placing on an elevated platform, 30 min) produces long-lasting block of the hippocampal-PFC LTP in rats, which were subsequently anaesthetized. Hippocampal HFS failed to induce LTP in the PFC of anaesthetized rats within 180 min following the end of the stress period. Values are mean \pm SEM of the normalized hippocampal-PFC post-synaptic response amplitude. HFS is represented by arrows. Inset: representative average waveforms (four) from one experiment were taken at the times indicated by the numbers. Horizontal bar = 10 ms; vertical bar = 0.2 mV.

evoked after low-frequency stimulation (LFS) of the hippocampus: tianeptine did not affect the amplitude of synaptic responses ($n = 5$; $103.3 \pm 8.5\%$ and $86.1 \pm 6.4\%$ during the first 30 min after LFS and last 30 min of recording; $P > 0.05$) when compared with pre-LFS baseline.

In nonstressed rats, tianeptine (10 mg/kg i.p.) did not affect the robustness of the synaptic response to HFS ($n = 7$; $143.6 \pm 7.2\%$ and $137.1 \pm 11.2\%$ during the first 30 min after HFS and last 30 min of recording; $P > 0.05$) when compared to nonstressed rats injected with saline ($n = 6$; $138.1 \pm 8.8\%$ and $126.3 \pm 5.5\%$ during the first 30 min after HFS and last 30 min of recording; Fig. 3b). In these rats, hippocampal-PFC neurotransmission (pre-HFS baseline) was not affected by tianeptine (Fig. 3b).

In stressed rats treated with an acute injection of the antidepressant fluoxetine (10 mg/kg i.p.) 40 min prior to hippocampal HFS stimulation, a short LTP lasting 1 h was induced in the PFC ($n = 10$; $137.3 \pm 9.1\%$, $P < 0.001$ and $125.7 \pm 9.4\%$, $P < 0.05$ during the first 30 min and the 30–60 min period after HFS) when compared with pre-HFS baseline (Fig. 4). After this 1 h period and until the end of recording, LTP was totally blocked ($108.0 \pm 10.1\%$ and $91.4 \pm 8.5\%$ during the 60–90 min and the 90–120 min period after HFS; $P > 0.05$; Fig. 4). Fluoxetine thus partially prevented the effect of stress for a short period of time ($P < 0.05$ before and $P > 0.05$ after, this 1 h period of recording) when compared to stressed rats injected with saline ($n = 8$; $111.1 \pm 7.3\%$ and $103.6 \pm 4.8\%$ during the first 30 min and the 30–60 min period after HFS; $105.9 \pm 4.1\%$ and $91.4 \pm 8.5\%$ during the 60–90 min and the 90–120 min period after HFS; Fig. 5).

The respective potencies of the drugs in preventing the effects of stress on hippocampal-PFC synaptic plasticity are shown in Figure 5. Although all drugs had a significant effect on the early stages of LTP, tianeptine had a longer-lasting effect in preventing the effects of stress on LTP than fluoxetine.

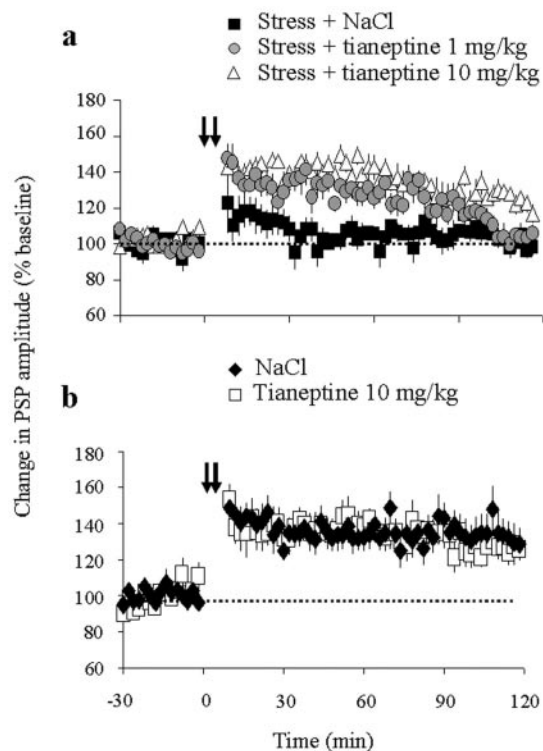


Figure 3. Effects of the antidepressant tianeptine upon LTP induced in the PFC. (a) Stressed rats. Both doses of tianeptine restore LTP from stress-induced impairment with a longer lasting effect at the highest dose. (b) Unstressed rats. Tianeptine (10 mg/kg) does not affect LTP. Values are mean \pm SEM of the normalized hippocampal-PFC post-synaptic response amplitude. HFS is represented by arrows.

