Journal of Neuroimmunology 204 (2008) 38–42

Contents lists available at ScienceDirect

Journal of Neuroimmunology

ournal homepage: www.elsevier.com/locate/jneuroim

Inter-strain differences in glucocorticoid and mineralocorticoid effects on macrophage and lymphocyte functions in mice

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ARTICLE INFO

Article history:
Received 15 May 2008
Received in revised form 2 August 2008
Accepted 11 August 2008

Keywords:
Mice strains
Immune cells
Corticosteroids
Glucocorticoid receptors
Mineralocorticoid receptors
Corticosteroid sensitivity

ABSTRACT

We showed previously and we confirm here that macrophages from three mouse strains are differentially sensitive to the inhibition of expression of key inflammatory proteins (iNOS-II, IL-1β) by dexamethasone, a specific glucocorticoid receptor agonist (C57BL/6>DBA/2>BALB/c). Here we show that aldosterone (a specific mineralocorticoid agonist) has no effect on iNOS-II or IL-1β expression in macrophages from these mouse strains but decreases IL-1ra expression, with small inter-strain differences. This mechanism may be involved in the pro-inflammatory effect of this hormone. Concanavalin A-stimulated lymphocytes proliferation is also differentially sensitive to dexamethasone according to the strain, but insensitive to aldosterone.

1. Introduction

Corticosteroid hormones, glucocorticoid (GC) and mineralocorticoid (MC), released in response to the activation of the hypothalamo-pituitary-adrenal (HPA) axis are involved in the regulation of several physiological mechanisms and pathophysiological processes. They affect immune and central nervous system activities, mediate the stress response, and regulate glucose and fat metabolism (Staples et al., 2003). GC are the most studied anti-inflammatory hormones particularly known by their action on immune response. They affect circulating blood cells of the immune system, a major GC target tissue. Indeed, in monocytes/macrophages and lymphocytes, GC decrease many cellular functions including interleukin secretion, enzyme synthesis, cell differentiation, proliferation and migration (Elenkov et al., 1999; Herold et al., 2006; Medzhitov and Janeway, 1997; Sharif et al., 2007). Large genetic differences have been described in HPA axis functioning in several species (Mormede et al., 2002). Inter-strain differences have also been described with regards to inflammation and immunity functions (Harizi et al., 2007; Tumes et al., 2007). Taken together this suggests that genetic variations in HPA activity could interfere with variations in immune functions. Indeed, we have previously shown that macrophages from different strains of mice exhibit different sensitivities to an exclusive GR agonist, dexamethasone (Harizi et al., 2007).

Endogenous corticosteroid hormones act through two types of receptors: the glucocorticoid receptor (GR) and the mineralocorticoid receptor (MR) (Fuller et al., 2000; Liberman et al., 2007). Corticosteroid hormones act through these two closely related receptors and a common DNA response element (Glucocorticoid Response Element, GRE). There is very little evidence to support a specific action of MR on DNA through a non-GRE sequence (Fuller et al., 2000; Grossmann et al., 2007). *In vivo*, the MR is potentially activated by endogenous corticosteroid hormones such as corticosterone and mineralocorticoids such as aldosterone.

MR are present in immune tissues and there is some evidence for their action with corticosteroid hormones on monocytes or promonocytes (Calle et al., 2003; Miller et al., 1993; Sauer et al., 1996) but, compared to glucocorticoids, little is known about the effect of mineralocorticoids on immune cells. It is not known whether mouse macrophages or lymphocytes are responsive to MR agonists and if there are different degrees of sensitivities such as the ones seen with an exclusive GR agonist (dexamethasone) (Harizi et al., 2007). Thus, we investigated here the effect of aldosterone on macrophages and lymphocytes obtained from C57BL/6, DBA/2 and BALB/c mice strains. We analyzed LPS-induced macrophage protein expression and concanavalin (ConA)-stimulated lymphocyte proliferation under aldosterone and dexamethasone, and compared their effects.

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doi:10.1016/j.jneuroim.2008.08.004

2. Materials and methods

2.1. Animals

C57BL/6, DBA/2 and BALB/c mice were obtained at weaning from Charles Rivers (Lyon, France). Mice were fed standard pellets and water *ad libitum* and maintained at 22 ± 1 °C on a 12 h light–dark cycle. Eight-week-old animals were used. All procedures followed the French legislation on research involving animal subjects, and the recommendations of the European Community Council for the Ethical Treatment of Animals (no. 86/609/EEC).

