Multimodal early-life stress induces biological changes associated to psychopathologies

Lívea Dornela Godoya, Eduardo H.L. Umeokab, Deidiane Elisa Ribeiroc, Victor Rodrigues Santosb, José Antunes-Rodriguesa, Samia Regiane Lourenço Joca, Norberto Garcia-Cairasoc,⁎

a Physiology Department, Ribeirão Preto School of Medicine, University of São Paulo, Brazil
b Neurosciences and Behavioral Sciences Department, Ribeirão Preto School of Medicine, University of São Paulo, Brazil
c Translational Neuropsychiatry Unit, Department of Clinical Medicine, Aarhus University, Denmark

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ABSTRACT

Evidences suggest the contributive role of early-life stress (ELS) to affective and anxiety disorders. Chronic exposure to the same stressor may generate habituation, while the exposure to different and repeated stressors gradually promotes maladaptive plasticity. Therefore, to further understand the effects of heterotypic stressors during early life period, male Wistar rat pups (P1-P21) were exposed to Multimodal ELS paradigm. Results indicate pups did not habituate to multimodal ELS and neonates respond to both physical and psychogenic stressors. Adult rats that underwent ELS protocol showed significant lower sucrose intake, decreased latency to immobility in the forced swim test and increased latency to light compartment in the light-dark test when compared to control group. Although it has been shown that ELS-induced changes in hippocampus can be used as biomarkers, multimodal ELS did not significantly alter BDNF, Tyrosine Kinase B (TrkB) receptor expression or neurogenesis in the hippocampus. Taken together, these findings indicate that multimodal ELS protocol can be an interesting experimental model for understanding long-term psychiatric disorders associated with stress. Indeed, our data with neurogenesis, BDNF and TrkB, and conflicting data from the literature, suggest that additional studies on synaptic plasticity/intracellular cascades would help to detect the underlying mechanisms.

1. Introduction

Adversities in early life are associated with vulnerability to psychopathologies later in life, resulting in long-term impact in emotional function (Chrousos, 2009; Gold et al., 1988; Heim and Nemeroff, 2002; Jurjena, 2013; Lippmann et al., 2007; Lupien et al., 2009).

Patients suffering with stress-related psychiatric disorders appear to be especially sensitive to the effects of early life stress (ELS), which is supported by epidemiological data (Baes et al., 2014; Jurjena, 2013). For instance, traumatic childhood experiences such as abuse, neglect and parental losses increase the incidence of Major Depression (MD) (Anda et al., 2006) which could reach in adult life between 59% and 75% (Widom et al., 2007). Depression affects millions of people and causes significant impairments on patient's quality of life (Ustün et al., 2006). Epidemiological data ranks depression in the top fourth causes of global burden of disease (Mathers and Loncar, 2006; Murray and Lopez, 1997), thus representing a serious problem of public health worldwide. Projections estimate that in 2020 nearly one in ten people on the planet (676 million) will present a depressive episode (World Health Organization, 2017).

Anxiety disorders are often observed as comorbid with depression, indicating common neurobiological mechanisms between these mental illnesses (Craske et al., 2009; Craske and Stein, 2016). People that experience early emotional traumas are 1.9 to 3.6 fold more likely to develop anxiety disorders (Fernandes and Osório, 2015). Depression-anxiety comorbidity is strongly associated with impairment in health, as well as in emotional functions (Kroenke et al., 2007).

A better understanding of how stress in early life impacts brain and behavior in adulthood is, therefore, of fundamental importance to the study of the neurobiology of psychiatric disorders. Although plenty of evidences indicate that ELS exposure leads to behavioral changes in adulthood (Bale et al., 2011; Gee and Casey, 2015; Lai and Huang, 2011; Loi et al., 2014; Lupien et al., 2009; Walker et al., 2017), there are some reports proposing that there is a period during early life in which the response to stress is reduced or absent, also known as the stress hyporesponsive period (SHRP). Interestingly, ELS experiences can
is in fact complex and not completely understood (Castrén and Rantanäki, 2010). Nevertheless, a clear direction (increase vs decrease) of the expression of either hippocampal BDNF or TrkB after ELS has not been detected (Daskalakis et al., 2015), neither it has been reported a distinction between dorsal and ventral hippocampal sub-regions. Additionally to BDNF-TrkB signaling, disturbed adult neurogenesis may also contribute to hippocampus malfunctioning and symptom development in depressed patients (Lee et al., 2013).

