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Individual Variation in Coping with Stress: A Multidimensional Approach of Ultimate and Proximate Mechanisms

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Key Words

Aggression · Coping style · Evolution · Neurobiology · Serotonin · 5-HT

Abstract

Ecological studies on feral populations of mice, fish and birds elucidate the functional significance of phenotypes that differ individually in their behavioral and neuroendocrine response to environmental challenge. Within a species, the capacity to cope with environmental challenges largely determines individual survival in the natural habitat. Recent studies indicate that individual variation within a species may buffer the species for strong fluctuations in the natural habitat. A conceptual framework will be presented that is based on the view that individual variation in aggressive behavior can be considered more generally as a variation in actively coping with environmental challenges. Highly aggressive individuals adopt a proactive coping style whereas low levels of aggression indicate a more passive or reactive style of coping. Coping styles have now been identified in a range of species and can be considered as trait characteristics that are stable over time and across situations. The dimension of coping style seems to be independent of an emotionality dimension. Hence, in the analysis of the proximate mechanisms of stress and adaptation, one has to consider the possibility that the mechanisms which determine

the type of stress response might be independent from those underlying the magnitude of the response. The two coping styles differ in a number of important neurobiological and neuroendocrine systems. For example, proactive males differ significantly from reactive males in the homeostatic control of serotonergic activity resulting in completely opposite dose response relationships of various serotonergic drugs. The results so far show that proactive coping is characterized by a strong inhibitory control of the 5-HT neuron via its somatodendritic 5-HT_{1A} autoreceptor. It is hypothesized that the regulation of serotonin release is causally related to coping style rather than emotionality. Understanding the functional individual variation as it occurs in nature and the underlying neurobiology and neuroendocrinology is fundamental in understanding individual vulnerability to stress related disease.

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Introduction

Stress research in humans has long recognized the fact that stress pathology does not develop widespread in the population. Rather, it is the individual human being that develops the pathology under specific environmental conditions. Hence, the challenge for contemporary clinical and preclinical stress research is to understand the

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biological basis of individual stress vulnerability. Preclinical research using animal models has long neglected the issue of individual vulnerability mainly because a reduction of individual variation has been the standard approach in animal research for decades. More recently, animal experimental studies aimed at understanding stress related disease have started to exploit individual variation in behavior and reactivity of neuroendocrine systems. Indeed, an increasing number of studies include a comparison of different strains of animals as part of their experimental design. The choice of strains is generally based on a phenotypical characterization and a differential response pattern under stressful experimental conditions. Still, the scientific rationale underlying the choice of strains, out of the hundreds of mouse and rat strains available, seems rather arbitrary. This paper is aimed at understanding the biology of individual differentiation using evolutionary and ecological viewpoints of the neurobiology and neuroendocrinology of stress and adaptation.

Individual variation appears to have an important function in nature. Behavioral ecology studies of feral populations of a wide variety of vertebrate and invertebrate species emphasize the importance of phenotypes that have differential fitness under different environmental conditions [Sih et al., 2004]. This emerging field of the behavioral sciences opens new vistas on the biological basis and evolutionary significance of individual variation within a species and might develop into a more solid scientific foundation in understanding the individual vulnerability to stress pathology.

Individual Variation from an Evolutionary Perspective

Individual variation is considered to be one of the driving forces in evolution. The general idea is that certain individuals have a higher fitness than others leading to higher reproductive success, better survival, dispersal, etc. This is supposed to give certain directionality in the evolutionary process and is thought to be the basis of speciation. However, recent studies in feral populations demonstrate that a certain degree of individual variation is maintained in the population; that is, some genetic variation might be evolutionarily stable [Saccheri and Hanski, 2006]. This also suggests that different phenotypes might have a function in the population ecology of the species. This notion goes back to the original hypothesis by Chitty [1967] that genetic variation in aggressive behavior