2.2. Preparation of bone marrow-derived macrophages

Macrophages were generated *in vitro* from C57BL/6, DBA/2, and BALB/c mice bone marrow (BM) according to Harizi et al. (2002) with slight modifications. Briefly, BM of three 10 week-old male mice was extracted from femurs and tibias. Myeloid precursors were pooled in serum free RPMI 1640 medium (GIBCO, BRL) and washed. Then precursor cells were plated at 10^6 cells/ml and differentiated into macrophages during 4 days in RPMI 1640 medium supplemented with 1% streptomycin (GIBCO BRL, 1000 μg/ml), 2 mM L-Glutamine (Sigma), 2 mM sodium pyruvate (Sigma), 5% heat-inactivated FCS (Dominique Dutscher, Brumath, France) and 10 ng/ml of murine Granulocyte Macrophage-Colony Stimulating Factor (mGM-CSF, Pepro Tech Inc, USA) at 37 °C and 5% CO_2. Mice bone marrow-derived macrophages obtained at ~98% purity were characterized by flow cytometry analysis as CD14 positive cells.

2.3. Western blot analysis

Macrophages obtained *in vitro* from bone marrow cells (Harizi et al., 2007), were stimulated (10^6 cells/ml) with LPS (1 μg/ml) in the presence of increasing concentrations of aldosterone, (Sigma) for 24 h. Controls included cells cultured alone and cells stimulated with LPS without aldosterone. At the end of stimulation period, the cells were washed twice with PBS and were subsequently lysed in ice-cold lysis buffer containing 10 mM HEPES (pH 7.6), 3 mM $MgCl_2$, 40 mM KCl, 2 mM DTT, 0.5% Nonidet P-40, 8 μg/ml aprotinin, 8 μg/ml leupeptin, and 10 μg/ml PMSF. The bicinchoninic acid protein assay reagent (Pierce, Rockford, IL) was used for analyzing the protein concentration. Cytoplasmic extracts (20 μg protein/lane) were resolved on 8% SDS-polyacrylamide gels, and Western blotting analysis was performed using an ECL kit (Amersham, Little Chalfont, U.K.). The blots were probed with specific Abs directed against COX-2 (1/2000 dilution; Cayman Chemicals), iNOS-II (1/2000 dilution; BD Transduction Laboratories, Lexington, KY), IL-1β (1/2000; Santa Cruz Biotechnology, Santa Cruz, CA), IL-1ra (1/1000; Santa Cruz Biotechnology, Santa Cruz, CA), or α-actin (1/2500; Sigma-Aldrich). The blots were subsequently incubated with the specific secondary Ab (peroxidase-labeled Ab) and analyzed by an Amersham ECL and Kodak XAR-5 film (Eastman Kodak, Rochester, NY).

2.4. Preparation and proliferation of spleen-derived lymphocytes

The splenocytes were isolated, washed with PBS and plated in 96 wells plates (10^5/well) with complete medium. They were first stimulated by concanavalin A (ConA) 2 μg/ml during 3 days. 3H-thymidine (2 μCi/well, Amersham) was then added and the cells were allowed to grow for 24 h with the same concentration of ConA added to various concentrations of drugs (aldosterone or dexamethasone). The plates were harvested onto glass-fiber filters with an IH-10 harvester (Ionetech, Dottikon, Switzerland), and the filters were counted for 1 min in a 1450 Millicroplate counter (Wallac, Turku, Finland) (Harizi and Gualde, 2002). ConA-stimulated wells expressed about 140,000 cpm.

2.5. Data analysis

The concentration of aldosterone reducing protein expression by 50% (ED50) was computed with the PRISM® software by nonlinear

