Behavioural Brain Research 291 (2015) 299–305

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Short Communication

Altered local field potential activity and serotonergic neurotransmission are further characteristics of the Flinders sensitive line rat model of depression

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HIGHLIGHTS

- FSL rats show elevated levels of serotonin in most cortical and subcortical brain regions.
- FSL rats show decreased alpha, beta and low gamma oscillatory activity in the medial prefrontal cortex and nucleus accumbens.
- Findings strengthen the translational validity of the FSL rat model of depression.

ARTICLE INFO

Article history:
Received 1 April 2015
Received in revised form 11 May 2015
Accepted 13 May 2015
Available online 27 May 2015

Keywords:
Major depression
Flinders sensitive line rats
Serotonin
Local field potentials

ABSTRACT

A significant portion of patients suffering from major depression remains refractory to available antidepressant treatment strategies. This highlights the need for a better understanding of the underlying neuropathology in order to develop rationale-based treatments. Here we aimed to further characterize neurobiological abnormalities of the Flinders Sensitive Line (FSL) rat model of depression. Biochemically, in FSL rats we mainly found increased levels of serotonin in most cortical and subcortical brain regions when compared to controls. Using electrophysiological measurements, in FSL rats we found decreased alpha, beta and low gamma oscillatory activity in the medial prefrontal cortex and nucleus accumbens and decreased alpha and beta as well as increased low gamma oscillatory activity in the subthalamicus nucleus when compared to controls. In summary, we show distinct neurochemical properties in combination with particular oscillatory activity patterns for brain areas thought to be pathophysiologically relevant for depression. Our data contribute to the further understanding of neurobiological alterations in the FSL rat model of depression that could provide a basis for research into future therapeutic strategies.
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1. Introduction

Major depression (MD) is a disabling psychiatric disorder estimated to affect 350 million people worldwide. Many of the patients do not respond sufficiently to either single or combined treatments, or even remain treatment refractory. A better understanding of how therapeutic strategies distinctly interact with MD pathophysiology is mandatory for a rationale-driven and more efficient selection of treatment options. Well-characterized animal models of MD allow for the investigation into neural substrates underlying depressive symptoms, thereby providing a basis for research into the pathophysiological and therapeutic mechanisms as well as potential new treatments.

The Flinders Sensitive Line (FSL) rat model exhibits a phenotype that matches many of the main symptoms of MD. FSL rats exhibit increased behavioral despair, display anhedonia after exposure to stress and tend to not develop active avoidance behavior in learned helplessness scenarios [1]. Behavioral deficits are paralleled by dysregulations in the serotonergic, cholinergic [1,2] and neuropeptide Y system [3]. These systems are also affected in MD patients. Further, all groups of clinically effective antidepressant therapies have

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http://dx.doi.org/10.1016/j.bbr.2015.05.027
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also been demonstrated to reduce swim test immobility in FSL rats [1]. These range from SSRIs and tricyclics [4] to electro-convulsive therapy [3] and deep brain stimulation (DBS) [5,6]. However, as basic knowledge of the neural processes underlying depressive symptomatology is still lacking, the mechanisms by which these different therapeutic strategies distinctly alter pathology remain unknown.

The aim of the present study was to further elucidate biochemical properties and neural population activity of several brain regions in FSL rats, with primary focus on the ventromedial prefrontal cortex (vmPFC, rodent equivalent of the subgenual cingulate (Cg25)), the nucleus accumbens (Nacc), and the subthalamic nucleus (STN). The Cg25 has been shown to exhibit abnormal metabolic activity in imaging studies of MD patients, which can be normalized by successful antidepressant treatment [7]. The Nacc is suggested to play a key role in anhedonia as well as deficits in reward processing in MD patients [8]. Both brain sites have successfully been tested for antidepressant DBS, in patients [7,9] and in rodents [6,10,11]. In contrast DBS of the STN has been associated with induction of depression-like symptoms in Parkinson's disease (PD) patients ([12]) as well as in rats [13].