might play an important role in the population dynamics of house mice. Genetic variation for aggression was suggested to be maintained in the population because the extremes in the population have differential fitness in different population densities. In nature, mouse populations are known to go through phases of growth and decline. Such population cycles might have a period from four to seven years and can be so extreme that the population suddenly collapses at the end of a cycle and becomes extinct [Boonstra et al., 1998]. There is still not a satisfactory explanation for the cyclic nature of mammalian populations. Factors such as predation risk, food availability, etc. seem to play a role. Chitty [1967] has suggested that the cyclic nature of rodent populations might be due to disruptive selection for aggressive behavior in the course of the population cycle. This hypothesis is supported by the early studies of van Oortmerssen [van Oortmerssen and Busser, 1989] on feral populations of house mice. Phenotypic characterization of the laboratory bred male offspring (F1) of breeding pairs caught from feral colonies revealed a bimodal distribution of attack latencies as measured in a standardized resident intruder paradigm. Subsequent selective breeding for high and low attack latencies resulted within five generations in a stable short attack latency (SAL) selection line. After a number of failures due to infertility of the offspring, we managed to obtain a long attack latency (LAL) selection line as well. Embryo transfer, cross-fostering and back-cross experiments show that the phenotypic differentiation in aggressive behavior as observed in the wild has a strong genetic basis that is marginally influenced by the maternal environment [Sluyter et al., 1996]. Several additional data support the general idea that stable genetic variation for aggressive behavior could be a factor in the population dynamics of the wild house mouse. Indeed, analysis of mortality in feral populations reveals a strong increase in dead females, juveniles and pre-weanling juveniles just before the crash of the population [van Oortmerssen and Busser, 1989]. It is tempting to consider the possibility that this is due to high levels of intermale aggression in that phase of the population cycle. During the whole population cycle, animals are migrating from the population. It seems that the non-aggressive phenotype is more successful in establishing a new colony than the highly aggressive phenotype. More recently, the ecological significance of genetic variation for aggression was also demonstrated in an extensive field study of a passerine bird, the great tit (*Parus major*) [Drent et al., 2003]. It was shown that individual variation in exploration of novel trees was stable over time and correlated with a variety of other behavioral characteristics in-

Fig. 1. The relationship between individual variation in offensive aggression displayed by adult male wild type rats in their home cage and (a) defensive burying of a shock probe and (b) immobility behavior in the presence of a shock probe.

cluding aggressive behavior [Verbeek et al., 1994]. Subsequent selective breeding experiments showed the genetic basis of this differentiation. Studies in wild populations of great tits showed a differential fitness of the two phenotypes under conditions of high and low food availability [Dingemanse et al., 2004].

In an extensive review, Sih and coworkers [2004] give several other examples in mammals, birds, fish and insects indicating that phenotypic variation has a function in the ecology of the species and is somehow maintained within a single natural population. These field studies support the general view that individual variation in behavior has an adaptive function in nature buffering the species against fluctuations in environmental conditions.

Typology and Terminology

Since the early studies by Henry [Henry and Stephens, 1977] scientists have tried to categorize individual variation into distinct trait characteristics. Currently, the general view is that trait characteristics should be stable over a considerable period of time and should be consistent across situations. Although stable trait characteristics are found in many animal species, there is a lack of consistency and agreement in the literature regarding the terminology used to describe and categorize trait character-

istics. Various terms are used to categorize the extremes of the individual variation such as shy versus bold, active versus passive or proactive versus reactive [Koolhaas et al., 1999]. Sih et al. [2004] used the term 'behavioral syndrome' indicating that trait characteristics should involve suites of correlated behaviors. This more neutral term might apply to any set of correlated behaviors that show consistency over time and across situations. However, a review of the relevant literature suggests that nature allows only a limited number of behavioral syndromes.

In a series of studies using rats and mice, we have presented experimental evidence that the concept of coping style might explain a considerable proportion of the individual variation in behavior. Coping styles might be defined as alternative response patterns in reaction to a stressor. The concept is based on the observation that individual variation in aggressive behavior is related to the response pattern in a variety of challenging conditions. This can be best demonstrated in tests that allow the animal a choice of different response patterns. For example, in the defensive burying paradigm [Treit et al., 1981] animals are confronted with an electrified probe inserted into their home cage. In response to a brief contact with the shock probe, the animal can either actively bury the probe with the bedding of the cage or show immobility and more passively avoid the electrified probe. Both response patterns can be considered successful coping, because in nei-

ther of the two response patterns the animal will ever touch the probe again. Figure 1a shows the positive correlation between offensive behavior measured in the resident intruder paradigm and burying behavior in the defensive burying test. Figure 1b shows the negative correlation between aggressive behavior and immobility.

This demonstrates the consistency of individual variation in behavior across situations; that is, the aggressive response to an intruder in the home cage predicts an active behavioral response in this non-social burying paradigm. These and other observations show that high levels of offensive aggressive behavior can be considered as the expression of a proactive coping style. Low levels of offensive aggressive behavior can be considered as a reactive coping style [Koolhaas et al., 1999]. It is important to note that the coping style concept implies that animals might react with alternative response patterns. Although the defensive burying paradigm is generally considered to be a test for anxiety, it can just as well be considered a test for the way in which anxiety is expressed behaviorally [De Boer and Koolhaas, 2003]. The same argument seems to hold for the forced swim test that is frequently used in rodents as a test for depression. Here too, aggressive males react with active swimming and climbing and non-aggressive males show predominantly floating behavior [Veenema et al., 2005]. Hence, in the interpretation of these tests one has to consider not only the magnitude of the behavioral response to a stressor but also the type of behavioral response.