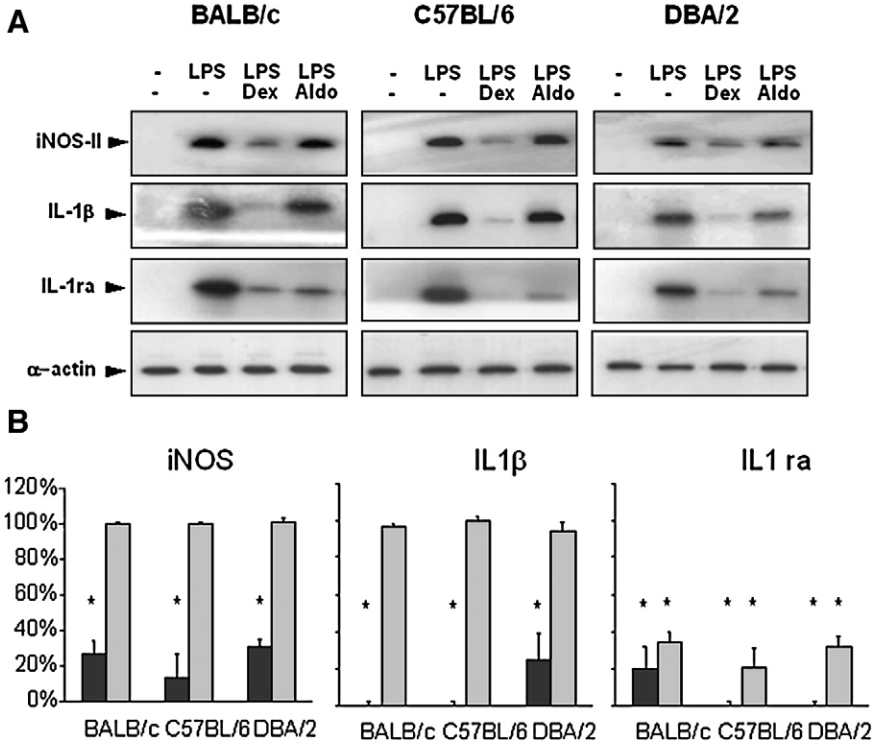

Fig. 1. Comparative protein expression of the effects of dexamethasone (10 nM) and aldosterone (10 nM) in bone marrow-derived macrophages of three mouse strains. (A) Western blot analysis of iNOS-II, IL-1β and IL-1ra protein expression. (B) Graphical display of relative densities of protein bands (mean ± S.D., $n = 3$); relative expression compared to LPS-stimulated cell. (black bars dexamethasone, gray bars aldosterone; * significantly different from control *i.e.* LPS-stimulated cells from the same mouse strain). Western blot for α-actin served as control for sample loading.