2. Methods

Rats were housed in a temperature- and humidity-controlled vivarium with 12-h light dark cycle (lights on 06:00 a.m.) with food and water available ad libitum. The study was carried out in accordance with the European Communities Council Directive of 24th November 1986 (86/609/EEC) and after approval of the Senate of Berlin. All efforts were made to reduce animal suffering and number of animals used. For studying biochemical properties, post mortem HPLC was applied as described previously [14]. Briefly, 10 FSL and 10 control rats (Flinders resistant line (FRL) rats) were decapitated and micropunches were taken from 0.5 to 1 mm thick brain slices from mPFC (subdivided into the anterior cingulate (AC), prelimbic (PL, correspondent to vmPFC), and infralimbic (IL) cortices), ventrolateral (vl) and dorsolateral (dl) orbito frontal cortex (OFC), thalamus (Thal), hippocampus (Hipp), Nacc, caudate putamen (CPu), entopeduncular nucleus (EP, rodent equivalent to human globus pallidus (GP) internus), GP externus and STN. Monoamines (dopamine (DA), serotonin) and their metabolites (DOPAC, HVA, 5-HIAA) were separated on a column (ProntoSil 120-3-C18-SH; Bischoff Analysentechnik und -geräte GmbH, Germany) and electrochemically detected (Chromsystems Instruments & Chemicals GmbH, Germany). Glutamate and GABA were precolumn-derivatized with *o*-phthalaldehyde-2-mercaptoethanol, separated on a column (ProntoSil C18 ace-EPS) and detected by their fluorescence at 450 nm after excitation at 330 nm. For studying electrophysiological properties, local field potentials (LFPs) were recorded under urethane anesthesia (1.2 g/kg i.p., Sigma–Aldrich, Germany) from 7 FSL and 5 control rats. Monopolar recording electrodes (polyimide insulated stainless steel, 0.125 mm, Plastics One, USA) were implanted ipsilaterally into the left vmPFC, Nacc shell and STN at the following coordinates with respect to bregma: vmPFC: AP = 3.5, ML = 0.6, DV = −3.4, Nacc: AP = 1.2, ML = 1.8, DV = −8.1, STN: AP = −3.6, ML = 2.5, DV = −7.6 [15]. Recordings were referenced against 1.2 mm steel screws affixed to the skull in close proximity to each recording electrode. Signals were bandpass filtered (0.05 Hz–300 Hz), amplified, sampled at 1 kHz and digitized using a programmable neuronal data acquisition system (Omniplex, Plexon, Texas, USA). Recordings were conducted over a period of five hours. Offline data from the vmPFC were inspected visually to identify and analyze epochs (20–50 s) of robust activated synchronization states (AS) which have been shown previously to reflect signals of awake behaving rats [16]. The same time segments identified to show robust AS in the vmPFC were also used for analysis of LFPs from the Nacc shell and the STN. Power spectral densities of the LFP data segments were calculated by employing the Fast Fourier Transform function (Spike 2 Version 6 data analysis software; Hanning Window (1024 ms), 0.9766 Hz resolution). Frequency spectrum was divided into five classical EEG bands [5]: theta (4–8 Hz), alpha (8–12 Hz), beta (12–30 Hz), low gamma (30–45 Hz) and high gamma (60–100 Hz). Power spectra were normalized to total power between 103 and 147 Hz and 153–197 Hz. Power was averaged across the specific frequency bands and further expressed in arbitrary units (a.u.).

Correct electrode tip placements were histologically verified. Biochemical data were subjected to one-way ANOVAs and electrophysiological data to *t*-tests. The chosen level of significance was $p < 0.05$.

3. Results

When compared to controls, FSL rats showed increased levels of serotonin and its metabolite 5-HIAA across all cortical regions investigated as well as in the DM, EP and GP. In the Nacc, serotonin but not 5-HIAA ($p = 0.066$) was increased whereas in the hippocampus 5-HIAA but not serotonin was increased; no difference was found for CPu and STN (Table 1 and Fig. 1). FSL rats further showed increased levels of glutamate in the Nacc and of GABA in the GP. LFP recordings displayed decreased oscillatory activity across all regions in the alpha (vmPFC: $t = 2.347$, $p = 0.047$; Nacc: $t = 3.436$, $p = 0.009$, STN: $t = 4.574$, $p = 0.002$) and beta band (vmPFC: $t = 3.574$, $p = 0.001$; Nacc: $t = 4.628$, $p < 0.001$; STN: $t = 4.224$, $p < 0.001$) in FSL as compared to control rats, whereas theta (vmPFC: $t = 0.382$, $p = 0.716$; Nacc: $t = -0.884$, $p = 0.411$; STN: $t = -0.042$, $p = 0.968$) and high gamma band oscillatory activity (vmPFC: $t = -0.795$, $p = 0.429$, Nacc: $t = 0.311$, $p = 0.756$; STN: $t = -0.490$, $p = 0.626$) were not changed across groups. With respect to low gamma activity, we found a region-specific dissociation with FSL rats showing decreased activity in the vmPFC ($t = 2.297$, $p = 0.028$) and Nacc ($t = 3.137$, $p = 0.004$) and increased activity in the STN ($t = -2.192$, $p = 0.036$) when compared to controls (Fig. 2).

4. Discussion

The goal of the present study was to further characterize biochemical and neural population activity in the FSL rat model of depression. On the biochemical level, we found increased levels of serotonin and its metabolite 5-HIAA in FSL as compared to control rats in several cortical and subcortical structures. This data adds on to what has been documented before. Increased levels of serotonin and 5-HIAA have previously been reported for the hypothalamus, hippocampus, Nacc and prefrontal cortex of FSL rats and suggested to reflect a compensatory mechanism for reduced availability of serotonin receptors [17]. Further, it was shown that behaviorally effective antidepressant treatment in FSL but not in naïve rats [2] is associated with a downregulation of serotonin levels. These data translationally implicate a prominent role of the serotonin system in MD pathology. However, patient data are not consistent with evidence showing no alteration, decreases as well as increases of the serotonergic system in MD (for review [18]). By now, it is widely acknowledged that depression is not a uniform disorder resulting from a mere monoaminergic deficit but a more heterogeneous syndrome arising from dysfunctional neural circuits. It is therefore plausible that different neurobiological states underlie different behavioral symptom profiles [19]. In FSL rats the depressive phenotype seems to be mostly associated with increased, intracellular, levels of serotonin. As such, the FSL rat model might constitute an approach to specifically investigate increased serotonergic activity

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