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The Central Nervous System Modulates the Immune Response to *Salmonella*

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1. Introduction

Salmonella infection induces an immune response, the first and principal element of which is a local activation in the intestine. This intestinal response and the systemic response of the immune system have multidirectional interactions with the nervous and endocrine systems (Berczi and Szentivanyi 2003). The central nervous system (CNS) signals the immune system via hormonal and neural pathways, and the immune system signals the CNS through various cytokines. Whereas most information regarding these interactions is related to functions of the systemic immune response (Berczi, Nagy et al. 1981; Chrousos 1995; Madden and Felten 1995; Elenkov, Wilder et al. 2000; Webster, Tonelli et al. 2002; Berczi and Szentivanyi 2003), much less is known about the interactions between the hypothalamus, the pituitary, and local gastrointestinal immune reactions (Berczi, Nagy et al. 1981; Ottaway 1991; Bienenstock 1992; Chrousos 1995; Madden and Felten 1995; Elenkov, Wilder et al. 2000; Webster, Tonelli et al. 2002; Berczi and Szentivanyi 2003; Campos-Rodriguez, Quintanar-Stephano et al. 2006).

The CNS regulates the intestinal immune system through the three divisions of the autonomic nervous system: sympathetic, parasympathetic, and enteric. By signals sent along sympathetic and parasympathetic fibers, the CNS controls the enteric nervous system (ENS),which in turn regulates gastrointestinal functions, including immune functions (Cooke 1986; Ottaway 1991; Gonzalez-Ariki and Husband 1998; Bueno 2000; Spiller 2002). Moreover, the CNS regulates the mucosal immune system through the hypothalamic–pituitary–adrenal (HPA) axis, an essential part of whichis glucocorticoid production (Sternberg 2001; Webster, Tonelli et al. 2002; Jarillo-Luna, Rivera-Aguilar et al. 2008).

Ongoing research to clarify the bidirectional communication between the immune and central nervous systemshas in part been carried out byproducing electrolytic or pharmacologic lesions in several areas of the brain, such basal ganglia, striatum, hypothalamus, hippocampus and thalamus, and then observing the resulting immune response. This approach has been used in our recent studies (Campos-Rodriguez, Quintanar-Stephano et al. 2006; Rivera-Aguilar, Querejeta et al. 2008; Quintanar-Stephano, Abarca-Rojano et al. 2010) to observe the effect of brain lesions on the immune response to *Salmonella* and one of its main components, lipopolysaccharide (LPS). It has been found that brain lesions modify the number and functions of lymphocytes in the spleen, thymus and blood (Jankovic and Isakovic 1973; Payan, McGillis et al. 1986).

The aim of this chapter is to describe the effects of CNS lesions on the immune response to *Salmonella*. The mechanisms are explored by which these lesions affect the systemic and intestinal immune responses. Since the production of intestinal IgAis fundamental in the protection against *Salmonella* invasion, an evaluation is made of the role of neurotransmitters, glucocorticoids and neuroendocrine molecules in the regulation of such production.

2. Hypophysectomy and neurointermediatepituitary lobectomy reduce the humoral immune response to *Salmonella enterica* serovar Typhimurium

The hypothalamus induces the secretion of anterior pituitary hormones, and in this way the CNS can have both an immunostimulatory and immunosuppressor effect. In this sense, the immune response is stimulated mainly by the release of growth hormone (GH) and prolactin (PRL) (Berczi, Nagy et al. 1981; Block, Locher et al. 1981; Nagy and Berczi 1981; Berczi, Nagy et al. 1984; Edwards, Yunger et al. 1991; Nagy and Berczi 1991; Edwards, Arkins et al. 1992; Nagy and Bercz 1994; Madden and Felten 1995; Berczi and Szentivanyi 2003), and inhibited by the hypothalamic-pituitary-adrenocortical (HPA) axis, which causes the release of adrenocorticotropin (ACTH), which in turn stimulates the secretion of adrenocortical glucocorticoids (Chrousos 1995; Sternberg 2001; Webster, Tonelli et al. 2002). This increase of circulating glucocorticoids (GCs) is caused when the HPA axis is activated during many bacterial and viral infections.

In vivo, we have demonstrated that arginine vasopressin (AVP) released from the posterior pituitary affects humoral and cell mediated immune responses (Organista-Esparza, Tinajero-Ruelas et al. 2003; Quintanar-Stephano, Kovacs et al. 2004; Quintanar-Stephano, Organista-Esparza et al. 2004; Quintanar-Stephano, Chavira-Ramirez et al. 2005; Quintanar-Stephano, Organista-Esparza et al. 2005; Quintanar-Stephano, Abarca-Rojano et al. 2010). Regarding *Salmonella enterica* serovar Typhimurium (*Salmonella typhimurium*) infection, there is experimental evidence that pituitary hormones have a protective effect (Edwards, Yunger et al. 1991; Edwards, Ghiasuddin et al. 1992). For instance, the increased susceptibility to intraperitoneal *Salmonella typhimurium* infection found in hypophysectomized (HYPOX) rats is countered by GH treatment, which restores normal resistance. In intact rats and mice, GH and PRL enhance resistance to *Salmonella typhimurium* infection through an increase in phagocytosis and intracellular destruction of bacteria by peritoneal macrophages. *Salmonella* or other challenges to the immune system, such as immobilization stress and burn injury, increase the levels of GCs, which in turn increase bacterial translocation from the gastrointestinal tract to the mesenteric lymph nodes (Jones, Minei et al. 1990; Fukuzuka, Edwards et al. 2000; Dunn, Ando et al. 2003).

