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Journal of Psychiatric Research 37 (2003) 249–259

JOURNAL OF PSYCHIATRIC RESEARCH

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Tail-suspension induced hyperthermia: a new measure of stress reactivity

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Received 18 June 2002; received in revised form 30 December 2002; accepted 2 January 2003

Abstract

The tail suspension test (TST), an antidepressant screening paradigm, uses the uncontrollable, inescapable stressor of tail suspension to elicit immobility. As hyperthermia occurs following numerous stressors, hyperthermia might exist following the TST. We tested whether tail suspension induced hyperthermia (TSIH) was a distinct variable for TST. Hyperthermia was measured by two methods: a rectal probe and a subcutaneously implanted microchip (ELAMS™). In outbred ICR male mice, TSIH was robustly demonstrated compared to control (No-TST) mice. TSIH peaked after TST and remained elevated at 120 min. Among five (129/SvEvTac, A/J, C57BL/6J, NMRI and ICR) strains examined for TSIH, significant strain variations were detected. NMRI showed the highest temperature rise (2.3 °C) and A/J mice showed the lowest (0.6 °C). Sex differences were found for the C57BL/6J and NMRI strains on TSIH. TSIH and duration of immobility were not significantly correlated ($r = 0.22$, $P = 0.17$) in outbred mice. Both duration of TST immobility and TSIH were measured when ICR male mice were administered diazepam, imipramine (a TCA antidepressant), venlafaxine (a SNRI antidepressant), sertraline and paroxetine (SSRI antidepressants), propranolol and nadolol (β-adrenergic receptor blockers), CP-154,526 (a CRF_1 receptor antagonist), and indomethacin (a cyclo-oxygenase inhibitor). Diazepam dose-dependently increased immobility and decreased TSIH. Propranolol blocked TSIH, but nadolol had no effect. Antidepressants showed more complex patterns of effects with venlafaxine, sertraline, and paroxetine inhibiting TSIH. TSIH demonstrated inter-strain variability, sex differences and a distinct pharmacology, suggesting that TSIH provides an independent, robust physiologic parameter to supplement the TST paradigm. This TSIH method may prove useful for pharmacologic, transgenic, and mechanistic studies.

Keywords: Hyperthermia; Stress; Sex differences; Strain differences; Tail suspension test; Emotion

1. Introduction

The regulation of body temperature is a highly evolved, physiologically regulated, and easily measurable trait with a complex network of homeostatic regulators (Boulant, 1997). While studies of fever have documented the roles of thermosensitive neurons in the hypothalamus, pyrogenic cytokines, and the pharmacology of anti-pyretic drugs (Mackowiak, 1997), the phenomena and etiology of "psychogenic fever" or emotional hyperthermia remain less well understood [reviewed (Oka et al., 2001)].

Emotional or stress induced hyperthermia (SIH) is the rise of body temperature following exposure to psychological stress and has been demonstrated across species (mice, rats, pigs and humans) (Borsini et al., 1989; Briese, 1995; Briese and De Quijada, 1970; Briese et al., 1991b; Groenink et al., 1994, 1995; Hajos and Engberg, 1986; Hasan and White, 1979; Kleitman, 1945; Lecci et al., 1990b; Renburn, 1960; Van der Heyden et al., 1997; Zethof et al., 1995). In humans, anticipatory anxiety seems sufficient to induce hyperthermia (Briese, 1995; Renburn, 1960). This rise in temperature provides one dimension of an acute stress response that varies among individuals. In rodents, mild psychological stressors inducing hyperthermia include placing animals in novel environments (e.g. an open field arena), restricting an animal's activity (e.g. restraint tube), noise, and handling animals in a variety of ways (e.g. cage change). In

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0022-3956/03/$ - see front matter © 2003 Elsevier Science Ltd. All rights reserved.
doi:10.1016/S0022-3956(03)00004-9

the "stress-induced hyperthermia" (SIH) paradigm, group-housed mice (e.g. 10–15 mice per cage) are sequentially removed at 1-min intervals and rectal temperatures are measured immediately upon removal (Lecci et al., 1990b; Zethof et al., 1994). While the first three mice show little change in temperature, by the 10th animal (10 min), there is a robust increase in temperature, which is maintained for 60-min after the procedure. Also, a singly housed mouse version of this technique has been developed with repeated disturbance as the stressor, offering an advantage when mice are a limiting resource (Van der Heyden et al., 1997). These robust SIH phenomenon in mice have been validated pharmacologically and interpreted as a stress reaction.