Therefore, it is conceivable that the controllability and predictability of stimuli are important developmental determinants for the adult capacity to cope with environmental demands (Koolhaas et al., 2011). Considering this, our study investigated the effects of a new variable protocol of early life stress on behavioral and molecular changes related to depression, later in adulthood, with the aim to provide a new framework for understanding how changes in neuroendocrine function and their relationship with depression and anxiety behavior can be better explored.

2. Material and methods

2.1. Animals

Female rats between 18 and 21 days of pregnancy were acquired from the Central Vivarium of the University of São Paulo, Ribeirão Preto Campus (USP-RP) and monitored twice a day until birth. Animals were housed in transparent acrylic boxes (45x32x17cm), at the Animal Facility of the Physiology Department of the Ribeirão Preto School of Medicine at the University of São Paulo, under controlled ventilation and temperature (25 ± 2°C) with light/dark cycle of 12h (lights on 7:00 A.M.) and with free access to water and regular chow. After birth, litters were culled to 6 males and 2 female pups. On PND21, the pups were weaned and males were separated. In all protocols described below, procedures (undisturbed or stress) were applied to the entire litter, which were randomly assigned. Different batches of animals were used in each experiment (Table 1).

All procedures involving animals were conducted accordingly to the Ethical Principles in Animal Experimentation, avoiding unnecessary or intentional pain and discomfort. This study was approved by the Ribeirão Preto Medical School - USP Ethics Committee (CETEA) under the protocol number 80/2014.

2.2. Experiment 1—effects of different modalities of acute stresses during early life on plasmatic corticosterone concentration

To test the hypothesis that pups present a different hormonal response to different modalities of stresses, naïve animals at PND12 were acutely exposed to different modalities of stresses (same employed on ELS protocol). Maternal separation for 60 min (n = 8) or 10 min (n = 6); restraint with agitation for 60 min (n = 8) or 10 min (n = 8); cold exposure for 10 min (n = 8); propylene glycol injection (n = 8) or an undisturbed control group (n = 19). After stressor exposure animals were returned to their homecages and were decapitated 30 min after the end of each stressor. Trunk blood was collected between 8:00 and

Table 1

<table>
<thead>
<tr>
<th>Condition</th>
<th>P3</th>
<th>P12</th>
<th>P21</th>
<th>P22</th>
<th>P82-92</th>
<th>P88-94</th>
<th>P90-94</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experiment 1</td>
<td>Acute multiple stresses on P12</td>
<td>Trunk blood</td>
<td>Trunk blood</td>
<td>Trunk blood</td>
<td>Trunk blood/HPA axis organs</td>
<td>6–19</td>
<td></td>
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<tr>
<td>Experiment 2</td>
<td>Multimodal ELS 1-21</td>
<td>Trunk blood</td>
<td>Trunk blood</td>
<td>Trunk blood</td>
<td>8–17</td>
<td></td>
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<tr>
<td>Experiment 3</td>
<td>Multimodal ELS 1-21</td>
<td>SCT</td>
<td>FST</td>
<td>Trunk blood/fresh brain collection/HPA axis organs or perfusion</td>
<td>12–14</td>
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<tr>
<td>Experiment 4</td>
<td>Multimodal ELS 1-21</td>
<td>SCT</td>
<td>LDT</td>
<td>Fresh brain collection</td>
<td>10–13</td>
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</tr>
</tbody>
</table>

SCT = sucrose consumption test, FST = forced swim test, LDT = light dark test.
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