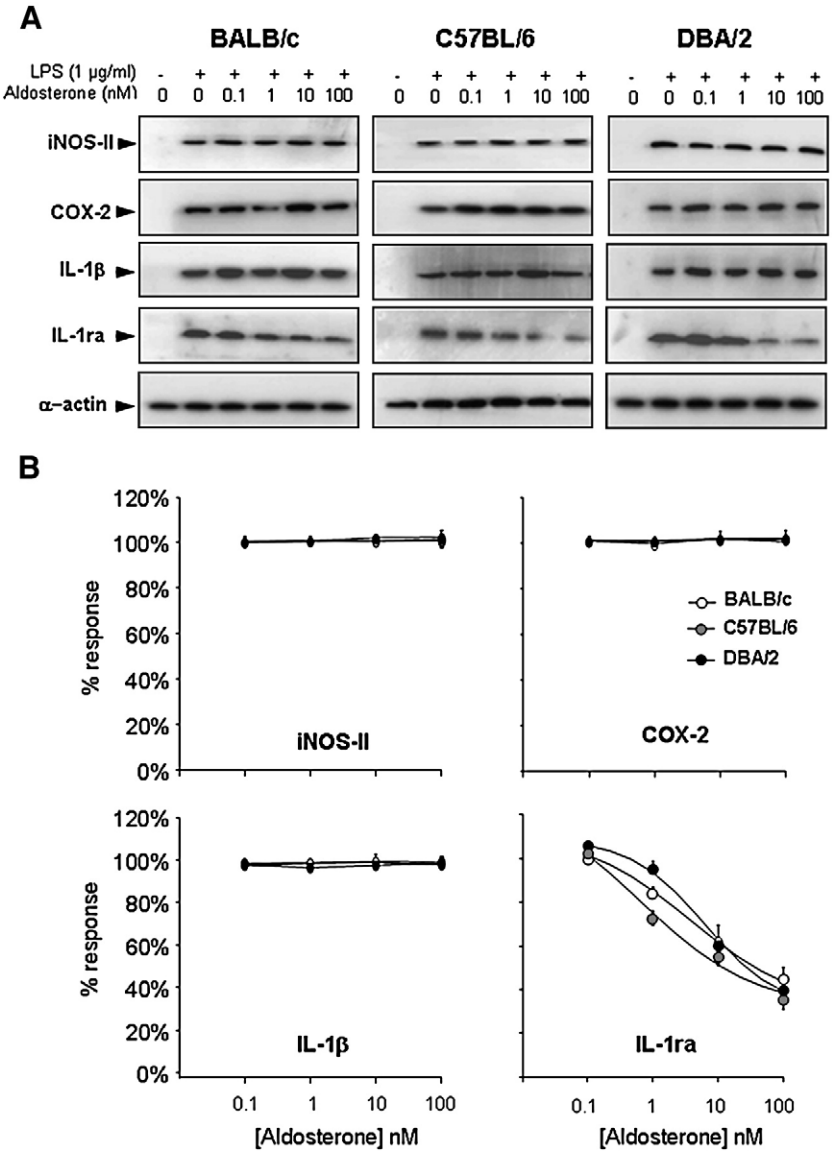

Fig. 2. Dose–responses to aldosterone on the expression of iNOS-II, COX-2, IL-1β and IL-1ra in bone marrow-derived macrophages of three mouse strains (BALB/c open circles, C57BL/6 grey circles, DBA/2 filled circles). Results are expressed as percentage of LPS-stimulated values. (A) Protein (iNOS-II, COX-2, IL-1β, IL-1ra) expression upon aldosterone treatment (Western blots). (B) Graphical display of protein expression showing a significant dose-dependent inhibition of IL-1ra upon aldosterone treatment.

regression (sigmoid dose–response curve) and differences among group means were computed by Kruskal–Wallis tests followed by pairwise comparisons by Wilcoxon tests.

3. Results

3.1. Effects of corticosteroid hormones on inflammatory protein synthesis of bone marrow-derived macrophages

We recently showed inter-strain differences of sensitivity towards dexamethasone in the macrophage inflammatory response (Harizi et al., 2007). We confirm in the present experiment that dexamethasone (10 nM) decreases iNOS-II and IL-1β protein levels in bone marrow-derived macrophages and extend these data to the effect of dexamethasone on IL-1ra protein levels (Fig. 1). The three mouse strains studied were differentially sensitive to dexamethasone inhibition as previously shown (C57BL/6>DBA/2>BALB/c) (Harizi et al., 2007).

In the present study, the effect of aldosterone (10^{-11} to 10^{-7} M), a specific mineralocorticoid receptor agonist, was also investigated on iNOS-II, COX-2, IL-1β and IL1-ra protein expression. Aldosterone failed

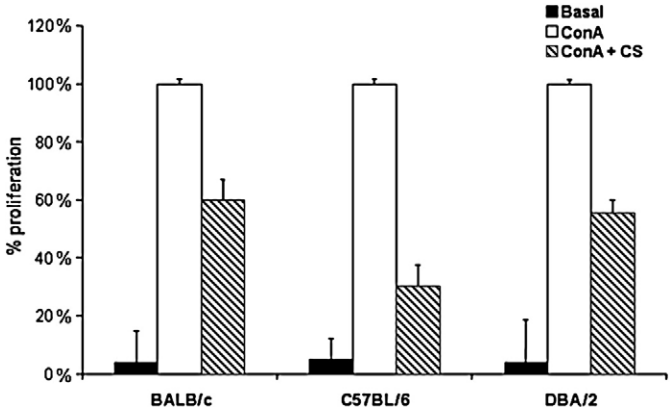

Fig. 3. Effects of concanavalin A (Con A, 2 μg/ml, filled bars) and Con A added corticosterone (CS, 10 nM, hatched bars) on the proliferation of lymphocytes of three mouse strains (BALB/c, C57BL/6, DBA/2). Results of three different experiments are expressed as percentage of Con A-stimulated values.

to elicit any modification of iNOS-II, COX-2 or IL-1β protein concentrations in macrophages whatever the mouse strain (Fig. 2). Conversely, IL1-ra protein expression was dose-responsively decreased by aldosterone, and macrophages from C57/BL6 were significantly more sensitive compared to the two other strains (EC50: C57/BL6 0.6 nM, DBA/2 3.8 nM and BALB/c 6.2 nM respectively, $p<0.01$). However, the inhibition caused by the highest tested dose of aldosterone (100 nM) was similar in the three strains (C57/BL6 42±2, DBA/2 50±6 and BALB/c 49±2% of LPS-stimulated level).

