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Lack of Aggression and Anxiolytic-Like Behavior in TNF Receptor (TNF-R1 and TNF-R2) Deficient Mice

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Abstract

The mechanisms underlying violence and aggression and its control remain poorly understood. Using the Resident-Intruder paradigm, we have discovered that resident mice with combined deletion of TNF receptor type 1 (TNF-R1) and type 2 (TNF-R2) genes show a striking absence of aggressive behavior, which includes fighting, sideways postures, and tail rattling. In parallel, resident TNF-R1 and TNF-R2 knockout mice show an increase in non-aggressive exploration of the intruder mice. Given the relationship between aggression and anxiety, we also measured anxiety-related behavior, as reflected by performance in the Open Field and the Light-Dark Choice Test. Compared with wild type mice, TNF-R1 and TNF-R2 deficient mice spent significantly more time and showed increased movement in the center of the Open Field and in the illuminated compartment of the light-dark box, suggesting an anxiolytic-like profile. Together, these data show that combined deletion of TNF-R1 and TNF-R2 results in a striking absence of aggressive behavior, an increase in non-aggressive exploration, and anxiolytic-like effects. These findings identify potent roles for TNF in regulating aggression and anxiety-related behavior, and suggest that TNF receptor signaling tonically modulates activity in brain regions underlying these behaviors.

Keywords

TNF; TNF receptors; TNF-R1; TNF-R2; aggression; anxiety; proinflammatory cytokines

1. Introduction

In recent years, several groups have reported that a positive relationship exists between pro-inflammatory cytokines and aggression/hostility (see Zalcman and Siegel, 2006). For example, Suarez and colleagues showed in healthy male subjects that scores on the Buss-Perry Aggression Questionnaire, which measures hostility, anger, and aggression, were associated with increased production of tumor necrosis factor (TNF) α (Suarez et al., 2002). A positive relationship between hostility and pro-inflammatory cytokine production was likewise found in a study of male Dutch military personnel before deployment

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(Mommersteeg et al., 2008) and in a study of healthy middle aged adults (Marsland et al., 2008). Studies using patients' population, receiving cytokine immunotherapy, provide further support for the link between cytokines and anger/hostility (Kraus et al., 2003; McHutchison et al., 1998). A possible genetic basis for this relationship is suggested by a study by Petitto and colleagues who showed that cytokine production was higher in mice bred for high aggression than in mice bred for low aggression (Petitto et al., 1994). Together, these studies show that a positive association exists between pro-inflammatory cytokines and measures of aggressive behavior in patient and non-patient populations. It is also noteworthy that exposure to conflict in humans, and aggressive encounters or social disruption in rodents also modulate immune function (Glaser et al., 2005; Avitsur et al., 2005; Stefanski, 2001).

Studies conducted in our laboratory have focused on the role of pro-inflammatory cytokines and their receptors in the hypothalamus and midbrain periaqueductal gray (PAG) in modulating feline aggression (Zalcman and Siegel, 2006). We recently extended these studies to identify cytokines that mediate the effects of LPS on aggression in cats. We found that LPS-induced modulation of defensive rage is mediated, in part, through peripheral TNF- α (Bhatt et al., 2009). Immunocytochemical studies further revealed that TNF receptors were present in abundant quantities throughout defensive rage sites in the medial hypothalamus (unpublished finding). These studies suggest a role for TNF signaling in modulating aggressive behavior. Over the past decade, a number of studies have utilized TNF receptor deficient mice to study such processes as fear conditioning (Simen et al., 2006) and sickness behavior (Palin et al, 2009) which establishes the use of this model for the study of other related behavioral processes. Thus, to better understand the role played by TNF signaling in aggression, we sought to evaluate the effects of TNF receptor deletion on the varied components of aggressive behavior and related processes.

2. Material and Methods

2.1 Subjects

Male wild type (WT) (B6129SF2/J) (n=6) and combined TNF receptor type 1 and type 2 knockout (KO) mice [B6129S-Tnfrsf1a^{tm1Imx}Tnfrsf1b^{tm1Imx}/J] (n=6) from different litters, were purchased from Jackson Laboratories, Bar Harbor, Maine at 5-wk of age. The mice were housed in standard polypropylene 'shoebox' cages in groups of four until one week prior to testing whereupon they were individually housed. The animals were maintained on a 12 hour light/12 hour dark light cycle (7 am – 7 pm), and permitted free access to standard laboratory chow and water. Changes in body weight occurring during the period beginning 1-week after arrival of the mice in our facility and ending upon termination of testing were as follows: WT mice gained 4.0 ± 0.25 g while TNFR-KO mice gained 4.0 ± 0.20 g. At the end of testing, the mice were euthanized by CO₂.

