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Review article

Untangling the neurobiology of coping styles in rodents: Towards neural mechanisms underlying individual differences in disease susceptibility

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ABSTRACT

Considerable individual differences exist in trait-like patterns of behavioral and physiological responses to salient environmental challenges. This individual variation in stress coping styles has an important functional role in terms of health and fitness. Hence, understanding the neural embedding of coping style variation is fundamental for biobehavioral neurosciences in probing individual disease susceptibility. This review outlines individual differences in trait-aggressiveness as an adaptive component of the natural sociobiology of rats and mice, and highlights that these reflect the general style of coping that varies from proactive (aggressive) to reactive (docile). We propose that this qualitative coping style can be disentangled into multiple quantitative behavioral domains, e.g., flexibility/impulse control, emotional reactivity and harm avoidance/reward processing, that each are encoded into selective neural circuitries. Since functioning of all these brain circuitries rely on fine-tuned serotonin signaling, autoinhibitory control mechanisms of serotonergic neuron (re)activity are crucial in orchestrating general coping style. Untangling the precise neuromolecular mechanisms of different coping styles will provide a roadmap for developing better therapeutic strategies of stress-related diseases.

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1. Introduction

Health and disease are generally considered to be influenced by a rather complex interplay between environmental demands and the individual's capacity to deal or cope with these challenges. Throughout life, we are all exposed to stressors ranging from relatively minor daily hassles and worries to severe major life-events and life-threatening traumas. Remarkably, while the majority of

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individuals successfully adapts to these stressors and maintains healthy behavioral and physiological functioning, only a relatively small proportion of individuals develop stress-related illnesses. For example, more than two-thirds of people in the general population experience an uncontrollable traumatic stress event at some point in their lifetime, but only 10–15% develop post-traumatic stress disorder (Kessler et al., 2005; Galea et al., 2005). Similarly, only 20–25% of individuals exposed to stressful events develop major depression (Cohen et al., 2007). Clearly, it is not the average population that gets a certain stress-related disease, but usually susceptible individuals that display particular behavioral and physiological traits under rather specific environmental conditions (Yehuda et al., 2006). Moreover, different types of stress-pathology seem to be associated with distinct behavioral and physiological response patterns.

For ages, researchers have tried to determine the individual vulnerability for stress-related diseases using estimates of individuals' behavioral trait-characteristics, i.e., the temporal and contextual consistency of a behavior that characterize an individual. These attempts date back to the ancient times of Hippocrates who marked out four types of "temperamentums": choleric (hostile/impulsive), sanguine (optimistic/sociable), phlegmatic (calm/thoughtful) and melancholic (depressive/introvert). Each of these temperaments was supposed to reflect a particular behavioral attitude in dealing with everyday problems, and were thought to originate as a consequence of different mixtures of four bodily chemical components e.g., blood, yellow bile, black bile, and phlegm. Half a millennium later, Galenus picked out the melancholicus as being particularly prone to cancer and infectious diseases. Flash-forwarding to the 20th century, the hypothesis that personality influences the development and course of physical illness gained true momentum by the landmark studies of Friedman and Rosenman (1959), demonstrating that people which are hostile, easily angered, competitive, impatient and hard-driving (e.g., type "A" personality) are more prone to cardiovascular, metabolic and autoimmune diseases than their more relaxed type "B" counterparts (Friedman and Rosenman, 1971; Irvine et al., 1982; Dembroski and MacDougall, 1985; Krantz et al., 1989; Ravaja et al., 2000; Trigo et al., 2005; Smith and MacKenzie, 2006; Steptoe and Molloy, 2007; Sirri et al., 2012). In contrast, people with a more avoidant or passive coping style (so-called type "B" or "C" personality) that are characterized by behavioral patterns such as suppression of emotions (primarily anger), denial and avoidance of conflicts, were shown to have a higher risk for infectious diseases and cancer (Baltrusch et al., 1991; Zozulya et al., 2008). Despite ample clinical evidence that personality characteristics are connected to disease susceptibility, plausible neurobiological mechanisms underlying this link have not been clearly revealed yet.