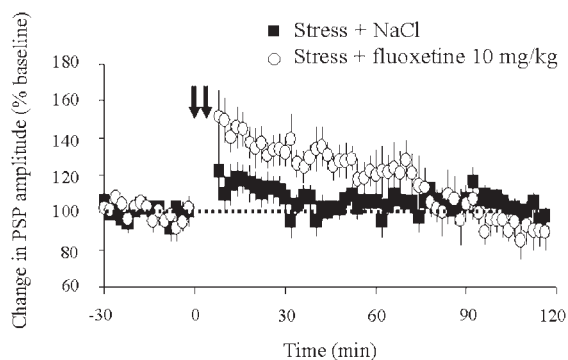


Figure 4. Effects of the antidepressant fluoxetine upon LTP induced in the PFC. Fluoxetine partially overcomes the stress-induced impairment in frontal LTP. Values are mean \pm SEM of the normalized hippocampal-PFC post-synaptic response amplitude. HFS is represented by arrows.

Discussion

Stress and LTP

The present study shows that acute platform stress in rats caused a remarkable and long-lasting inhibition of LTP in the frontal cortex evoked by stimulation of hippocampal outflow. This result extends to the frontal cortex the inhibitory effect of stress on LTP in the hippocampus firstly demonstrated by Foy *et al.* (1987; for a review, see Kim and Diamond, 2002). Thus,

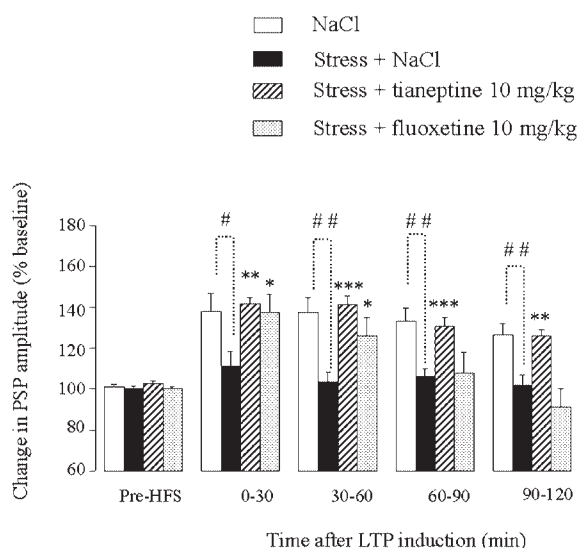


Figure 5. Comparison of the effects of tianeptine and fluoxetine on stress-induced impairment in hippocampal–cortical LTP at different time points. The first and following groups of columns represent, respectively, 30 min periods of mean \pm SEM of the normalized hippocampal–PFC postsynaptic response amplitude before and after tetanus. # $P < 0.05$ and ## $P < 0.01$ between nonstressed and stressed rats with HFS stimulation; * $P < 0.05$, ** $P < 0.01$ and *** $P < 0.001$ between drug- and NaCl-pretreated stressed rats.

the hippocampal–frontal circuitry, which is important for spatial and temporal context, is particularly sensitive to stress. By using a similar protocol for inducing stress, previous work has suggested that glucocorticoid receptor activation mediates the stress-induced inhibition of LTP in the CA1 region of the hippocampus (Diamond *et al.*, 1992; Xu *et al.*, 1998). Stress and glucocorticoids may inhibit LTP (Xu *et al.*, 1997) by favouring LTD. This impairment in synaptic plasticity may be responsible for the acute deleterious effect of glucocorticoids on memory and, in chronic situations, for hippocampal atrophy. The frontal cortex could also be a target for glucocorticoids involved in the stress response since administration of glucocorticoids induces a dendritic reorganization in pyramidal neurons of the medial PFC (Wellman, 2001).

Reversal of Stress-induced Impairment in LTP by Antidepressants

The frontal area studied corresponds, in so far as it is possible to predict across species, to the area of the anterior cingulate cortex in humans, where a decreased activation has been repeatedly found in depression (see Introduction). Our aim in this study was to test if antidepressants of various types had beneficial effects on the plasticity at the hippocampal–frontal circuitry, impaired by stress. In agreement with a recent report addressing these effects on LTP in intrinsic hippocampal circuits (Shakesby *et al.*, 2002), we demonstrate that tianeptine rapidly (40 min) reverses the inhibitory effects of stress on LTP at hippocampal–prefrontal synapses without affecting the baseline excitatory transmission. Our field response, previously identified through unit recordings, is a predictive marker of LTP on the extrinsic pathway linking the hippocampus to the PFC. So, these recordings reflect an effect on plasticity which may ultimately be expressed in terms of neuronal connectivity and cognitive function. This beneficial outcome

