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Full-length Review

Coping style and immunity in animals: Making sense of individual variation

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Abstract

Predicting the individual vulnerability to immune mediated disease is one of the main challenges of modern biomedical research. However, the question of individual behavioral and physiological characteristics that might predict this vulnerability has been subject of research and debate for a long time. This paper will argue that animal models aimed at individual vulnerability should consider the biological function of variation in nature. An increasing number of studies show the ecological significance of variation within a species. Based on behavioral studies in several vertebrate species two coping style can be distinguished. Variation in coping style appears to play a role in the population dynamics and the evolutionary fitness of the species. Coping styles are reflected in a stable differentiation in the behavioral and physiological stress responsiveness over time and across situations. Based on the observations that the individual level of offensive aggressive behavior (i.e., the tendency to defend the home territory) is strongly related to the way animals react to various other environmental challenges, it is argued that the individual's level of offensiveness is an important indicator and component of a more trait-like behavioral and physiological response pattern (coping style) to environmental demands. The coping style of aggressive animals is principally aimed at a (pro)active prevention or manipulation of a stressor whereas the non-aggressive individuals tend to passively accept or react to it. Proactive coping is associated with high sympathetic reactivity to stressors whereas the more passive or reactive coping style generally has a higher HPA axis reactivity. In view of the immune modulating nature of these major neuroendocrine stress systems, one might expect that coping styles will be reflected in a differential vulnerability to immune mediated disease as well. Indeed, several studies have demonstrated such a relationship, indicating that the functional variation in coping style and related neuroendocrine stress reactivity, as it occurs in nature, might be a good standard for studies aimed at understanding individual vulnerability. This is in agreement with more recent views that also in humans stress reactivity may be the best predictor for the individual vulnerability to immune mediated diseases. This asks for a more fundamental and translational approach of individual disease vulnerability based on a common biological basis of individual differentiation in behavior and physiology in humans and animals.

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Keywords: Stress; Coping style; Individual variation; Immunity

1. Introduction

Health and stress-related disease is generally considered to be influenced by a complex function of the actual environmental demands and the individual's capacity to cope with these demands. A wide variety of medical, psychological and biological studies both in humans and in animals

demonstrate that individuals may differ in their capacities to cope with such environmental demands. Understanding the origin and underlying mechanisms of this individual coping capacity and hence individual disease vulnerability is one of the major challenges of modern biomedical research. Factors that have been shown to affect the individual coping capacity include genotype, ontogeny, adult experience, age, social support, etc. Starting with the four temperaments of Hippocrates, scientists have tried for ages to understand the individual vulnerability to stress-related

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diseases using estimates of the individual coping capacity. The suggested relationship between temperament or personality and disease has been debated ever since. Also in the field of psychoneuroimmunology, some authors found a relationship between personality dimensions and immunity whereas others cast serious doubts on such a relationship (Kemeny and Laudenslager, 1999; Segerstrom, 2003). Despite the controversy, one seems to agree that the individual stress reactivity is a major determining factor in the vulnerability for stress-related disease (Kavelaars and Heijnen, 2006; Cohen and Hamrick, 2003; Marsland et al., 2002).

Also, in studies using animal models, there is a growing interest in understanding individual disease vulnerability. A general approach is to compare the stress immune interaction of two different laboratory strains of rats or mice. The choice of strains used for such a comparison is usually based on one or two dissociating characteristics. However, in view of the hundreds of strains available the choice is often rather arbitrary. While most of the studies on individual vulnerability are in the realm of the biomedical sciences, there is a growing interest in the biological basis of individual differentiation in behavior and physiology in the science of ecology and evolutionary biology. Individual variation in coping with challenges in the natural habitat determines evolutionary fitness and is considered to be the origin of speciation. Moreover, it may be an important factor in the regulation of populations as well. It seems that coping styles have been shaped by evolution to form general adaptive response patterns in reaction to everyday challenges in the natural habitat (Bell, 2007a,b; Sih et al., 2004). The aim of the present paper is to explore the biological basis of individual variation in stress reactivity in terms of individual coping styles in animals as they might be observed in nature and to discuss the consequences with respect to stress reactivity and immunology.