The idea that the quality of a behavioral response might be a dimension separate from the magnitude of the response is supported by a more analytical examination of behavioral syndromes in cattle by van Reenen and colleagues [2002, 2004, 2005]. They measured behavior in a variety of behavioral test paradigms and used principle component analysis to extract independent factors that might explain the individual variation. Generally, four vectors were found that explained more than 80% of the individual variation. One of these vectors seems to be associated with coping style, and another one with emotional reactivity. The fact that emotional reactivity and coping style seem to be independent vectors in this study is consistent with the two tier model suggested by Steimer et al. [1997] on the basis of their behavioral analysis of rats genetically selected for high and low active avoidance behavior. They too present experimental evidence that emotional reactivity is independent of the coping style dimension as defined by the way in which emotion is expressed behaviorally.

Fig. 2. Two tier model with coping style and emotionality as two independent dimensions of stable trait characteristics. The four quadrants indicate the type of animal when varying on the two dimensions simultaneously.

Figure 2 gives a graphic representation of such a two tier model using emotionality and coping style as two independent trait characteristics. Considering the four quadrants of this model, one can use different labels for the four extreme characteristics. Many studies use the terms shy and bold. These terms have not been defined very well, but they seem to include both aspects of emotionality and coping style in terms of the differential behavioral expression of emotionality. In this model, the shy individuals are positioned in the top left quadrant and the bold individuals can be found in the lower right quadrant. Animals in the lower left quadrant might be characterized as docile, and animals in the top right quadrant as panicky. Although these terms are rarely used in animal research these types can easily be recognized in any group of animals.

In conclusion, it seems that individuals may show stable, trait-like variation on two independent axes, an emotionality axis and a coping style axis. The model might help in further characterizing genetic selection lines of various species. Depending on the selection criterion, genetic selection lines could show different degrees of variation in these two dimensions. Our data in mice and rats show that selection on the coping style axis, i.e. aggression or attack latency, results in little or no variation on the emotionality axis [De Boer et al., 2003]. It is conceivable that selection on the emotionality axis might result

in little or no variation on the coping style axis. Indeed, rats genetically selected for high or low levels of anxiety (HAB and LAB respectively) vary between 0% and 63% on the emotionality dimension, such as anxiety, but differ between 0% and 30% in aggressive behavior as a component of the coping style dimension [Veenema et al., 2007].

Neurobiology of Coping Styles

Several studies in rats and mice show a widespread central nervous differentiation between proactive and reactive coping styles, for example at the level of the peptidergic modulation of the central nucleus of the amygdala [Roozendaal et al., 1992], the vasopressinergic neurons in the bed nucleus of the stria terminalis and its innervation of the lateral septum [Compaan et al., 1992; Koolhaas et al., 1998], the suprachiasmatic nucleus [Bult et al., 1993], pre- and post-synaptic 5-HT_{1A} receptor sensitivity [Van Der Vegt et al., 2001; Caramaschi et al., 2007], hippocampal mossy fiber system [Sluyter et al., 1994], and striatal dopaminergic mechanisms [Benus et al., 1991]. With the exception of serotonin, the causal involvement of these neurobiological substrates in the individual differentiation in coping style is far from clear. They may be considered as a suite of correlated neurobiological trait characteristics, which in concert might determine the tendency to cope either proactively or reactively with environmental challenges. For more than 40 years now, the phylogenetically ancient and anatomically well conserved serotonergic system has been postulated to be essential in the control of aggressive and impulsive behavioral traits in many animal species, ranging from invertebrates such as fruit flies, crickets and lobsters [Kravitz and Huber, 2003] to vertebrates including lizards [Summers et al., 2005], fish [Øverli et al., 1999], birds [Ison et al., 1996], rodents [Miczek et al., 2002] and primates including humans [Higley et al., 1992; Lesch and Merschdorf, 2000]. In most animal species, high levels of aggressive behavior are associated with low levels of brain serotonin and its metabolite 5-HIAA. This is confirmed in a recent study by Caramaschi et al. [2007]. She compared three lines of mice that have been genetically selected for high and low levels of aggressive behavior. Lower 5-HT levels were consistently found in the high aggressive lines in the prefrontal cortex, hippocampus and brain stem.