2.2 Procedure

To study the role played by TNF receptors in aggression, we evaluated the varied components of aggressive behavior in wild type (WT) mice and combined TNFR KO mice in a resident-intruder paradigm. We conducted additional tests to determine the effects of TNFR gene deletion on related processes that may have contributed to or confounded effects on aggression, including anxiety-like behavior (open field center:margin time ratios, performance in the light-dark choice test) and social behavior (non-aggressive investigation of a sex matched conspecific). Testing began on PD60. The mice were exposed to tests with a 1-week inter-test interval. The mice were exposed to the resident-intruder test followed by the open-field test and the light-dark choice test. Studies in our laboratory have consistently found that the order of testing does not affect responses in these paradigms.

Aggressive Behavior—We used the *resident-intruder paradigm* to study intermale aggression. WT and combined TNF-R1 and TNF-R2 KO mice served as residents and non-aggressive Balb/c mice (Charles River Labs, MA) served as intruders. During the latter phase of the light cycle (i.e., approximately 4PM) an intruder mouse was introduced into the home cage of a resident mouse for 15-min. The session was videotaped and scored at a later date by an experienced rater. The following resident behaviors were measured: fighting (the incidence and duration of bouts), aggressive postures (sideways postures and tail rattling), and pursuit episodes. We also measured the time spent engaged in non-aggressive contact (exploratory sniffing) of the intruder.

Anxiety-related behavior—To determine whether TNF receptors affect anxiety related behavior, which is positively correlated with aggression, we determined whether combined TNF-R1 and TNF-R2 deletion affects responding in an open field and the Light-Dark Choice Test.

Open Field: The mice were individually placed into an open field (automated TruScan test arena, Coulbourn Inc., PA) for 2-hr in normal illumination. The test arenas are equipped with photobeam sensor rings that sense in the X-Y dimension and in the Z plane vertical dimension (for rearing). Precision is twice the arena's beam resolution (.76 cm for beam spacing). Each arena is linked via a station interface box to a computer, which runs on Windows 98. The ratio of the time spent in the center and margins of the arena, which reflects, at least in part, anxiety-related responding, was subsequently determined. Mice typically spend more time along the margins of the open field. Thus, a decrease in the time spent in the center of the arena relative to the margins suggests anxiogenic-like behavior while an increase suggests anxiolytic-like behavior.

Light-Dark Choice Test: To better characterize anxiety-related behavior, we also exposed the mice to the light-dark choice test. When given a choice between a well illuminated area and a darkened area, mice typically spend more time in the darkened area. An increase in the time spent in the illuminated area is thought to reflect anxiolytic like responding. A black opaque box was placed into each of the automated TruScan test arenas thereby dividing the arena into 'light' and 'dark' compartments. The 'light' compartment was illuminated with a 40W bulb. The mice were individually placed into the dark compartment and behavior was recorded for 10-min. The following behaviors were measured: the number of moves, and movement time in each compartment.

3. Results

Aggressive Behavior

To evaluate the effects of TNF receptor deletion on the varied components of aggressive behavior, we tested mice in a Resident-Intruder paradigm, in which wild type and TNF receptor deficient mice served as residents, and a non-aggressive Balb/c mouse served as intruders. The results showed a significant effect of genotype on fighting (number of bouts) $F(1, 10) = 16.33, p < .005$ (Figure 1A).

Indeed, there was a striking absence of fighting in the TNFR deficient mice. Whereas WT mice had 7 ± 1.7 bouts per 15-min test session, KO mice had 0 bouts. In WT mice, the mean duration of bouts was 41.6 ± 6.8 s. Of further importance, there were significant between-group differences in aggressive postures, including sideways postures ($F(1, 10) = 12.79, p = .005$; Figure 1B), tail rattling ($F(1, 10) = 12.62, p = .006$; Figure 1C), and pursuit episodes ($F(1, 10) = 5.69, p < .05$, Figure 1D). It should be underscored that as was the case for fighting, a striking absence of sideways postures, and tail rattling was evident in TNFR

deficient mice. Regarding pursuit, two-thirds of the TNFR deficient mice tested showed an absence of pursuit episodes. Parenthetically, data for pursuit are presented as percent control given the inter squad variability in responses (but not in direction of effect). It is also important to note that TNFR deficient mice spent significantly more time than WT mice in non-aggressive exploration of the intruder (Figure 1E). Thus, when confronted with an intruder mouse, resident TNF-R1 and TNFR2 deficient mice showed a lack of aggressive behavior and an increase in nonaggressive exploration.

