The Complexity of Reliably Investigating Effects of Novelty Stress in Rats: Dynamics and Correlations of Behavioral, Cardiovascular, Endocrinological and Electroencephalographic Responses Under Simultaneous Measurement

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ABSTRACT

Stress research in animals is generally hampered by limited possibilities to measure various relevant stress parameters simultaneously and by confounding stress effects of sampling procedures. The aim of this study is to analyze correlations between physiological, hormonal, electroencephalographic (EEG) and behavioral stress parameters, and their dynamics, under strictly controlled conditions with minimized confounding factors due to sampling procedures.

Therefore, stress parameters were measured simultaneously in freely-moving rats both under undisturbed, well-habituated home cage conditions and after novel cage exposure, which is considered a mild psychological stressor with good face validity and translational value.

First, male Sprague-Dawley rats were implanted with a telemetry transmitter for blood pressure, heart rate, body temperature, locomotor activity and cortical EEG and with a jugular catheter for blood sampling. Next, using a Williams experimental design, novelty stress was induced for 15 min by placing a rat in a new, clean, empty home cage. Telemetric read-outs (Data Sciences Instruments: TL11M2-C50-PXT) and home cage behavior (analysis via The Observer XT) were recorded and analysed off-line. Simultaneously, blood was sampled automatically every 10 min to determine plasma corticosterone levels.

Novelty exposure induced increases in sniffing behavior (66.3 ± 6.3% vs. 1.5 ± 1.4%, $p<0.001$), in rearing (9.2 ± 1.6% vs. 0.4 ± 0.3%, $p<0.001$) and in grooming (18.2 ± 6.2% vs. 2.6 ± 1.4%, $p<0.02$), together with a reduction in immobility (0.4 ± 0.4% vs. 84.3 ± 11.8%, $p<0.001$). This indicates that the animals were behavioral active during the exposure to novelty. During the first 20 min after this exposure to novelty, an increase in sniffing (11.7 ± 1.6% vs. 0.5 ± 0.2%, $p<0.001$), rearing (1.5 ± 0.7% vs. 0.0 ± 0.0%, $p=0.037$), grooming (18.0 ± 2.5% vs. 4.4 ± 2.0%, $p=0.001$), immobility (41.0 ± 10.2 % vs. 93.3 ± 2.5%, $p<0.001$) remained and an increase in food uptake (19.0 ± 9.2% vs. 0 ± 0%, $p=0.045$) was induced. During novelty exposure, behavioral changes concurred with an increase in blood pressure (max 14.8 ± 2.9 mm Hg), heart rate (max 102.5 ± 9.3 bpm), body temperature (max 1.0 ± 0.2 °C), locomotor activity (max 22.2 ± 2.5 counts/min) and plasma corticosterone (max 131.9 ± 24.7 ng/ml). The latency to reach these maximum response values varied across parameters. Analyses of the EEG in terms of vigilance states showed results that were in accordance with these behavioral observations. Values for all parameters remained stable under control conditions, while in the stressed situation values gradually returned to stable baseline levels. This confirms that our approach

allows un-confounded measurement of several parameters simultaneously.

In summary, novelty stress causes physiological, hormonal, electroencephalographic and behavioral response that can be reliably measured with different time profiles during and after mild stress exposure. Various interesting correlations between the different read-outs are identified which can now be interpreted in conjunction. It is concluded that the present outcomes confirm the added value of simultaneous assessment of multi-factorial stress effects under well-controlled, un-confounded conditions.