In view of the two tier model presented above, one might wonder how serotonin relates to the two dimensions of the model. Numerous studies over the past two

decades have convincingly shown that pharmacological compounds that activate 5-HT_{1A} or 5-HT_{1B} receptor subtypes potently suppress the display of aggressive behavior in various animal species ranging from invertebrates, fish, rodents, guinea pigs to primates, including man [De Boer and Koolhaas, 2005]. Despite this overwhelming evidence, it is still a matter of debate which brain area is the most important site of action of these compounds. The 5-HT_{1A} and the 5-HT_{1B} receptors are not only found post-synaptically, they have also an important function in the negative feedback control of the 5-HT neuron itself. The 5-HT_{1B} receptor is present pre-synaptically at the 5-HT axon terminals, where it inhibits 5-HT release. The 5-HT_{1A} receptor located at the soma and dendrites of the serotonergic neuron at the level of the raphe nuclei acts as an inhibitory autoreceptor reducing the activity of the 5-HT neuron [Pineyro and Blier, 1999]. Hence, at the level of the postsynaptic receptors, the agonists mimic the effects of enhanced 5-HT signaling. However, at the level of the autoreceptor they reduce 5-HT signaling. A proper interpretation of the role of serotonin in aggression therefore depends on the predominant site of action of the 5-HT agonists. Using S15535, which is a selective agonist of the somatodendritic 5-HT_{1A} autoreceptor and a partial antagonist at the postsynaptic 5-HT_{1A} receptor, de Boer and Koolhaas [2005] showed a decisive and behaviorally selective reduction in aggressive behavior. This means that the aggression reducing effect of 5-HT_{1A} agonists is most likely due to their action on the autoreceptors. Analysis of the dose response relationship of S15535 reveals a tenfold difference between high and low aggressive male rats, i.e. the high aggressive males have a far more sensitive 5-HT_{1A} autoreceptor mediated inhibition. This enhanced inhibitory control of the serotonergic neuron in the aggressive males might explain the negative correlation between baseline levels of 5-HT and 5-HIAA and aggression found in so many species [De Boer and Koolhaas, 2005].

In view of the intricate and causal involvement of serotonin in aggressive behavior and the strong individual differentiation in autoreceptor feedback control in relation to aggression as a trait characteristic, one could wonder whether serotonin is more generally involved in coping style. Indeed, 5-HT_{1A} and 5-HT_{1B} receptor agonists also reduce swimming behavior in the Porsolt forced swim test [Cryan et al., 1997] and burying behavior in the defensive burying test [Barf et al., 1996; De Boer and Koolhaas, 2003]. So far, these and similar data have been interpreted in terms of emotionality, anxiety or depression. However, one cannot exclude the possi-

Fig. 3. Positive correlation between offensive behaviors performed in the home cage by adult male wild type rats and (a) the plasma noradrenalin response (area under the curve), and (b) the plasma adrenalin response (area under the curve) in reaction to social defeat.

bility that serotonin is related to the coping style axis rather than the emotionality axis. Considering individual variation in the behavioral effects of 5-HT_{1A} receptor agonists in the forced swim test, there is a clear qualitative difference in the way the animals at both ends of the range react to these compounds. The reactive coping males show a reduction of immobility and an increase in escape attempts, whereas the proactive coping animals show a decrease in escape and an increase in immobility behavior. In other words, activation of the 5-HT_{1A} autoreceptor leads to a reduction of the preferred behavioral response in this test, and to an increase in the alternative behavioral response rather than to a general reduction in anxiety [Veenema et al., 2005]. It is tempting to interpret this in terms of the two tier model as presented in figure 2. If the serotonergic system is related to the coping style axis rather than the emotionality axis, one might indeed expect opposite dose response relations in the extremes of the behavioral variation. If serotonin were associated with the emotionality axis, one would have expected a decrease in immobility and swimming/escape at the two ends of the distribution respectively, and not a shift to the alternative response. Preliminary data in the resident intruder test in rats also show opposite dose response relations in the extremes of the population. Clearly, the hypothesis that the two dimensions of the model are associated with different neurobiological substrates needs careful further explo-

ration using the natural individual variation within a species subjected to tests that allow different expressions of coping.