2. Coping styles

A growing body of literature confirms the biological function of within species variation. Individual variation that is both stable over time and across situations has now been demonstrated in a wide variety of species ranging from primates to rodents, birds, fish and insects (Bell, 2007a; Reale et al., 2007; Sih et al., 2004). Although different terms like behavioral syndromes, personality, temperament and coping style are used, the general view is that the different types of behavior patterns can be considered to be aimed at successful environmental control contributing to the individual fitness.

Much of our current thinking on coping styles is derived from the work of Jim Henry (Henry and Stephens, 1977). He suggested, on the basis of social stress research in animals and man, that two different stress response patterns may be distinguished. The first type, the active response, was originally described by Cannon

(1915) as the fight–flight response. Behaviorally, territorial control and aggression characterize the active response. Engel and Schmale (1972) originally described the second type of stress response as the conservation–withdrawal response. This response pattern is characterized behaviorally by immobility and low levels of aggression. These ideas led to the hypothesis that the individual level of aggressive behavior, i.e., the tendency to defend the home territory, is related to the way individual males react to environmental challenges in general. The hypothesis was tested by Benus (Benus et al., 1991a) using male house mice, originating from a feral population, that were genetically selected for either short attack latency (SAL) or a long attack latency (LAL). The results of a series of experiments not only in mice but also in feral rats, demonstrate that the individual tendency to initiate aggressive behavior is indeed predictive for the individual reaction to other, non-social environmental challenges (De Boer and Koolhaas, 2003; De Boer et al., 2003). This pattern of behavioral responses is consistent with the concept of coping styles. It seems that aggressive males have a strong tendency to take the initiative irrespective of the situation, i.e., attack, active avoidance, nest building, defensive burying, etc. Non-aggressive males seem to accept the situation more easily as it is, responding only when absolutely necessary. This difference in response initiation forms the basis of the terminology we currently use for the different coping styles. In our view, high levels of aggression are a reflection of a more general proactive coping style, whereas a low level of aggression reflects a reactive coping style (Koolhaas et al., 1999).

Experiments in rats, mice and pigs using variable mazes indicate that the proactive coping animal is adapted to stable environmental conditions (Benus et al., 1987; Bolhuis et al., 2003). After all, proactive behavioral control works best under highly predictable conditions. The reactive coping style does better under variable and unpredictable environmental conditions. Indeed, the few available field studies on feral populations indicate that the success of a coping style depends on environmental conditions such as space, density and food availability (Dingemans et al., 2004). In conclusion, coping styles can be considered as alternative emotional response patterns, each pattern being optimized for different environmental conditions. One may wonder how stable these coping style characteristics are. By definition, coping styles have to show some stability over time and across situations. In rats and mice they are stable over several months, whereas in larger animals such as cattle, they are stable over years (Van Reenen et al., 2005). The individual variation in response to inescapable stress in piglets shortly after birth is predictive for adult coping style (Schouten and Wiegant, 1997). Phenotypic plasticity may occur, in particular during development. Depending on the mouse strain studied the influence of developmental factors may range from zero (Sluyter et al., 1996) to a clear gene environment interaction (Nyberg et al., 2004).

3. Coping styles and stress reactivity

Coping styles are not only characterized by differences in behavior but also by differences in physiology and neuroendocrinology. High sympathetic reactivity is consistently found in proactive coping males rats and mice not only in terms of plasma levels of adrenalin and noradrenalin but also measured in heart rate and blood pressure (Koolhaas et al., 2007; Sgoifo et al., 1997). Various other studies emphasize the differences between the two coping styles in autonomic balance. The reactive coping style is characterized by a higher parasympathetic reactivity as can be observed by a strong bradycardia response in reaction to a sudden unpredicted stressor.

