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High and abnormal forms of aggression in rats with extremes in trait anxiety — Involvement of the dopamine system in the nucleus accumbens

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Summary A better neurobiological understanding of high and abnormal aggression based on adequate animal models is essential for novel therapy and prevention. Selective breeding of rats for extremes in anxiety-related behavior resulted in two behavioral phenotypes with high and abnormal forms of aggression. Rats bred for low anxiety-related behavior (LAB) consistently show highest levels of aggression and little social investigation in the resident-intruder (RI) test, compared with non-selected low-aggressive (NAB) rats. High anxiety-related (HAB) rats also show higher levels of aggression than NAB rats, but to a lesser extent than LAB rats. Accordingly, extremes in inborn anxiety in both directions are linked to an increased aggression level. Further, both LAB and HAB, but not NAB males, display abnormal aggression (attacks towards vulnerable body parts, females or narcotized males), which is particularly prominent in LABs. Also, only in LAB rats, the nucleus accumbens (NAc) was found to be strongly activated in response to the RI test as reflected by increased *c-fos* and *zif268* mRNA expression, and higher local dopamine release compared with NAB males, without differences in local dopamine receptor binding. Consequently, local pharmacological manipulation by infusion of an anesthetic (lidocaine, 20 μg/μl) or a dopamine D2 (haloperidol, 10 ng/μl), but not D1 (SCH-23390 10 ng/μl), receptor antagonist significantly reduced high aggression in LAB rats. Thus, LAB rats are an adequate model to study high and abnormal aggression. In LAB males, this is likely to be linked to hyperactivation of the reward system, as found in psychopathic patients. Specifically, activation of the accumbal dopamine system is likely to underlie the high aggression observed in LAB rats.

1. Introduction

Although aggressive behavior is important for assuring survival of an organism, strict species-specific rules have established in order to minimize injuries and killing. However, in

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human society, excessive aggression is a major health and social problem. More than 700,000 people die worldwide each year because of aggressive assault (Bartolomeos et al., 2007). Violent forms of aggressive behavior can occur as a symptom of psychopathologies, such as personality disorders, schizophrenia or depressive illnesses (Eronen et al., 1998; Haller and Kruk, 2006), but underlying neurobiological mechanisms of excessive and abnormal forms of aggression are largely unknown. It has been hypothesized that alterations of the reward system play an important role in individuals with psychopathic traits showing violent behavior. More specifically, hyper-activity of the mesocorticolimbic dopamine system was recently reported in psychopathic patients (Buckholtz et al., 2010). These studies have been supported by recent rodent studies which implicated dopamine and the reward circuitry in the regulation of aggression (Ferrari et al., 2003; Couppis and Kennedy, 2008). Other brain factors likely to be involved in the regulation of high levels of aggression include, e.g., serotonin, vasopressin, γ-aminobutyric acid and glucocorticoids (Miczek et al., 2002; Mikics et al., 2004; Ferris, 2005; Haller and Kruk, 2006; Neumann et al., 2010; Veenema et al., 2010).

We could recently establish an animal model for high aggressive behavior with the aim to further study the underlying neurobiological mechanisms (Veenema et al., 2007b). Rats selectively bred for low (LAB) and high (HAB) anxiety-related behavior, respectively (Liebsch et al., 1998a; Landgraf and Wigger, 2002; Bosch et al., 2006), were found to substantially differ in various aspects of social behavior (Neumann et al., 2010), including inter-male aggression, with LAB rats displaying an extremely high and HAB males displaying a rather intermediate level of aggression compared with non-selected (NAB) rats (Veenema et al., 2007b).

The pronounced aggressive behavior of LAB rats is accompanied by an elevated level of neuronal activity within the paraventricular nucleus and an elevated corticotropin response to social stimuli such as the resident-intruder (RI) test (Veenema et al., 2007b) suggesting an association between high aggression and high social stress responsiveness. Additionally, LAB rats show a reduced arginine vasopressin response and neuronal activation within the lateral septum during the RI test. Manipulation of this neuropeptide system within the septum did not affect aggression while increasing anxiety, indicating rather an indirect effect of septal vasopressin on aggression in LAB rats (Beiderbeck et al., 2007). However, a possible involvement of the reward system, specifically the dopaminergic system of the nucleus accumbens (NAc) has not been studied in the context of high aggression in these rats.

In the present study, we generated a detailed behavioral profile of LAB, HAB and NAB male rats and investigated the potential association between anxiety and aggression. We further studied whether the high level of aggression of LAB and HAB rats is accompanied by different types of abnormal aggression and ignorance of species-specific rules reflected by attacking vulnerable body parts, non-estrus female rats or a narcotized rat. In this context, we quantified the mRNA expression of two immediate-early genes (*c-fos*, *zif268*) using *in situ* hybridization in response to the display of aggression. As we could show an increased neuronal activation in the NAc specifically of high-aggressive LAB rats, we tested the hypothesis that an increased activation of the reward system contributes to the high level of aggression in these rats. Therefore, we monitored local dopamine release during the RI test using intracerebral microdialysis comparing high aggressive LAB and low aggressive NAB rats. The elevated neuronal activation together with an increased dopamine release within the NAc of LAB rats prompted us to investigate the behavioral consequences of manipulation of the dopamine system within the NAc of LAB rats. Thus, by using bilateral infusion of either an anesthetic or of a selective dopamine D1 or D2 receptor antagonist, we aimed to reveal detailed brain mechanisms underlying hyper-aggression in LAB rats.

2. Materials and methods

2.1. Animals

Experiments were carried out on male Wistar rats, selectively bred for low (LAB) or high (HAB) anxiety-related behavior in the animal facilities of the University of Regensburg, Germany, (Liebsch et al., 1998a; Landgraf and Wigger, 2002; Neumann et al., 2010) and on non-selected male Wistar rats (NAB; Charles River, Sulzfeld, Germany). Rats were constantly kept under controlled laboratory conditions (12:12 h light/dark cycle; lights on at 6:00 h, 21 ± 1 °C, 60% ± 5% humidity, standard rat nutrition and water *ad libitum*) and housed in groups of 3–4 of the same line in standard rat cages unless mentioned otherwise. At the age of nine weeks, all LAB and HAB rats were tested on the elevated plus-maze (EPM). All experiments were scored by experienced observers blind to breeding line and treatment. Experiments were approved by the Committee on Animal Health and Care of the Government of the Oberpfalz and are in accordance with the *Guide for the Care and Use of Laboratory Animals* produced by the National Institute of Health.

2.2. Elevated plus-maze (EPM)

Anxiety-related behavior was quantified on the standardized EPM (Pellow et al., 1985) as described before (Beiderbeck et al., 2007). Briefly, it consists of a plus-shaped platform elevated 80 cm above the floor, with two open (50 cm × 10 cm; 100 lx) and two closed (50 cm × 10 cm × 40 cm; 20 lx) arms. Rats were placed in the center square facing a closed arm. The following parameters were recorded by means of a video/computer system (Plus-maze version 2.0; Ernst Fricke) during the 5-min test: time spent in open and closed arms, number of entries into open and closed arms, latency to enter an open arm. Here, statistical analysis is only presented for the percentage of time spent on the open arms [100 × time on open arms/(time on open arms + time in closed arms)].

2.3. Resident-intruder (RI) test

Aggressive behavior was quantified using the RI test as has recently been described (Beiderbeck et al., 2007). Briefly, adult LAB, HAB and NAB male rats (16–22 weeks of age) were housed in an observation cage (40 cm × 24 cm × 35 cm) together with a female Wistar rat (Charles River, Sulzfeld,