Neuroendocrinology of Coping Styles

Coping styles are not only characterized by differences in behavior and neurobiology, but also by differences in neuroendocrinology. As mentioned earlier, tests that measure aspects of initiative or proactivity seem to be most discriminating. The defensive burying test in rodents is such a test, which allows the animal a choice between proactive and reactive coping. In general, high plasma noradrenaline and relatively low plasma adrenaline and corticosterone accompany defensive burying, whereas freezing behavior is associated with relatively low plasma noradrenaline and high plasma corticosterone levels [De Boer et al., 1991; Korte et al., 1992]. In a strain of wild-type rats, the more aggressive males showed the highest levels of burying behavior and showed a larger catecholaminergic (both plasma noradrenaline and adrenaline) reactivity after electrified prod exposure than the non-aggressive rats [Sgoifo et al., 1996]. Also during social defeat, the more competitive proactive male rats react with higher responses of blood pressure and catecholamines than the more reactive rats. In addition, these competitive males had high-

Fig. 4. Absence of a correlation between offensive behaviors performed in the home cage by adult male wild-type rats and the plasma corticosterone response (area under the curve) in reaction to social defeat.

er baseline levels of noradrenaline. Figure 3a and b show the highly significant positive correlation of the individual plasma noradrenaline and adrenaline response respectively, calculated as area under the curve, with offensive aggressive behavior as measured a few weeks before the social defeat test.

The same relationship between coping style and sympathetic reactivity can be observed in a comparison between strains. On average, the aggressive wild-type rats responded to social defeat with larger sympathetic (plasma noradrenaline levels) reactivity and concomitantly lower parasympathetic reactivity (as measured by increased heart rate response and decreased heart rate variability) than the less aggressive Wistar rats [Sgoifo et al., 2005]. One might conclude that proactive coping is characterized by a high sympathetic reactivity. In contrast, reactive coping rodents show higher parasympathetic reactivity.

A number of publications suggest that reactive coping is associated with a higher baseline activity and reactivity of the HPA axis. With respect to baseline HPA activity, higher circadian peak plasma corticosterone levels and lower plasma ACTH levels have been observed in non-aggressive mice as compared to aggressive mice [Veenema et al., 2003, 2004]. No differences were observed in glucocorticoid and mineralocorticoid receptor

binding in the hippocampus. In response to a stressor, the general view is that the reactive coping animal reacts with the highest corticosterone response. For example, in the forced swim test, the non-aggressive males show the highest ACTH and corticosterone response. Similar data were found in a variety of species, leading to the general idea that reactive coping is characterized by high HPA reactivity. However, the absence of a convincing correlation (fig. 4) could indicate that the HPA axis is more related to the emotionality rather than the coping style dimension. This notion is confirmed by van Reenen and colleagues [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, they found that the parameters of the HPA axis loaded significantly on the emotionality factor but not on the coping style factor.

One might also conclude that for neuroendocrine reactivity as a trait characteristic it is worthwhile to consider coping style and emotionality as two independent dimensions.

Concluding Remarks

One of the main challenges of contemporary stress research is to understand the individual vulnerability for stress mediated disease. A lot of research effort is currently aimed at the genetic and epigenetic factors that determine adult stress vulnerability [Parmigiani et al., 1999; Mineur et al., 2006]. Ideally, these studies should have a firm basis in evolutionary biology and the ecology of the species under study. This will provide, for example, some idea of the degree of individual variation in nature. This is important because a comparison between the frequency distribution of aggressive behavior in a standard laboratory rat strain with that of laboratory bred wild rats reveals that a considerable number of the more aggressive phenotypes in wild rats are completely absent in the laboratory strain [De Boer et al., 2003]. Hence, selecting a laboratory strain has the risk of a strong selection bias in the experimental results. This risk of a selection bias can easily be demonstrated in figures 1, 3 and 4. Because Wistar rats will not perform more than 30% offense in the resident intruder paradigm, all data points higher than 30% will disappear from the correlation shown in these figures.

The choice of originally wild animals and its wide individual variation has also resulted in the concept of coping style, that is, the notion that a single given environ-

mental challenge might have equally adaptive behavioral solutions. It is tempting to consider the consequences of the two tier model presented in figure 2. The model suggests that the type of response in terms of coping style might be independent from emotionality, which is defined as the process determining the magnitude of the response. Consequently, for each factor that affects the response to a stressor (pharmacological, genetic, developmental, neuroendocrine, etc.) one has to consider the question of whether it affects coping style, emotionality or both. The first experiments aimed at this question sup-

port the hypothesis that serotonin relates to coping style rather than emotionality [Veenema et al., 2005]. If this is true, the two tier model might provide a biological basis for the fact that human beings also show strong individual differences in their response to serotonergic compounds [Lesch and Gutknecht, 2005]. Finally, using functional variation as it occurs in nature to study proximate mechanisms underlying the capacity for individuals to respond to environmental challenges should provide a solid basis for further genetic analyses of stress and adaptation as well.

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