Preclinical research using domesticated laboratory animals has long neglected the issue of individual disease vulnerability mainly because a reduction of individual variation through inbreeding and rigorous standardization has been the common experimental approach. However, even under highly standardized conditions it was clear that animals of the same sex and age within a given strain show consistent individual differences in their behavioral and physiological response patterns (coping style) to environmental demands (Koolhaas et al., 1999). As a matter of fact even in highly inbred laboratory strains, genetically identical subjects may be considerably more or less susceptible to similar experimental manipulations (Krishnan et al., 2007). Rather than viewing individual differences as a limitation or impediment to preclinical research, it should be considered a valid biological factor and focused on in any experimental animal model of human disease. The increasing acknowledgement of the biological significance of individual variation is currently starting a valuable paradigm shift in preclinical behavioral neuroscience studies, e.g., to focus more on individual phenotypic variations rather than solely on traditional group averages. For example, it appears to be essential to distinguish susceptible from resilient individuals on the basis of predefined behavioral and physiological characteristics (Ebner et al., 2005; Krishnan et al., 2007; Walker et al., 2009; Russo et al., 2012; Schmidt, 2011; Cavigelli et al., 2013; Wood, 2014; Holly and Miczek, 2016). As a matter of fact, clinical research routinely compares select "susceptible" patient groups with "resilient" healthy subject control groups. Hence, for translational validity it seems imperative to adopt this paradigm-shift to focus on and select for particular phenotypic variability.

Although traditionally most of these studies are conducted in the realm of biomedical sciences, there is also a rapidly growing interest of the biological significance of animal personality and/or behavioral and physiological differences among individuals in the science of ecology and evolutionary biology (Sih et al., 2004; Reale et al., 2007; Wolf et al., 2007; Van Oers et al., 2004; Dingemanse and Wolf, 2010). Recent ecological evidence shows that these coping styles should be considered as individual phenotypic adaptations to different environmental conditions. For example, a bird study of the fitness consequences of aggressiveness and/or boldness in the great tit *Parus major* showed that food availability in the field was a major determinant in the differential survival of fast- and slow-exploring animals from year to year (Dingemanse et al., 2004). Consequently, different personality types may ultimately obtain equal overall fitness in terms of gene preservation and will be maintained in the population given frequent alternation of the critical environmental conditions. Basically, resilience and vulnerability becomes a matter of match (adaptation) or mismatch (maladaptation) between expressed personality/coping style and actual or perceived environmental demands (Schmidt, 2011). Obviously, this individual variation in coping with everyday problems encountered in the natural habitat has important evolutionary-fitness consequences and apparently protects the species against fluctuations in their natural environment (Dingemanse et al., 2004; Øverli et al., 2007; Dingemanse and Wolf, 2010; Sih et al., 2004). The basic evolutionary biological concept is that certain individuals under particular environmental conditions have a higher fitness than others leading to a better survival, wider dispersal and higher reproduction. Hence, natural selection favors individuals that contribute most to the gene pool of the population (see Fig. 1). It is tempting to consider this adaptive explanation for the individual variation in animal coping styles as the biological origin of human affect, personality and temperament (Smith and Blumstein, 2008).

In this review, individual differences in trait-aggressiveness are presented as a fundamental and adaptively significant component of the natural sociobiology and ecology of rodents, and used as a starting point in the characterization of the neurobiological causes of stress coping styles in laboratory rats and mice. An important point highlighted in this review is that unraveling and probing this phenotypic variation neurobiologically is fundamental in not only understanding disease susceptibility/resiliency but also in the development of personalized approaches to precision treatments and/or strategies for curbing stress-induced diseases.

2. The sociobiology of feral rodents and individual variation in aggressiveness

Throughout the animal kingdom, aggression is one of the most conspicuous and widespread forms of social behavior that ultimately contributes to reproductive success and survival of individuals. Clearly, aggression is the behavioral weapon of choice for essentially all animals and humans to gain and maintain access to desired resources (food, shelter, mates), defend themselves and their offspring from rivals and predators, and establish and secure