3.2. Effects of GR and MR agonists on proliferation of spleen-derived lymphocytes

Lymphocyte proliferation was stimulated by Con A (2 μg/ml) for 3 days. The endogenous GR and MR ligand corticosterone (CS, 10 nM) decreased proliferation of lymphocytes of the three mouse strains: C57BL/6 30±7%, DBA/2 55±5% and BALB/c 60±7% (compared to control—ConA-treated—cells, 100%) (Fig. 3).

The endogenous specific MR ligand aldosterone (0.1 to 100 nM) failed to elicit any modification of lymphocyte proliferation whatever the mouse strain (Fig. 4A). A MR antagonist, spironolactone, had no effect either (not shown). Conversely, the specific GR agonist dexamethasone dose-dependently decreased ConA-stimulated lymphocyte proliferation (Fig. 4B). Lymphocytes from the three strains expressed a different sensitivity to the effects of dexamethasone (EC50 C57/BL6 1.1 nM, DBA/2 2.0 nM and BALB/c 1.7 nM respectively, $p<0.01$). Cells from C57/BL6 were significantly more sensitive compared to the two other strains. The inhibition caused by the highest tested dose of dexamethasone (100 nM) was also significantly higher in cells from C57/BL6 (18±13% of LPS-stimulated level) compared to the two other strains (DBA/2 and BALB/c, 52±2 and 49±9%, respectively, $p<0.01$).

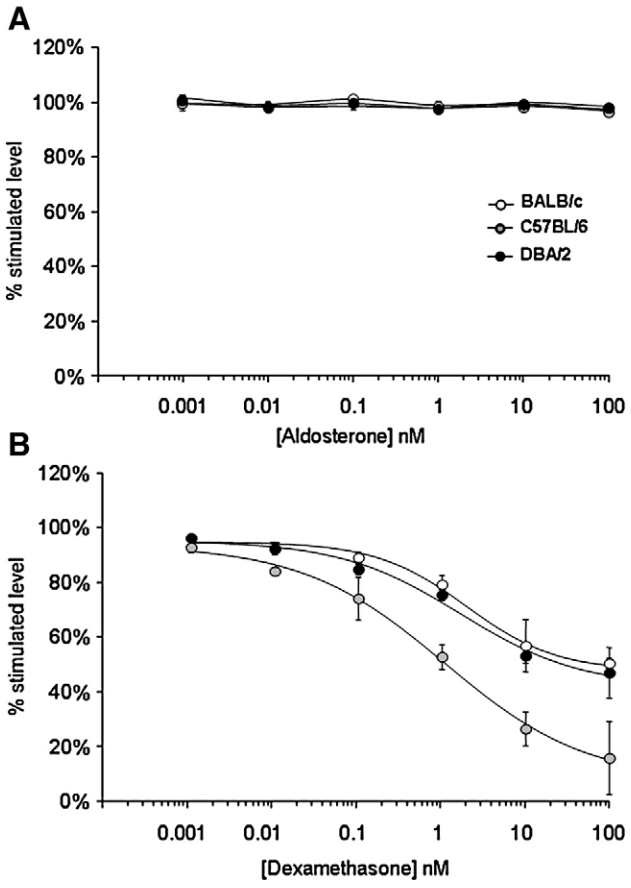

Fig. 4. Dose–responses to aldosterone or dexamethasone on the proliferation of lymphocytes of three mouse strains (BALB/c open circles, C57BL/6 grey circles, DBA/2 filled circles). Results are expressed as percentage of LPS-stimulated values. (A) Lack of effect of aldosterone on lymphocyte proliferation. (B) Significant dose-dependent inhibition of proliferation by dexamethasone.

4. Discussion

Corticosteroid hormones interact—among many other tissues—with the immune system through two receptors, MR and GR. Consequently, deciphering the respective consequences of one or the other receptor activation requires pharmacological manipulations. We investigated the effects of ligands of both receptors on two types of immune cells lymphocytes and macrophages using cell proliferation or protein synthesis evaluation.

