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Koolhaas, J.M.; van Oortmerssen, G.A.

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INDIVIDUAL DIFFERENCES IN DISEASE SUSCEPTIBILITY AS A POSSIBLE FACTOR IN THE POPULATION DYNAMICS OF RATS AND MICE

by

J.M. KOOLHAAS AND G.A. VAN OORTMERSSEN

(Department of Animal Physiology, University of Groningen, P.O. Box 14, 9750 AA Haren, The Netherlands)

SUMMARY

Factors affecting health and disease are somewhat neglected in the study of the dynamics of mammalian populations. The present paper summarizes a number of studies on social stress in rats and mice. Social situations induce classical stress responses in terms of corticosterone and catecholamines. More important is the fact that there is a considerable individual differentiation in the magnitude of the responses in relation to the behavioural stategy in a social situation. These physiological differences render individuals differentially susceptible for stress pathologies such as cardiovascular diseases and immune deficiencies. Moreover, the behavioural strategy largely determines the position of an animal in the social structure and hence the frequency of behavioural and physiological activation. The data suggest that the individual behavioural and physiological reactivity determine in interaction with the social environment the susceptibility for diseases. The relevance of these observations for the dynamics of a population is discussed.

KEY WORDS: aggressive behaviour, coping, catecholamines, corticosterone, FFA, immunology.

INTRODUCTION

Social behaviour is generally considered as an important factor in the dynamics of mammalian populations. Its cohesive or dispersive nature affects the density of a population and it may affect breeding success (FLOWERDEW, 1987; CROWCROFT & ROWE, 1963). A somewhat neglected aspect of the role of social behaviour in population dynamics is the fact that social behaviour affect health and disease. Although a number of authors have emphasized the role of diseases in the regulation of numbers in popultions of wild animals (ANDERSON, 1981; LEADER-WILLIAMS, 1982; PRINS & WEYENHAUSER, 1987), the processes underlying the incidence of disease are much less understood. CHRIS̃-TIAN (1980) argued that stress originating from tension in the social structure of a population and its accompanying neuroendocrine processes might play an important role. As the individual members of a population are differentially involved in various social activities like

sex, agression and flight, they face different social problems that ask
for different solutions and adaptations. The fact that such adaptations
have their physiological costs and may even fail, is nicely illustrated
in field studies by BRADLEY et al. (1980) and McDONALD et al. (1981)
on populations of small marsupial spieces. They concluded that stess
induced by aggressive interaction during the mating season resulted
in strong neuroendocrine changes with consequent immunosuppres-
sion and death from gastrointestinal haemorrhage and infection by
parasites and microorganisms. Several laboratory studies demon-
trated an individual differentiation in the incidence of stress
pathologies in relation to having a suboptimal status in a complex
social structure. For example, both in monkeys (MANUCK et al., 1983)
and mice (HENRY & STEPHENS, 1977; ELY, 1981), social dominance in
a situation that is difficult to control is associated with increased
systolic blood pressure and coronary artery atherosclerosis. In colonies
of male rates, FOKKEMA (1985) found a high incidence of hypertension
in the subtop of the social hierarchy which is a sub-optimal position
for a number of rats, whereas stomach ulcers were observed in the
social outcasts of the colonies. Social status is also reflected in neuroen-
docrine parameters of individuals, like the pituitary adrenocortical
hormones (SAPOLSKY, 1982; SASSENRATH, 1973; HENRY & STEPHENS,
1977) and the plasma catecholamines (FOKKEMA et al., 1988). In
biomedical research it is well accepted that variation in these neuroen-
docrine parameters influence the susceptibility for certain diseases.
For example, plasma levels of the hormones of the pituitary
adrenocortical axis are powerful immunomodulatory agents (COMSA et
al., 1982). Plasma catecholamines are strongly involved in car-
diovascular regulation and deviations in this neuroendocrine system
may affect cardiovascular pathology (ORBIST, 1981). This supports the
hypothesis that tension in the social structure affects neuroendocrine
systems and in this way the incidence of disease in a population.
Hence, we hypothesize that the success of an animal living in a com-
plex social group seems to depend on the individual capacity to adapt,
both behaviourally and physiologically to its social environment. In
the analysis of the hypothesis, four major questions arise. Firstly, do
social stimuli result in qualitatively and/or quanitatively different
physiological responses? Secondly, to what extent do individual
animals differ in this respect? Thirdly, is there any relationship
between this individual differentiation and the position of individuals
in a social hierarchy? Finally one may wonder whether the individual
behavioural and phsysiological responsiveness in interaction with
social status might implicate a differentiation in the incidence of stress
pathologies.

