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Research Report

Social factors modulate restraint stress induced hyperthermia in mice

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ABSTRACT

Stress-induced hyperthermia (SIH) was examined in three different social conditions in mice by thermographic measurement of the body surface temperature. Placing animals in cylindrical holders induced restraint stress. I examined the effect of the social factors in SIH using the thermograph (body surface temperature). Mice restrained in the holders alone showed SIH. Mice restrained in the holders at the same time as other similarly restrained cage mates (social equality condition) showed less hyperthermia. Interestingly, restrained mice with free moving cage mates (social inequality condition) showed the highest hyperthermia. These results are consistent with a previous experiment measuring the memory-enhancing effects of stress and the stress-induced elevation of corticosterone, and suggest that social inequality enhances stress.

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1. Introduction

The presence of a conspecific can modify an animal's response to stress, and this stress-reducing effect is called social buffering (DeVries et al. (2003) and Hennessy et al. (2009) for review). One crucial factor of social buffering is the relative relationship between the levels of stress experienced by each individual. For example, pain response induced by formalin injection was reduced by presence of other individuals suffering less pain but enhanced by presence of individuals with stronger pain in mice (Langford et al., 2006).

The purpose of the present experiment is to examine social factors that modify stress. Stress has a memory-enhancing effect on aversive experiences (Miracle et al., 2006; Roozendaal et al., 2009), and I have previously examined the modification of this memory-enhancing effect using three social conditions in mice (Watanabe, 2011b). Restraint stress enhanced aversive memory of a floor that delivered an electric shock. This enhancement was reduced when restraint stress was applied while cage mates were similarly restrained (social equality condition) and increased when restraint stress was applied while cage mates were free-moving (social inequality condition). Corticosterone levels, which act as a common stress proxy, were highest after restraint stress applied with free-moving cage mates and lowest after restraint stress applied with restrained cage mates. These results suggest that social equality reduces the intensity of stress whereas social inequality amplifies the intensity of stress.

I employed stress-induced hyperthermia (SIH) as an index of the stress in the present experiment. Stress causes several autonomic responses, including changes in heart rate, blood pressure, and respiration rate. Stress also raises body temperature (Bouwknecht et al. (2007) for review). A variety of stressors have been reported to induce hyperthermia,

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including a novel cage (Houtepen et al., 2011), social threat (Pardon et al., 2004), social defeat (Keeney et al., 2001), and restraint (Thornhill et al., 1979; van der Heyden et al., 1997; Van Eijl et al., 2006). SIH indicates a rise in the set point of thermoregulation (Oka et al., 2001) and has been used to examine the effect of anxiogenic drugs in rodents (see Vinkers et al. (2008) for review). Using contextual fear conditioning with shock, Kiyokawa et al. (2004) observed that the presence of unfamiliar rats reduced SIH. More interestingly, unfamiliar rats that had not experienced the electric shock were more effective in the SIH attenuation than those that had experienced the shock. Later experiments by the same researchers did not, however, support the social buffering of hyperthermia induced by tone-shock conditioning (Kiyokawa et al., 2007).

Rectal temperature has traditionally been used to measure the core temperature of animals (van der Heyden et al., 1997), though radio-telemetry has recently been employed to measure core temperature while avoiding the potential for handling and rectal measurement itself to induce a rise in body temperature (Conley and Hutson, 2007; Houtepen et al., 2011). Using a radiation thermometer, Hishimura and Itoh (2009) measured body surface temperature of ICR mice in a resident-intruder paradigm and observed SIH in the intruders, thus demonstrating that body surface temperatures rise in response to stress in a way that is analogous to the rise in core body temperatures. I employed a similar infrared radiation thermograph in this study. The technique non-invasively measures body surface temperature, and temperature of several animals can be measured simultaneously. I compared SIH measured by rectal temperature and thermograph (see Supplemental experiment).

The main aim of the present experiments was to understand whether the social equality and/or inequality influences SIH by restraint stress in mice. Using optogenetics Kataoka et al. (2014) showed activation the dorsomedial hypothalamus–raphe nuclei pathway resulted in hyperthermia. Thus, activation of the hypothalamo–raphe pathway by psychological stress causes SIH. Equality/inequality condition is higher social cognition and neocortical system, perhaps prefrontal system, processes such higher cognition. Sensitivity of SIH to the social condition indicates cortico-hypothamo-raphe system in stress. I compared SIH across three different social conditions, namely, single, equality and inequality conditions. In the single stress condition, the body surface temperature was measured in a free-moving state before the mouse was inserted into a holder. Each mouse was then inserted into a holder and the body temperature was measured 3 times through 60 min period. In the equality condition, all four animals in each cage were restrained in individual holders at the same time, and the holders were placed in a parallel arrangement facing the center of the living cage so that each animal could see all other animals. In the inequality condition, only one mouse in each cage was restrained in the holder, while the three other cage mates remained free to move around.

Restraining an animal in a holder may physically increase their body surface temperature. To assess the presence of a passive rise in body surface temperature, the change in body surface temperature after injection of pentobarbital was compared between free (non-restrained) and restrained conditions. Pentobarbital causes hypothermia, and therefore if restraint in the holder physically raises the body temperature or has a heat-insulating effect, the pentobarbital-induced reduction in body temperature will be less in the restraint condition than in the free condition.

2. Results

Fig. 1 presents results of the three social conditions. A one-way ANOVA of SIH revealed a significant effect of social conditions ($F(2,71)=7.09$, $P<0.005$). Restraint induced hyperthermia under each social condition (single group t-

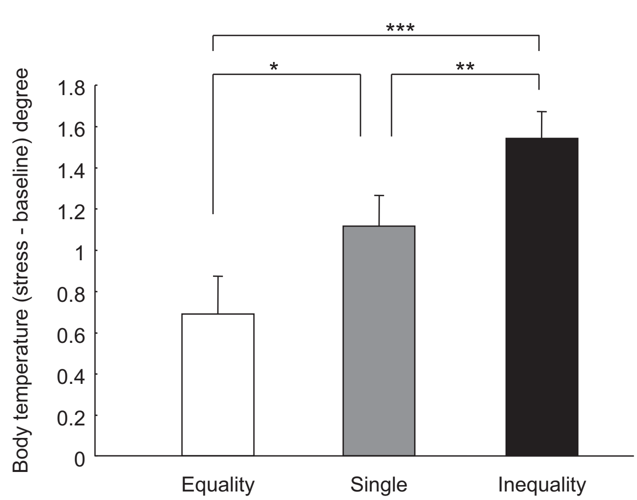

Fig. 1 – Hyperthermia induced by restraint stress. The vertical axis indicates difference in body temperature between baseline (before stress) and stress. Mice received restrain stress alone in the Single condition, the stress together with cage mates in the Equality condition and the stress with not-restrained cage mates in the Inequality condition. Each condition caused hyperthermia, but SIH (stress-induced hyperthermia) was greatest in the inequality condition. Vertical bars indicate SE. *$P<0.10$, **$P<0.05$, **$P<0.005$.

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