Lymphocyte proliferation is a primary mode of response of these cells to inflammatory signals (Boyman et al., 2007; Krammer et al., 2007). In our *in vitro* model, ConA induced lymphocyte proliferation that was reduced by corticosterone that displays both MR and GR agonist properties. This effect was mimicked by the selective GR agonist dexamethasone. Conversely, the selective MR agonist aldosterone did not demonstrate any effect. Thus, the effects of the endogenous corticosteroid hormones on lymphocyte proliferation are likely to be limited to activation of GR. It is interesting to note that the sensitivity of lymphocytes to the effect of GR ligands is different from one mouse strain to the other. Such a variation has been reported in another model of immune cells *i.e.* macrophages (present results and Harizi et al., 2007) in which inter-strain differences in dexamethasone sensitivity of the macrophage inflammatory response has been described. The cells from these strains follow the same order of sensitivity for the GR ligand either for lymphocyte proliferation or protein synthesis in macrophages. This argues for a general effect on gene transcription and not to a phenomenon limited to *in vitro* differentiated macrophages. In DBA/2 and BALB/c lymphocytes the highest tested dose of dexamethasone did not achieve the maximal effect seen in C57BL/6 lymphocytes. Whether this is due to a subpopulation of lymphocytes resistant to dexamethasone or qualitatively differently sensitive to ConA, or to a global resistance of all cells to dexamethasone remain to be established (Lee et al., 2007).

Cytokine synthesis is a primary mode of response of macrophages to inflammatory stimuli (Elenkov and Chrousos, 2002). The synthesis by macrophages of cytokines as well as enzymes involved in inflammatory processes is reduced by the GR agonist dexamethasone (Harizi et al., 2007; Joyce et al., 1997). MR activation appears to influence neither lymphocyte proliferation, nor COX-2, iNOS, nor IL1β expression. Although aldosterone is able to modify iNOS and COX-2 expression in rat cardiac cells (Chun et al., 2003; Rebsamen et al., 2004), it did not alter either iNOS or COX-2 expression in our model of macrophages. Presumably, this tissue selectivity rests upon variations of tissue-specific MR cofactors. Conversely, aldosterone inhibited the production of IL-ra by bone-derived macrophages, and the three strains of mice exhibited slightly different sensitivities to this exclusive MR agonist, although the difference across strains was less than with the synthetic pure GR agonist, dexamethasone. This means that MR can be efficiently activated in these mouse cells: mineralocorticoid hormones are therefore able to regulate at least some inflammatory and immune functions of macrophages. An effect of aldosterone has also been reported in human macrophages *in vitro* (Sauer et al., 1996). IL-1ra is a member of the IL-1 gene family, which despite binding to the IL-1r with approximately equal affinities as IL-1α and IL-1ß, has no known agonist activities (Eisenberg et al., 1990; Elenkov et al., 1999; Hannum et al., 1990). LPS or peptidoglycan stimulates an increase in IL-1ra gene expression and protein synthesis. Thus, IL-1ra represents an endogenous actor through which the pro-inflammatory action of IL-1 can be modulated. IL-1ra isoforms are expressed within a variety of cell types, including epithelial cells, fibroblasts, keratinocytes, monocytes/macrophages and polymorphonuclear leukocytes (Holtkamp et al., 1999; Jenkins and Arend, 1993;

Poutsiaka et al., 1991). We show here that IL-1ra is regulated by mineralocorticoid hormones in macrophages. By such a mechanism, aldosterone may exert a pro-inflammatory effect. One should notice that pro-inflammatory effects of aldosterone or anti-inflammatory effects of MR antagonists (aldactone or eplerenone) have been described in other models (Corbould, 2007; Joffe and Adler, 2005; Lam et al., 2006; Savoia et al., 2008; Young, 2008). Sensitivity to aldosterone is variable according to the strain of mouse they were derived from, C57BL/6 being the most and BALB/c the least sensitive. Sensitivity of protein expression to aldosterone thus follows the same order than sensitivity to dexamethasone.

Taken together our results further demonstrate the existence of inter-strain differences in GR-mediated responses: two types of immune cells (lymphocytes and macrophages) exhibit a concordant degree of sensitivity to agonists of GR according to the strain of mouse they were derived from. Our results also show at least one peptide (IL-1ra) regulated both by GR and MR actions in macrophages displays a similar degree of sensitivity in relation to the mouse strain (although weaker for MR actions). The molecular mechanisms involved in strain-related sensitivity are still to be investigated.

Acknowledgement

Hedi Harizi is the recipient of a fellowship from INRA, Animal Genetics Department.

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