In this paper we will present some of our own work aimed at the hypothesis that social behaviour may not only have a direct effect on the population (by means of reproductive success), it may just as well have indirect influences by affecting health and disease.

METHODS

In order to study the individual endocrine and cardiovascular effects of various social factors, it is important to have a good experimental control over the social environment of the experimental animal. As has been described elsewhere (KOOLHAAS *et al.*, 1980; FOKKEMA *et al.*, 1985) this can reliably be achieved by using the attribute of adult male rats to establish a territory when housed permanently in a fairly large cage (85 x 50 x 50 cm) together with a female. Three complex social situations relevant to the maintenance of social structures can be studied by using such an experimental setup.

a. Victory: When the experimental animal, housed in its home cage is confronted with an unfamiliar male intruder of about the same weight, it will attack this intruder. As a rule, the home cage owner (experimental animal) will be the victor of this interaction.

b. Defeat: The same experimental animal can also be used as an intruder into the home cage of another male rat. Especially when this latter animal is a trained fighter, the experimental animal will be defeated.

c. Psychosocial stimulation: In order to study the influence of the mere presence of the dominant (a former victor of the experimental animal), this rat was enclosed in a small wire-mesh cage and briefly presented to the experimental animal. In this way direct physical interactions were prevented.

The effects of these three social situations on behavioural, endocrine and cardiovascular parameters of the experimental animal were studied in 10 minute tests. In order to study the relevance of these findings obtained in dyadic interactions for more complex social structures, we also studied male rats in a semi-natural colony situation. Before colony housing, each animal was characterised behaviourally in five victory tests in terms of attack latency and relative time spent on offensive behaviour. Each colony consisted of ten male rats and five females housed in an enriched environment of 6 square metres with ad libitum food and water supply.

Several physiological measurements are relevant to the questions mentioned in the introduction. These measurements were made in the dyadic test situations only, using chronic cannulation methods. With these techniques it is possible to follow in detail the endocrine and car-

diovascular changes induced by the various social situations in relatively free moving animals. As an indicator of the cardiovascular consequences of the social situations, continuous blood pressure (BP) recordings were made using chronic intra-arterial catheters (FOKKEMA *et al.*, 1985). Blood pressure will be expressed as the mean between systolic and diastolic blood pressure. Blood samples for hormone assays were taken via chronic jugular vein cannula. As an index of the activity of the pituitary adrenocortical system we measured plasma corticosterone (C) levels by means of a competitive protein binding assay (MURPHY, 1967). Another important neuroendocrine system in stress physiology is the sympathetic-adrenomedullary system. As indicators of the activity of the sympathetic nervous system plasma adrenaline and noradrenaline concentrations were determined by means of an enzyme-radiochemical method. In some tests plasma glucose and free fatty acids (FFA) were measured. Glucose was determined by means of the ferricyanide method of Hoffman, and FFA measurement was based on the chloroform-soluble copper salts of the long chain fatty acids (ANTONIS, 1965). Finally, in some situations plasma testosterone was measured by means of a radioimmunoassay.

SOCIAL STIMULI AND THE PHYSIOLOGICAL STRESS RESPONSES

In order to illustrate to what extent the various complex social situations induce a stress response, figure 1 summarizes the concentrations of plasma corticosterone (C), adrenaline, noradrenaline, and the mean blood pressure response (BP) for the three social situations studied. All three situations induce a significant rise in the physiological parameters ($p < 0.01$). The differences between the social situations are also significant ($p < 0.01$) with the exceptions of the corticosterone concentration during the psychosocial test which does not differ from the level during victory. Hence the differences are mainly of a quantitative nature, in which defeat results in the strongest response.