on neuronal plasticity could be explained by direct effects of tianeptine on glutamatergic systems. The increase induced by tianeptine in CA1 firing *in vivo* and excitatory post synaptic potentials amplitude in the CA1 field following Schaffer collateral stimulation *in vitro* (Dresse and Scuvee-Moreau, 1988; Spedding *et al.*, 1998) could facilitate the glutamatergic input to the frontal cortex. Furthermore, frontal LTP in our paradigm is dependent on dopaminergic tone, with dopamine acting predominantly on the D1 receptors involved in the selective gating of information flow from the hippocampus (Gurden *et al.*, 1999, 2000) and previous work has shown that a normal range of dopamine with an optimal level of D1 receptor activation appears necessary for efficient signalling, i.e. functional glutamatergic inputs to prefrontal neurons (for a review, see Goldman-Rakic *et al.*, 2000). Tianeptine at the highest dose tested here causes an increase in dopamine in the frontal cortex for at least 120 min (Sacchetti *et al.*, 1993).

Interestingly, fluoxetine which raises extracellular dopamine but also serotonin in the PFC (Pozzi *et al.*, 1999; Bymaster *et al.*, 2002) did restore partially LTP after stress in our study. Thus, systemic administration of two different types of drugs that both enhance dopamine in the PFC to a limited degree but have an opposite effect on 5HT restores plasticity on the hippocampal–prefrontal pathway. Tianeptine has also direct effects on glutamatergic transmission (Spedding *et al.*, 1998). These results raise the possibility that the restoration of plasticity in the PFC has a role in the antidepressant properties of these drugs. Future studies need to consider the effects of other SSRIs (citalopram) that produce robust increases in extracellular prefrontal 5HT without significant changes in prefrontal dopamine (Bymaster *et al.*, 2002).

Antidepressant effects may be obtained by several mechanisms, such as inhibition of serotonin uptake, for fluoxetine. Tianeptine is an antidepressant which is well tolerated in the aged and does not resemble serotonin uptake inhibitors (Wilde and Benfield, 1995; Saiz-Ruiz *et al.*, 1998). This drug is active in recent models of depression associated with stress, in rats as well as in tree shrews, although, as with the other recent antidepressant, less active in classic antidepressant models. In rats, tianeptine reverses hippocampal atrophy, compartmental changes and spatial memory dysfunction caused by stress or glucocorticoids (Conrad *et al.*, 1999; Magarinos *et al.*, 1999).

The drug reverses the dendritic atrophy in hippocampal pyramidal CA3 neurones caused by chronic restraint stress or administration of glucocorticoids (Watanabe *et al.*, 1992; Conrad *et al.*, 1999; Magarinos *et al.*, 1999) while other antidepressants such as fluoxetine do not prevent dendritic atrophy in this model (Magarinos *et al.*, 1999). Furthermore, chronic administration of tianeptine to tree shrews prevents both hippocampal atrophy and altered neurogenesis in the dentate gyrus induced by social stress (Czeh *et al.*, 2001). Consistent with a hippocampal mechanism, tianeptine improves memory retention in rats with partial lesion of an afferent pathway to CA3, the medial septum (Morris *et al.*, 2001). Thus, this drug has been shown to have a strong impact on the deleterious effects of stress in the hippocampus and our data extend these effects to the frontal cortex, even at low doses.

The current data show that antidepressants of various types, i.e. tianeptine and fluoxetine, at doses normally used in antidepressant testing, restore LTP impaired by prior acute stress. Reversal of the effects of stress in this paradigm can be

considered as a further indication that the hippocampus–PFC circuitry is important in depression. These effects are acute, but such effects on plasticity, if maintained over long periods, would result in major chronic changes in these key brain areas, seen in depression.

The major importance of this animal model is that it includes both plasticity at hippocampal to PFC synapses, a neural circuitry which is known from human neuroimaging studies to be affected in depression, and stress, recognized as a vulnerability factor in this disease. Antidepressants are able to reverse stress-induced impairments in plasticity. We propose that an imbalance between hippocampal, perhaps amygdala (Almaguer-Melian *et al.*, 2003; Maroun and Richter-Levin, 2003) and frontal systems may represent an important aspect of psychiatric diseases, in that the development of a disproportion of context and emotive stimuli would allow anxious or depressed behaviour: restoration of a normalized functional balance in the stressed state would be an alternative means of obtaining anxiolytic and antidepressant effects. Antidepressants may act via restoring function in hippocampal/frontal circuits and this may also explain their action as anxiolytics by restoring context in the presence of inappropriately controlled emotive drive.

Under such conditions animal models are needed which represent the transnosographical reality of clinical disease: this model is being used to reveal potential new drug therapies.

Notes

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