Differences in endocrine activity have also been observed for HPA axis activity both under baseline and stress conditions. In aggressive mice, reduced circadian peak plasma corticosterone levels and higher plasma ACTH levels have been observed as compared to non-aggressive mice (Korte et al., 1996; Veenema et al., 2003a,b). The general view is that the reactive coping animal reacts in response to a stressor with the highest corticosterone response. For example, in the forced swim test, the non-aggressive males show significantly higher ACTH and corticosterone responses than high aggressive males (Veenema et al., 2003b). Similar data were found in fish (Overli et al., 2007) leading to the general idea that reactive coping is characterized by high HPA reactivity. Also, in a situation of chronic social stress, the reactive coping male shows a more chronic activation of the HPA axis (Veenema et al., 2005). However, convincing correlations between HPA axis activity and coping style are not always found and seem to depend on the type of stressor used (Koolhaas et al., 2007). This may indicate that the HPA axis is more related to the emotionality rather than the coping style dimension. This notion is confirmed by van Reenen (Van Reenen et al., 2005). Using a principal component analysis on the individual variation of both the behavioral and the neuroendocrine response of cattle in a variety of challenging situations, he found that the parameters of the HPA axis loaded significantly on the emotionality factor and not on the coping style factor. These and other observations formed the basis of a two tier model in which coping style and emotional reactivity form two independent dimensions (Koolhaas et al., 2007). In this model, the magnitude of the stress response is considered to be independent of the quality of the response in terms of coping style. Currently, we think that the neuroendocrine differentiation is a consequence of coping style rather than the cause. Because the proactive coping style is characterized by preparation for action on the basis of a prediction, this coping style is usually associated with a high sympathetic response and generally also with a moderate HPA axis response. Hence, in most conditions, the differentiation in coping style will correlate well with the differentiation in sympathetic and HPA axis reactivity. However, under conditions where a coping style is not successful, such as social

defeat, proactive males appear to respond with a corticosterone response which is even higher than the response in socially defeated reactive males.

4. Coping style and immunity

In humans, personality and coping are frequently considered to be important factors in the explanation of individual variation in immunology and vulnerability to immune mediated disease (Buske-Kirschbaum et al., 2001; Kiecolt-Glaser et al., 2002; Segerstrom, 2003). Psychoneuroimmunology emphasizes the role of the HPA axis and the sympathetic branch of the autonomic nervous system in the communication between the brain and the immune system (Besedovsky and Rey, 2007; Malarkey and Mills, 2007). In view of the differential reactivity of these systems in the two coping styles one may expect to see differences in the immune system as well. Unfortunately, there is a limited amount of evidence supporting the idea that the coping style dimension is an important factor in explaining individual variation in stress reactivity and immunity. Sandi et al. (1991) addressed this question using the Roman-high (RHA) and low-avoidance (RLA) rats. These rats have been genetically selected on the basis of their active avoidance behavior (Driscoll et al., 1990) and have been shown to differ in a number of behavioral and neuroendocrine stress responses in a similar way as the proactive and reactive coping styles as mentioned above (Steimer and Driscoll, 2005). It was shown that the NK cell activity and the proliferation response of splenocytes to mitogenic stimulation was lowest in the RLA males, a difference that was even more pronounced after the stress of active shock avoidance learning. This differentiation in cellular immunity was confirmed in studies in pigs. Pigs also differentiate in behavior and neuroendocrine reactivity on a coping style axis. Using antibody responses to keyhole limpet hemocyanin (KLH) and *in vitro* lymphocyte proliferation responses, it was concluded that reactive coping pigs had a lower cellular immunity but a higher humoral immunity in comparison to proactive coping pigs (Hessing et al., 1995; Bolhuis et al., 2003; Schrama et al., 1997).

A few studies confirm the idea that coping style-related differences in the immune system as described above have consequences for disease vulnerability as well. In an unselected strain of wild type rats, it was shown that proactive coping male rats are far more vulnerable for the experimental induction of the autoimmune disease EAE (experimental allergic encephalomyelitis). This high vulnerability was suggested to be due to the high sympathetic reactivity in the proactive coping males, expressed in higher plasma levels of noradrenalin and an upregulation of proinflammatory cytokines (Kavelaars et al., 1999). In an extensive study on social stress in mice, Vegas et al. (2006) demonstrated that coping style was an important variable in explaining the development of tumor after social stress. Male mice, characterized by low levels of aggression and subordination, i.e., reactive coping males, developed most