The fact that psychosocial stimulation with a dominant male results in physiological responses that are intermediate between victory and defeat responses, shows that the psychological component of the social situation may be an important factor in addition to the physical aspects of the interaction.

Summarizing one can say that all three social situations studied induce a classical stress response, i.e. a rise in the blood pressure, corticosteroids and catecholamines.
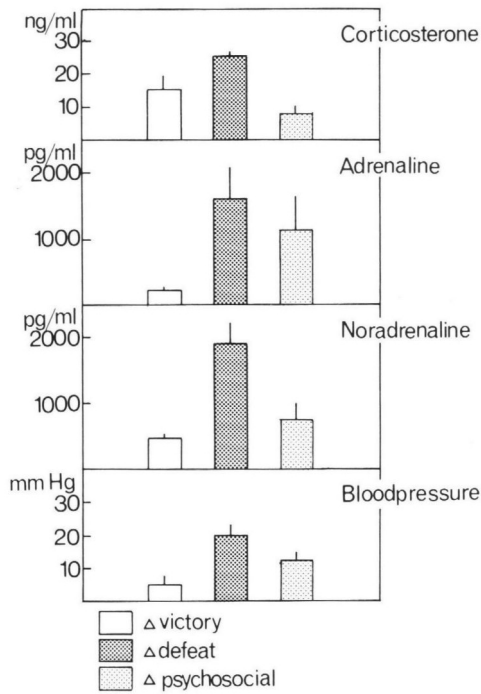
Fig. 1. Magnitude of the blood pressure response and plasma concentrations of cor-
ticosterone, adrenaline and noradrenaline during three different social situations.

INDIVIDUAL DIFFERENTIATION

Social behaviour, like other behavioural features, shows considerable
variation between individuals which is possibly based on genetic and
ontogenetic factors. For example, there is a wide and consistent
individual variation in the tendency to defend the home territory
against unfamiliar male intruders. Some animals readily attack an
intruder, whereas others do not perform any aggressive behaviour at
all. This attack latency is a robust characteristic with a clear genetic
background for its variation, that can be measured realiably (VAN
OORTMERSSEN & BAKKER, 1981; VAN OORTMERSSEN et al., 1985).
Because it can also be used as a predictor of future position in the
social hierarchy (see below), this behavioural characteristic is taken as
a reference in the study on individual differentiation. Several studies
indicate that animals differentiate in individual behavioural, neuroen-
docrine and cardiovascular responsiveness during social confronta-

tions (MANUCK *et al.*, 1983; SAPOLSKY, 1982; SASSENRATH, 1973; v.HOLST, 1986).

In order to find out to what extent such a differentiation indicates a differentiation in individual appraisal of the social environment rather than a reflection of the physical stress of the different environmental stimuli, the psychosocial test situation can be used. In this test situation, the experimental animal only sees or smells the opponent without much behavioural interaction.

With respect to the responses of the physiological variables during the psychosocial tests, we found that aggressive males (characterized by a short attack latency) had a more reactive blood pressure ($Rs = 0.81$; $p < 0.01$) (FOKKEMA & KOOLHAAS, 1985). Measurements of plasma noradrenaline and adrenaline showed significantly higher responses in the aggressive male than in the non aggressive animals (FOKKEMA *et al.*, 1988).

From the baseline levels of testosterone, corticosterone, glucose, free fatty acids and blood pressure, only testosterone was positively correlated with aggressive behaviour in the home cage victory tests ($Rs = 0.75$; $p < 0.01$). The higher the amount of aggressive behaviour performed against the intruder, the higher the baseline levels of T under resting conditions, a phenomenon that is also known in rhesus monkeys (ROSE *et al*, 1971; SCHUURMAN, 1980).