Anxiety-Related Behavior

To study anxiety-related behavior, we evaluated performance in the Open Field and in the Light-Dark Choice Test. In the Open field, a decrease in the time spent in the center of the arena suggests anxiogenic-like responding while an increase in center time reflects anxiolytic-like responding. In the Light-Dark Choice Test, an increase in activity in the dark compartment is thought to reflect anxiogenic-like responding while increases in the illuminated compartment is thought to reflect anxiolytic-like effects.

The ratios of the time spent and the distance traveled in the center of the open field relative to the margins were markedly higher in TNFR deficient mice than in WT mice, $F(1,10) = 37.56$, $p = .0001$ (Figure 2A), and $F(1,10) = 16.93$ (Figure 2B), respectively. In the Light-Dark Box, the number of moves ($F(1, 10) = 30.46$, $p = .0002$; Figure 2C) and move time ($F(1, 10) = 9.39$, $p = .01$; Figure 2D) in the illuminated compartment were also significantly increased in TNFR deficient mice compared to WT mice. Thus, TNFR deficient mice displayed anxiolytic-like responding in both the open field and in the Light-Dark Box.

Collectively, these data show that deletion of TNF-R1 and TNF-R2 results in a striking lack of aggressive behavior, an increase in non-aggressive behavior, and anxiolytic-like effects. These findings support the view that activation of TNF receptors and thus TNF receptor signaling is associated with heightened aggression and related processes.

4. Discussion

We found that combined deletion of TNF-R1 and TNF-R2 results in a striking absence of aggressive behavior, which includes fighting and various aggressive postures. In parallel, increases in non-aggressive exploration and anxiolytic-like responding were evident in these mice. These findings provide support for the view that activation of TNF receptors potentially regulates aggression and anxiety-related behavior in rodents.

This study did not permit any conclusions to be drawn regarding possible differential effects of TNF-R1 and TNF-R2 in their modulation of either aggression or anxiety-like behavior. Nonetheless, it is of interest to note that Simen et al. (2006) showed that deletion of TNF-R1 results in decreased fear conditioning. It is well established that fear and fear conditioning are clearly linked to aggressive behavior and, in fact, it is recognized and constitutes one of the early and fundamental models of aggression (Moyer, 1968; Siegel, 2005). Thus, in light of the fact that rodents showing increased fear conditioning likewise show increased aggression, it is tempting to speculate that TNF modulation of aggressive behavior is mediated through TNF-R1. Moreover, Simen and colleagues (2006) further showed that deletion of TNF-R1 or TNF-R2 does not appreciably affect anxiolytic-like responding. In view of the linkage between fear (anxiety) and aggression, and since TNF-R1 and TNF-R2 deficient mice presently showed anxiolytic-like behavior, we suggest that combined deletion of TNF-R1 and TNF-R2 is required to affect anxiety-related behavior. Of further importance, in light of the discovery made by Palin and colleagues that TNF-R1 mediates TNF- α -induced sickness behavior (Palin et al., 2009), we tentatively conclude that the

present effects of TNFR deletion on non-aggressive exploration are likewise mediated by TNF-R1.

A separate issue that may be raised is whether the inhibitory effects of TNF deletion upon aggressive and anxiety related behaviors are due to non-specific factors. For example, it could be argued that TNF deletion causes a non-selective depression of motor responses. Such a possibility may be ruled out since such responses were clearly demonstrated in tests of anxiety and exploratory conditions (i.e., as shown in Fig. 2, TNFR-KO mice show increased motor activity in the Open Field (center:margin ratios), and an increase in the number of moves in the illuminated portion of the Light-Dark Box.). Consistent with this finding, TNFR-KO mice did not exhibit freezing behavior. Parenthetically, it has been shown that, anti-anxiety drugs (e.g., diazepam) may affect anxiety-related behavior in the open field without affecting total locomotion, suggesting that motor activity may be dissociated from anxiety-related behavior (Choleris et al., 2001). Anxiolytic-like responses are similarly not necessarily related to changes in motor activity. Moreover, deletion of TNF receptors has been shown to result in other abnormal behaviors or responses that may influence aggression, notably sleep disturbances (Deboer et al., 2002; Fang et al., 1997) and enhanced stress responses (Gimsa et al., 2009). However, such effects would be expected to potentiate aggressive behavior. Moreover, it is possible that TNFR deletion results in a release of other compensatory cytokines. It remains to be determined whether relevant site-specific compensatory increases in inflammatory cytokines occur in the CNS of unchallenged TNF receptor deficient mice, and whether possible changes modulate aggressive behavior. A possible role for IL-1 may be tentatively ruled out, however; at least in the cat, IL-1 in the medial hypothalamus and PAG facilitates aggressive behavior (see Zalcman and Siegel, 2006), although species differences with regards to cytokine effects on aggression need to be considered.

