Short Communication

Intracerebroventricular Injection of Anti-Fas Activates the Hypothalamus-Pituitary-Adrenal Axis and Induces Peripheral Interleukin-6 and Serum Amyloid A in Mice

Comparison with Other Ligands of the Tumor Necrosis Factor/Nerve Growth Factor Receptor Superfamily

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Fas is a receptor of the tumor necrosis factor (TNF)/nerve growth factor (NGF) receptor superfamily that mediates apoptosis and some inflammatory changes. As the central administration of TNF is known to activate the hypothalamus-pituitary-adrenal axis (HPAA) and to induce peripheral responses including induction of serum interleukin (IL)-6 and serum amyloid A (SAA), we investigated the effects of intracerebroventricular (i.c.v.) administration of agonist anti-Fas monoclonal antibody Jo2. Centrally administered anti-Fas (1 µg/mouse, i.c.v.) induced elevated levels of corticosterone, IL-6, and SAA comparable to those observed after i.c.v. administration of recombinant murine TNF. On the other hand, administration of murine NGF did not elevate serum corticosterone or IL-6, but induced SAA. Thus, Fas can trigger a centrally mediated anti-inflammatory response (HPAA activation) and induce a peripheral acute-phase response comparable to that induced with TNF, whereas NGF induces only acute-phase proteins. (*Am J Pathol* 1998, 153:1377-1381)

Fas is a cell surface receptor belonging to the tumor necrosis factor (TNF)/nerve growth factor (NGF) receptor superfamily that mediates apoptotic death upon activation by Fas ligand or agonist antibodies.^{1,2} Lymphocyte-

mediated apoptosis may play a role in a variety of autoimmune diseases,³ and Fas expression was recently reported in the brain of multiple sclerosis patients⁴ and was suggested to be involved in other diseases of the central nervous system.⁵ In addition to inducing apoptosis, Fas induces typical inflammatory changes, including increase of interleukin (IL)-6 and IL-8 secretion and activation of nuclear factor- κ B.^{6,7}

In vivo administration of Fas ligand or the agonist anti-Fas monoclonal antibody (MAb) Jo2 induces fulminant hepatitis⁸ and lethality in *Propionibacterium acnes*-pretreated mice.^{8,9}

One of the main protective mechanisms against TNF-mediated systemic toxicity is represented by the activation of the hypothalamus-pituitary-adrenal axis (HPAA), resulting in an increase in serum corticosteroid levels.^{10,11} Several cytokines activate the HPAA, including IL-1¹² and TNF,¹³ whereas other cytokines, (IL-6, IL-11, ciliary neurotrophic factor, leukemia inhibitory factor, and cardiotrophin-1) potentiate this induction.¹⁴

Activation of the HPAA, either by cytokines or stress, represents a negative feedback mechanism that inhibits the production of pro-inflammatory cytokines.^{11,15} In fact, adrenalectomized mice are extremely sensitive to cytokine-mediated lethality.¹⁶ Activation of the HPAA is also important in the recovery from experimental autoimmune encephalomyelitis,^{17,18} and an impairment of this re-

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sponse was associated with the susceptibility of Lewis rats to arthritis.¹⁹

Activation of the HPAA is not the only action of pro-inflammatory cytokines on the central nervous system. There is evidence that also induction of peripheral responses (IL-6 and liver acute-phase proteins) can be induced through a centrally mediated action. In fact, we previously reported that intracerebroventricular (i.c.v.) injection of lipopolysaccharide (LPS), TNF,²⁰ or IL-1²¹ induces higher circulating levels of IL-6 than when the inducer is injected peripherally. It has also been known for a long time that centrally injected IL-1 induces a liver acute-phase response at doses that are ineffective when administered peripherally.^{22,23}

In a recent study using agonist antibodies or knock-out mice, we have shown that activation of the HPAA and induction of peripheral IL-6 induced by i.c.v. injection of TNF is mediated primarily by TNF receptor (TNFR) p55.²⁰ Due to the sequence homology and functional similarities between Fas and the TNFR p55,¹ we investigated whether in the central nervous system Fas could mediate an activation of the HPAA and an induction of a peripheral acute-phase response.

For this purpose, we injected mice i.c.v. with the agonist anti-Fas MAb Jo2 and measured serum corticosterone levels. We also measured serum levels of IL-6 and of the liver acute-phase protein, serum amyloid A (SAA). In these experiments, the effect of anti-Fas was compared with that of murine recombinant (rm)TNF and murine nerve growth factor (NGF), which was previously shown to induce acute-phase proteins *in vivo*.²⁴

Materials and Methods

Animals and Treatments

Procedures involving animals and their care were conducted in conformity with the institutional guidelines that are in compliance with national (D.L. 116, G.U. supplement 40, 18 February, 1992, Circolare 8, G.U. Luglio 1994) and international laws and policies (EEC Council Directive 86/609, OJ L 358, 1, December 12, 1987; Guide for the Care and Use of Laboratory Animals, U.S. National Research Council, 1996).