Neither the baseline values of corticosterone nor the absolute and relative changes of this hormone during the psychosocial test were related to aggressive behaviour. This is in contrast to some reports in the literature on the activity of the pituitary adrenocortical system and social status. Unfortunately, these reports are often contradictory with respect to the detailed relationship. Some authors found a low baseline in dominant mice (HENRY & STEPHENS, 1977) and monkeys (SAPOLSKY, 1982; SASSENRATH, 1973) and a low responsiveness. Others reported high corticoid levels (COE *et al.*, 1979; LESHNER & CANDLAND, 1972) and a high responsiveness (SAPOLSKY, 1982) in dominant males. Because in our experiments we did find the highest response of corticosterone in the most aggressive males during the victory test ($Rs = 0.82$; $p < 0.01$), it can be argued that the activity of the pituitary adrenocortical system may be a reflection of the social situation. Variables such as intensity of social interactions, species differences, duration of colony aggregation, etc. may account for the contradictory literature data. Nevertheless, our physiological data indicate that male rats differentiate in the appreciation of the social environment. They appear to react upon the mere sight or smell of an opponent with physiological responses the magnitude of which is related to the amount of aggressive behaviour performed later in vic-

tory tests. This differentiation can be summarized as follows. Physiologically, aggressive males seem to prepare for action in response to an environmental stimulus by activating the sympathetic nervous system as indicated by the responsiveness of BP and catecholamines. This preparation for action is nicely illustrated by the strong increase in plasma free fatty acids in the aggressive males during a psychosocial confrontation with an unfamiliar male, indicating that they prepare their fat metabolism for a high level of energy expenditure. Such preparations are absent in the non-aggressive males (fig. 2).
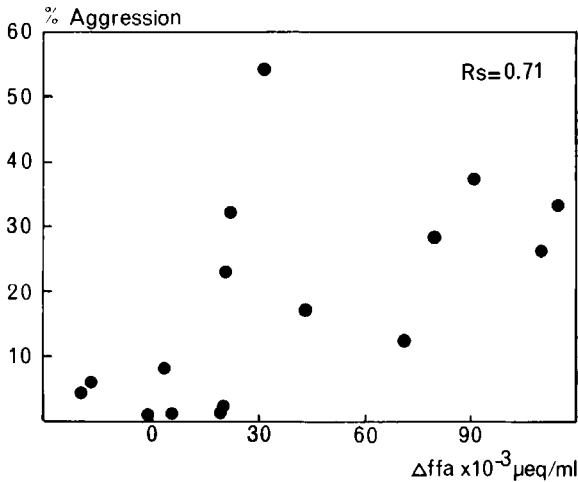

Fig. 2. Correlation between the change in plasma free fatty acids in response to a psychosocial stimulus and the independently measured level of aggressive behaviour.

Recent experiments show that aggressive males are behaviourally characterized by an active coping strategy in a wide variety of social and non-social situations (KOOLHAAS et al., 1986; BOHUS et al., 1987). Non-aggressive males on the other hand adopt a more passive coping strategy in response to an environmental challenge, i.e. they often freeze. Physiologically these animals are characterized by a low level of testosterone and a small sympathetic response. Our data show that Henry's conceptual model on behavioural and physiological response patterns in challenging situations (HENRY & STEPHENS, 1977) also holds for the individual differentiation in responses in a social situation. Aggressive behaviour seems to be an expression of a more

general active coping strategy and is similar to Cannon's fight/flight reaction. The passive coping strategy of the non-aggressive males is similar to the conservation-withdrawal response originally described by ENGEL & SCHMALE (1972).

COPING STRATEGY AND SOCIAL POSITION

In the previous section it has been shown that individual male rats differ in their coping strategy and the accompanying physiological state and responsiveness. In a study of wild house mice, VAN OORTMERSSEN *et al.* (1985, 1988) demonstated that active and passive copers play a different role in the social structure and the dynamics of the population. Aggressive mice have a high fitness in settled stable demes, whereas non-aggressive mice do better under colonising conditions. In this paragraph, the significance of these coping strategies for an individual living in a complex social structure will be demonstrated for rats. To this, the individual behavioural characteristic was determined on the basis of the amount of agonistic behaviour performed in five victory tests. One week after the completion of these tests, ten of these experimental males were put into a large enriched environment of eight square metres, together with five sterilized females. To determine the social structure of this group of animals, behaviour was observed regularly over a period of 3 months. Soon after the start of the colony housing one male appeared to be the dominant, i.e. it won all the social interactions with other males. By far the majority of the social interactions in the colony was between this dominant and the other colony members. Different colonies may vary in the stability of the social structure. Despite this variability between colonies, the behaviour during precolony victory tests appeared to have predictive value for the behaviour during colony aggregation. Generally, male rats that were found to be aggressive before colony housing were also socially active in the colony. In three different colonies this correlation ranged from 0.56 to 0.79 between different colonies. More important for the interpretation of these data in terms of coping strategies is the significant correlation between precolony aggression and escape and flight behaviour that is observed in some of the colonies ($Rs = 0.78$). Since this flight behaviour is mostly observed in interactions with the dominant, this shows that the potentially dominant males in a colony actively avoid social interactions with the dominant. This finding is consistent with the superior active avoidance by aggressive males observed in a non-social aversive situation (BOHUS *et al.*, 1987). This indicates that also in a rat colony the distinction between active and