While studying the tail suspension test (TST), a well-validated antidepressant screening test (Porsolt et al., 1987; Steru et al., 1987), we hypothesized that hyperthermia might be induced in response to this uncontrollable, inescapable stressor. The rise in rectal temperature following tail suspension (i.e. tail suspension induced hyperthermia, TSIH) might also provide a simple method for assessing individual differences in acute stress responses in mice. The TST paradigm hangs a mouse by its tail for 6-min. A typical response in this paradigm is struggling alternating with passive immobility. The duration of immobility is accumulated throughout the 6-min period and temperature is taken after tail suspension. This duration of immobility has been the principal measure in the TST and this immobility is interpreted as a measure of "behavioral despair". Traditionally, antidepressants decrease the duration of immobility. These initial experiments tested the validity and utility of an acute rise of body temperature following the TST as a measure of stress reactivity. Further experiments attempted to validate the paradigm by (1) demonstrating genetic and sex variation in TSIH responses and (2) characterizing TSIH pharmacologically, distinguishing this hyperthermic measure as a unique aspect of the TST response.

2. Materials and methods

2.1. Animals

One outbred strain (ICR) and four inbred strains (129/SvEvTac = 129S6, A/J, C57BL/6J, and NMRI) of mice were used in these experiments. Inbred strains were selected to demonstrate strain differences as a way to validate the paradigm (Porsolt, 2000). The choice of particular inbred strains was based on the strains commonly used for transgenic analyses (129 and C57BL6) and those with sequenced DNA genomes (129, A/J, C57BL/6J). The Swiss-derived NMRI strain was included as the most commonly used and robust responding strain in the literature for the TST paradigm. A readily accessible (available in the USA), Swiss derived, general purpose outbred strain was selected to reduce cost and to provide generalizability. ICR and 129S6 strains were obtained from Taconic (Germantown, NY). A/J and C57BL/6J strains were obtained from the Jackson Laboratory (Bar Harbor, ME). Inbred NMRI mice were obtained from B & K Universal Ltd. (E. Yorkshire, UK). Mice arrived at 7 weeks of age. F1 mice were bred from 129S6 dams and NMRI sires at UTSW. These F1(NMRIx129) mice were part of an ongoing genetic experiments on the inheritance of the TSIH and provided a readily available isogenic strain. All mice were ear-notched or implanted with ELAMS^{TM} transponders (microchips) for identification, and permitted 1 week for acclimation to their new housing conditions prior to testing. All mice were housed in groups of four with food and water freely available. This housing density (four /cage) was empirically determined from preliminary experiments, showing that this cage density minimized the hyperthermic effect due to sequential removal. The animals were maintained under a 12 h:12 h light:dark cycle with lights on at 06:00 h. For the pharmacological experiments, all mice were naïve and used just one time. All experiments followed the NIH Guide for Care and Use of Laboratory Animals and were approved by the local animal institutional committee along with their suggestions for reduction of animal usage.

2.2. Tail suspension

Automated TST devices (Med Associates Inc., St. Albans, VT) were used to measure the duration (sec) of immobility in the tail suspension test as described in detail (Liu and Gershenfeld, 2001). Mice were suspended by the tail with tape to the apparatus. The apparatus automatically calculated the total duration of immobility during a 6-min TST period. After each trial, the testing cubicles were cleaned to remove olfactory cues with a diluted solution of a deodorizing detergent.

2.3. Body temperature

A digital thermometer (Ret-3 rectal probe and a Thermalert TH-5 thermometer, Physitemp, Clifton, NJ) was used in these experiments. Rectal temperature was measured by inserting the probe 2 cm into the rectum of the mouse, while gently restrained manually. The probe was dipped into silicon oil before insertion and was held in the rectum for about 20 s, permitting readings to stabilize. Temperatures were determined to the nearest 0.1 °C.

In order to minimize the handling stress associated with measuring core rectal temperature, the ELAMS^{TM} (Electronic Laboratory Animal Monitoring System by BioMedic Data Systems, Inc. Seaford, DE) was used to