Male CD-1 mice (25 g body weight) from Charles River Italia, Calco, Como, Italy, were used. Mice were housed five per cage and fed *ad libitum*. The agonist anti-Fas MAb Jo2 (a kind gift from Dr. Shigekazu Nagata, Osaka University Medical School, Osaka, Japan) was injected i.c.v. via a 28-gauge needle into ether-anesthetized mice^{25,26} at the dose of 1 μ g/mouse. All i.c.v. injections were made in a final volume of 10 μ l. At 90 minutes, 3 hours, or 24 hours after injection, blood was obtained from the retro-orbital plexus under light ether anesthesia, and serum was prepared. Control mice received saline alone or an irrelevant MAb (anti-human TNFR p55, a kind gift from Dr. Wim Buurman, University of Limburg, Maastricht, The Netherlands), as previously described.²⁰ In some experiments, mice were injected i.c.v. with 1 μ g of rmTNF (kind gift of Prof. Walter Fiers, Ghent, Belgium) or

Figure 1. Central administration of anti-Fas activates the hypothalamus-pituitary-adrenal axis. Mice were treated i.c.v. with 1 μ g of anti-Fas, rmTNF, or both, and serum corticosterone was measured 1.5 and 3 hours later. Data are presented as mean $\pm$ SD ($n = 5$). * $P < 0.05$ versus saline alone by Duncan's test.

2.5 μ g of murine β -NGF. Murine NGF (2.5S) was purified from the salivary gland of adult male mice following the procedure described by Bocchini and Angeletti.²⁷ The concentration of pure NGF was determined by molar extinction, and the biological activity of the purified NGF was evaluated with the *in vitro* bioassay.²⁸

Biochemical Determinations

Serum corticosterone was measured by a radioimmunoassay using an antiserum for corticosterone radioimmunoassay obtained from Sigma (C-8784; Sigma Chemical Co., St. Louis, MO) and following manufacturer's indications. [³H]Corticosterone was purchased from Amersham (Arlington Heights, IL).

SAA was measured by a previously described ELISA (Hemagen Diagnostics, Waltham, MA).

IL-6 was measured as hybridoma growth factor using 7TD1 cells (a kind gift from Dr. Jacques van Snick, Brussels, Belgium) as previously described.²⁹ IL-6 activity is expressed as co-stimulatory units per milliliter using rIL-6 as a standard. The sensitivity of the assay was 50 U/ml.

Results

Mice received 1 μ g of anti-Fas antibody and were bled at 1.5, 3, or 24 hours for corticosterone or IL-6 and at 24 hours for SAA, based on previous results showing that these are the optimal time points for the effects under investigation when cytokines are injected i.c.v. It should also be noted that anti-Fas-injected mice did not look sick within this time frame (i.e., 24 hours).

Figure 1 shows the effect of an i.c.v. injection of anti-Fas on serum corticosterone 1.5 and 3 hours after injection. Control mice received saline i.c.v. alone. For pur-

Figure 2. Central administration of anti-Fas induces peripheral IL-6. Mice were treated i.c.v. with 1 μ g of anti-Fas, rmTNF, or both, and serum IL-6 was measured 1.5 and 3 hours later. Data are presented as mean $\pm$ SD ($n = 5$). ** $P < 0.01$ versus saline alone by Duncan's test.

Figure 3. Central administration of anti-Fas induces SAA. Mice were treated i.c.v. with 1 μ g of anti-Fas, rmTNF, or 2.5 μ g of mNGF, and SAA was measured in serum 24 hours later. Data are presented as mean $\pm$ SD ($n = 5$). ** $P < 0.01$ versus saline alone by Duncan's test.

pose of comparison, the effect of 1 μ g of rmTNF (also given i.c.v.) is also shown. It can be seen that both rmTNF and anti-Fas augmented approximately two- to three-fold serum corticosterone levels. Co-administration of the two resulted in an additive effect, although no direct comparison of anti-Fas and rmTNF can be made in terms of dose. In two separate experiments we tested an irrelevant antibody, as described in Materials and Methods, at doses up to 6 μ g/mouse, and did not see any augmentation of serum corticosterone compared with saline controls (data not shown), in agreement with previous reports.²⁰

Figure 2 shows that i.c.v. injection of anti-Fas markedly induced serum IL-6 levels, to an extent comparable to that of rmTNF. The levels of IL-6 after anti-Fas were 3512 U/ml at 1.5 hours and 6432 U/ml at 3 hours; those after rmTNF were 4433 U/ml and 1505 U/ml 1.5 and 3 hours later, respectively. As for corticosterone, an additive effect was observed between anti-Fas and rmTNF. An irrelevant isotype MAb (see Materials and Methods), at doses up to 6 μ g, did not induce any significant augmentation of serum IL-6 compared with saline controls (6 μ g of α hTNFR p55 produced undetectable levels of serum IL-6, ie, <50 U/ml in one experiment and 149 ± 104 U/ml in a second experiment), in agreement with previous reports.²⁰

Under the experimental conditions described above, i.c.v. administration of murine NGF (2.5 μ g/mouse) did not elevate serum corticosterone or IL-6 (data not shown).