pulmonary metastases in an experimental tumor model. This is consistent with studies by Teunis et al. (2002, 2004) in yet another model of coping style. Male rats, characterized by a hyper-reactive dopaminergic system showed a reduced tumor growth compared to males with a hypo-reactive dopaminergic system. Dopamine reactivity is one of the neurobiological characteristics of coping style in mice and rats selected for dopamine reactivity share many behavioral characteristics of the coping style dimension (Benus et al., 1991b; Cools et al., 1993). The proactive coping males are dopamine hyper-reactive and the reactive coping males are dopamine hypo-reactive. The differentiation in tumor development relates to a differentiation in angiogenesis and in NK cell activity. Evidence suggests that the extremes of the coping style dimension are characterized by a different balance between different T helper cells mediated by a differential HPA axis reactivity. High levels of glucocorticoids can shift the balance between Th1 and Th2 towards a Th2 response (Calcagni and Elenkov, 2006). Using a nematode infection (*Trichinella spiralis*) or experimentally induced periodontitis as Th2 dependent responses and EAE as a Th1 dependent response, it was demonstrated that male rats with a hypo-reactive dopaminergic system were more susceptible for EAE, whereas the dopamine hyper-reactive males were more susceptible for periodontitis (Breivik et al., 2000; Kavelaars et al., 1997). This latter observation is however not consistent with the higher vulnerability for EAE in the proactive wild type rats mentioned above (Kavelaars et al., 1999).

Finally, the importance of individual differences in stress induced changes in the immune system and disease vulnerability has been demonstrated in mice. Using a stress model of social disruption Avitsur et al. found evidence that some individuals develop glucocorticoid resistance of splenic lymphocytes. Subsequent infection experiments demonstrated a differential vulnerability to an experimentally induced viral and bacterial infections related to the development of glucocorticoid resistance (Avitsur et al., 2006a,b). The analysis of cytokine profiles indicates that the glucocorticoid resistance reduced the capacity to control the production of proinflammatory cytokines. The individual vulnerability was associated with early social experience and subsequent social status. Although the animals were not tested for the characteristics of coping style in the strict sense, it is tempting to consider the possibility that the individual differentiation might be explained by a differentiation in coping style.

5. Concluding remarks

One may wonder how the concept of coping style relates to human personality and temperament. The analysis of personality and temperament in humans is generally based on questionnaires and uses a much broader spectrum of characteristics than used in animal research. Personality characteristics in animals are based on observable behavior

in specific tests. To bridge this gap between human and animal research, much more effort should be put in translational tests addressing the same trait characteristics in humans and animals. The biology of personality is an emerging field of science that gradually starts to consider a more multidimensional approach (Koolhaas et al., 2007; Reale et al., 2007). Despite the clear state of the art differences in personality research between humans and animals, aggression seems to be an important common trait characteristic. Indeed, in a large sample of men that served in the US army, significant associations were found between individual differences in aggressive behavior and measures of cellular immunity (Granger et al., 2000). Clearly, much more experimental work is required to further substantiate the idea of a common biological basis and evolutionary origin of human and animal personality (Gosling, 2001).

As argued above, a wide individual variation has not only a biological function in nature it can also be used experimentally to unravel the factors underlying disease vulnerability. Ideally, the study of individual variation in stress reactivity and vulnerability to disease should have a solid basis in the biological function of individual variation in nature. The use of highly domesticated and often inbred strains of laboratory animals usually includes a strong selection bias in the experimental results. Indeed, a comparison of the frequency distribution of individual characteristics in an out-bred laboratory strain with the distribution in the wild rat clearly shows that the variation in the amount of aggressive behavior as an important component of coping style in the wild rat varies between 0% and 90% of the observation time. In the outbred Wistar rat, this varies between 0% and 25%. Hence, in the laboratory strain a complete phenotype is absent (De Boer et al., 2003). The field of psychoneuroimmunology and more generally stress research has to move towards a more subtle understanding of the factors and processes underlying the development of stress pathology. It might be far more informative to explore the individual adaptive capacity and the natural modulating factors. These factors may include not only functional genetic variation in coping style, but also gene environment interaction during development and adulthood.

To further increase the face validity of the animal models used, it seems wise to use stressors with a certain degree of ecological validity, such as social stress. Rather than pushing the animal towards a stress physiological ceiling, stressors should somehow challenge the natural defense mechanisms and hence call upon the adaptive capacity of the animal. The specific ecology and evolutionary biology of the species should be the basis to determine if one can expect the individual to have an adequate answer to a given challenge.

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