The neural substrates underlying the lack of aggressive behavior in TNF knockout receptor mice remain to be identified. Nonetheless, evidence from studies conducted in the cat suggest that pro-inflammatory cytokines and their receptors potently modulate aggression and rage in the hypothalamus and midbrain periaqueductal gray (PAG), which comprise basic components of the limbic-midbrain axis (Siegel et al, 1999). Specifically, it has been shown that cytokine receptor activation in the hypothalamus and PAG markedly alters response latencies for defensive rage behavior in cats (e.g., Bhatt and Siegel, 2006; Hassanain et al., 2003). Of particular importance with respect to these studies, the modulating effects of these cytokines upon the rage response were mediated through known neurotransmitter systems (see Zalcman and Siegel, 2006). The implication of these studies with respect to the present observations is that TNF receptor activation in the medial hypothalamus and PAG likely play principal roles in mediating the potentiating effects upon aggressive behavior seen in TNFR knockout mice.

Inasmuch as TNF receptors are found in the limbic-midbrain axis (Bette et al., 2003; Simen et al., 2006), future studies should aim to identify specific sites of action. It is reasonable to suggest that, based upon studies conducted in cats, affective aggression (expressed in the present study as fighting behavior) is generated through a mechanism situated in the medial hypothalamus and ultimately upon neurons in the midbrain PAG (Siegel et al, 1999; Siegel et al., 2007). It is of interest to note that a somewhat similar projection pattern was described in the rat concerning descending projections from the hypothalamus to the midbrain (Roeling, et al, 1994). Accordingly, we further suggest that such a mechanism involves the activation of TNF receptors present in the medial hypothalamus whose excitatory functions are mediated through known neurotransmitter systems (see Anisman et al., 2003; Dunn, 2006) in these regions of the brain such as 5-HT₂, catecholamine receptors, or NK₁ receptors, all of which are known to potentiate rage behavior (Siegel et al, 1999). Moreover,

since it has been established that the output functions of the medial hypothalamus are mediated through excitatory NMDA receptors in the dorsal PAG in cats (Lu et al., 1992; Schubert et al, 1996), we speculate that a similar mechanism may likewise be present in the rodent, in which the midbrain PAG is then viewed as the most caudal region of the CNS linked to the integration of fighting and rage behavior.

In view of the similar effects of TNF upon both aggression and anxiety seen in the present study, it is possible that overlapping neural structures underlie TNF modulation of these processes. It has recently been discovered that anxiety and related behaviors are associated with the PAG (Cunha et al., 2009) and the amygdala (LeDoux, 1998; Roozendaal et al., 2009). Therefore, it is possible that TNF modulation of anxiety and aggression are mediated through actions upon receptors in these regions. Other components of the limbic-midbrain axis known to modulate aggression remain possibilities as well, including the hypothalamus, prefrontal cortex, hippocampal formation and septal area (Siegel et al., 1999).

In conclusion, the present data identifies for the first time a previously unknown potent role that TNF receptors play in the expression of aggressive behavior in rodents. That aggressive behavior was absent in TNFR deficient mice suggests that TNF normally exerts a tonic potentiating effect on aggression. Presumably, these effects are manifest through interactions with neurotransmitters in the medial hypothalamus and PAG. We suggest that a greater understanding of this phenomenon may be gained by identification of molecular mechanisms governing TNF potentiation of aggressive behavior.

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Figure 1.

Measures of aggressive behavior (mean + s.e.m.) in Wild Type and TNF-R1 and TNF-R2 deficient mice (TNF-R1/TNF-R2 $-/-$) in the Resident-Intruder paradigm. A striking absence in the number of Bouts (A), Sideways Postures (B), and Tail Rattling (C), and a marked decrease in Pursuit Episodes (D) was evident in TNFR deficient mice. Non-aggressive exploratory sniffing was significantly increased ($p < .05$) in TNFR deficient mice.

Figure 2.

Effects of TNF receptor deficiency on anxiety-related behavior (mean + s.e.m.) in the Open-Field and Light-Dark Choice Test. Compared with Wild Type mice, TNF-R1 and TNF-R2 deficient mice (TNF-R1/TNF-R2 ^{-/-}) exhibited an significant increase in anxiolytic-like behavior as reflected by an increase in the amount of time spent (A) and distance traveled (B) in the center relative to the margins of the open-field. Of further importance, the number moves (C) and amount of time (D) in the illuminated (Left Half) of the Light-Dark Box was significantly increased ($p < .05$) in TNFR deficient mice.