As shown in Figure 3, i.c.v. administration of anti-Fas antibody induced marked levels (50 μ g/ml) of SAA 24 hours after treatment. The levels of SAA were very low after saline injection (7 μ g/ml). Also, rmTNF and murine NGF induced marked levels of SAA.

Discussion

Our paper shows that one central effect of anti-Fas administration is to increase serum levels of corticosterone, IL-6, and SAA. Elevation of serum corticosterone might have various suppressive actions on the immune system and, in particular, inhibit the synthesis of several cytokines.^{10,11} Activation of the HPA axis is generally viewed as an anti-inflammatory feedback response, but corticosteroids may have other actions, including induction of apoptosis in T cells.

Also, induction of IL-6 and SAA may be viewed as protective mechanisms. In fact, previous works have shown that induction of hepatic acute-phase proteins is important in the protective effect of IL-1 pretreatment against sepsis,³⁰ and administration of acute-phase proteins or their overexpression in transgenic animals is protective against endotoxemic shock or TNF-induced lethality.^{31,32} Another acute-phase protein, α 2-macroglobulin, has a protective effect in animal models of experimental autoimmune encephalomyelitis.³³

Furthermore, IL-6 might be regarded as protective. In fact, exogenous administration of IL-6 inhibits TNF production *in vitro* and *in vivo*^{34,35} and IL-6-deficient mice produce more TNF in response to endotoxin.^{35,36}

The fact that TNF, but not NGF, share with Fas the ability to induce serum corticosterone and IL-6 is in agreement with the differences in the various receptors of the TNF/NGF superfamily. This superfamily includes the two TNF receptors, the low-affinity NGF receptors, and other members. However, whereas the extracellular amino acid sequence of the extracellular region is relatively conserved, the cytoplasmic region is not, and in this case the similarities are restricted to Fas and TNFR p55.³⁷ If we consider that our previous work indicated that TNFR p55 is responsible for the central effects reported here,²⁰ it is not surprising that the action of TNF is

shared only by Fas and not NGF. The observed induction of acute-phase proteins after systemic²⁴ or central (this paper) administration of NGF might therefore be mediated either by the peripheral NGF receptor or by a receptor subtype other than the low-affinity one which belongs to the TNFR family.

It should be noted that Fas shares with the receptors for IL-1 and TNF (IL-1RI and TNFR p55, respectively) a signaling cascade involving MAP3K kinase ultimately resulting in the activation of NF- κ B,³⁸ a transcription factor of particular importance in the inflammatory response. As IL-1 and TNF, like Fas, are activators of the HPAA, common pathways are likely candidates as the mediators implicated in these effects. It is, however, difficult to explain the lack of effect of NGF in our system within this frame, as controversial reports have indicated either that NGF activates NF- κ B³⁹ or that, unlike TNF, NGF does not activate this transcription factor in neural tissue.^{40,41}

Thus, activation of the HPAA and induction of SAA seem to be a common feature of anti-Fas and TNF. It seems likely that the elevation of SAA by anti-Fas reported in this paper is mediated by IL-6, a key mediator of the acute-phase response,⁴² which is produced in the periphery after central administration of anti-Fas. This is very similar to what occurs with IL-1 that, when injected i.c.v., induces a peripheral acute-phase response,^{22,43} probably due to centrally mediated induction of peripheral IL-6.²¹

The fact that central injection of anti-Fas activates the HPAA might imply that hypothalamic neurons are responsive to Fas, ie, express Fas. To our knowledge, there are no studies on the localization of Fas in adult brain, but expression of Fas in the brain of adult mice was reported.⁴⁴

However, *in vitro* studies with cells of the central nervous system have shown that Fas is expressed in oligodendroglia, particularly astrocytes, rather than on neurons,⁴⁵ and similar results were obtained by immunohistochemistry in MS brains.⁴ It is thus possible that the activation of the HPAA reported in the present paper might be mediated by the activation of the cytokine cascade, as suggested by the induction of IL-6, although induction of serum corticosterone cannot be due only to induction of IL-6 as administration of IL-6 alone does not significantly increase serum corticosterone in our experimental model.^{14,35}

On the other hand, IL-6 is a potent inducer of SAA,¹⁴ and it cannot be excluded that it mediates the elevation of SAA observed after anti-Fas injection. The induction of an acute-phase protein by Fas reported here might be important in the observed elevation of acute-phase proteins in experimental autoimmune encephalomyelitis.^{33,46,47}

In conclusion, we have shown that activation of Fas in the central nervous system results in an induction of an acute-phase response and activation of the HPAA similar to those of TNF, previously reported to be mediated by TNFR p55. These actions, particularly elevation of corticosterone and of acute-phase proteins, might counteract pro-inflammatory cytokines and thus have a protective effect in some diseases associated with Fas activation.

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