passive coping strategies can be made and that the behaviour in the home cage victory tests is predictive for this.

Summarizing, the following picture emerges: males that are characterised by an active coping strategy can be considered as potentially dominant males in the colony. Since only one male can be the dominant, the other potentially dominant males take the subdominant position, but they are frequently involved in interactions with the dominant. The more passive males on the other hand remain passive in the colony, have little social interactions with the dominant and can be considered as subordinates.

SOCIAL POSITION AND DISEASE

In view of the previous sections, it seems likely that the incidence of disease in a population may be the result of the interaction between social environment, i.e. the frequency of winning, loosing or non-aggressive social interactions with colony members, and the individual behavioural and physiological make up or coping strategy. Although little research has been done so far, a number of experiments indicates that this may be indeed the process underlying the incidence of stress pathologies in a colony of rats. As has been shown, active copers are most frequently involved in interactions with the dominant. Moreover, these animals are physiologically characterised by a high sypathetic tone and responsiveness. Consequently, the frequent confrontations with the dominant cause a strong rise in blood pressure and FFA. The results of the psychosocial tests show that even the mere sight or smell of the dominant is sufficient to induce such a strong sympathetic output. This frequent and strong sympathetic activation may cause the high incidence of hypertension in the subdominants of a rat colony as reported by FOKKEMA (1985). The strong sympathetic activation is accompanied by increased levels of FFA. These higher levels of FFA are generally considered as a risk factor for the development of atherosclerosis. Although actual dominants also belong to the risk group in social colonies, they usually are normotensive. This can be explained by the absence of defeat experiences, the relatively small physiological responses during victory and the little effort it needs to maintain their position, i.e. the mere approach by the dominant is sufficient to induce flight behaviour in the subdominant.

A recent study (KOOLHAAS et al., 1987) has shown that the position in the social structure is also reflected in various parameters of the immune system. For example, subdominant males are characterized by thymus involution and lymphopenia, whereas a reduced in vitro prolipheration response is observed in the subordinates. This relation-

ship between social position and the immune system is not surprising since recent developments in the field of psychoneuroimmunology emphasize the significance of various neuroendocrine systems and the autonomic nervous system in immune functioning (FELTEN *et al.*, 1985). In the framework of the present paper, these data suggest a differential susceptibility for immune mediated diseases in relation to coping strategy and position in the social structure. This hypothesis is consistent with the increased incidence of infectuous diseases observed during the mating season in Marsupial species observed by BRADLEY *et al.* (1980).

CONCLUDING REMARKS

In the interactional model presented in this paper, much emphasis is laid to the role of the individual behavioural and physiological capacity to adapt to the social environment. The limitations of this ability may not only affect the incidence of disease, as has been argued, but may just as well have its consequences for the individual fitness in terms of reproduction. Although more research is necessary to demonstrate the relationship between coping strategy, social environment and reproduction, it also shows the necessity to understand the genetic and ontogenetic basis of these individual differences. VAN OORTMERSSEN & BUSSER (1988) recently showed the role of genetic factors underlying active and passive coping strategies in the population dynamics of wild house mice.

Further insight into the mechanisms underlying the maintenance of different coping strategies in wild populations may eventually bridge the gap between the theoretical approach in terms of hawk-dove models (Maynard Smith 1984) and the experimental behavioural and physiological approach of population dynamics presented in this paper.

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