All of the aforementioned suggests that anterior and posterior pituitary hormones participate as stimulating factors in the control of systemic and intestinal immune responses to *Salmonella*. To further explore this idea, we investigated the systemic and intestinal immune responses in HYPOX and neurointermediate pituitary lobectomy (NIL) rats orally infected with nonlethal doses of *Salmonella typhimurium* (Campos-Rodriguez, Quintanar-Stephano et al. 2006).The most relevant results are that the kinetics of intestinal *Salmonella* elimination in sham-operated (SHAM), HYPOX and NIL groupswas similar with no clinical signs of salmonellosis and no mortality.However, nine days after inoculation, the number of *Salmonella typhimurium* cells in Peyer's patches and spleens of HYPOX and NIL groups was higher than in the sham-operated group ($P < 0.001$) (Fig. 1), andthere were a greater number of bacteria in HYPOX than NIL animals ($P < 0.01$). The fact that the total or partial ablation of the hypophysis increased susceptibility to infection after oral inoculation with *Salmonella typhimurium* means that the pituitary gland is required for protection against infection by intraperitoneal *Salmonella* inoculation (Edwards, Yunger et al. 1991).

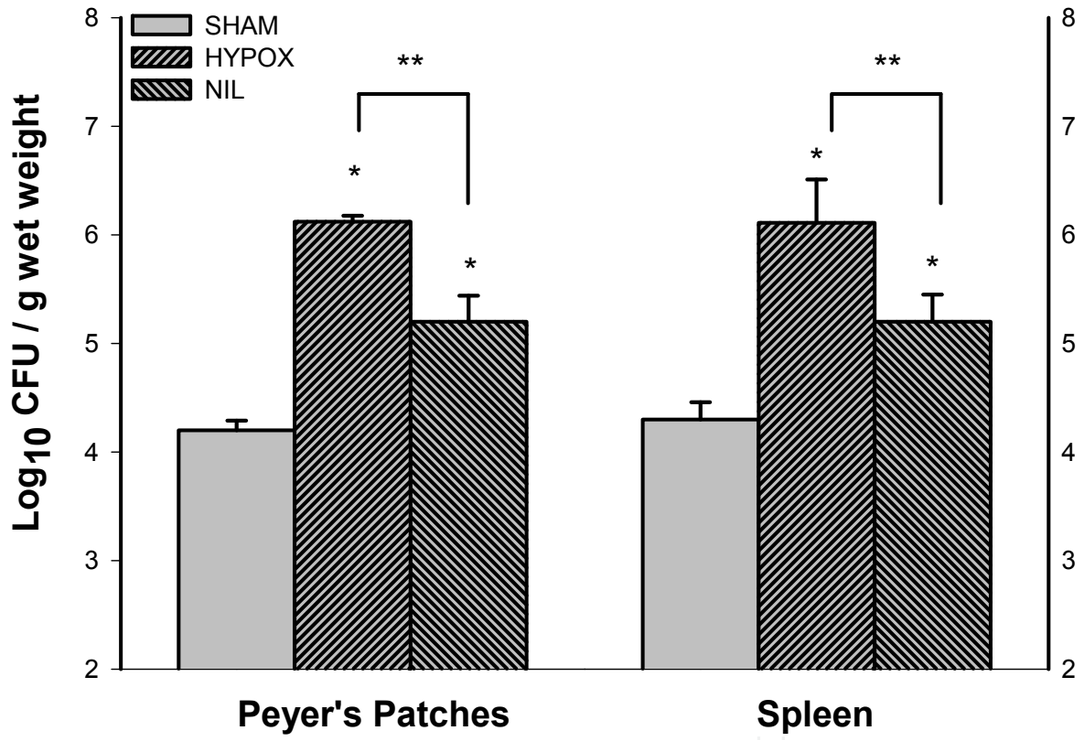

Fig. 1. Persistence of serovar Typhimurium infection in Peyer's patches and spleen. Sham-operated (SHAM), HYPOX, and NIL groups were orally infected and sacrificed 9 days postinoculation. Tissues were aseptically removed and processed for bacterial quantification. Data are expressed as means SD of results from four to six rats per group. In Peyer's patches and spleens, bacterial counts were significantly higher in HYPOX and NIL groups than in the sham-operated group (*, $P < 0.001$) and significantly higher in the HYPOX group than in the NIL group (**, $P < 0.01$). (From Campos-Rodriguez et al. Hypophysectomy and Neurointermediate Pituitary Lobectomy Reduce Serum Immunoglobulin M (IgM) and IgG and Intestinal IgA Responses to *Salmonella enterica* Serovar Typhimurium Infection in Rats. Infect Immun. 2006; 74(3):1883-1889).

Most pituitary hormones directly or indirectly modulate inflammatory/immune responses. For example, adrenocorticotropin increases the secretion of GCs, which in turn stimulate the immune function at physiological doses (Munck and Naray-Fejes-Toth 1992; Reichlin 1993; Chrousos 1995; Wiegers and Reul 1998; Sapolsky, Romero et al. 2000). GH, PRL, TSH and -endorphin produced in the anterior pituitary as well as the AVP released from the posterior pituitary have immunopotentiating and proinflammatory properties (Heijnen, Kavelaars et al. 1991; Navolotskaya, Malkova et al. 2002; Klein 2003). Therefore, the differences between NIL and HYPOX rats may be related to the amount of hormones that regulate the immune response located in the anterior and posterior pituitary. Another possible factor is that the partial or total removal of the pituitary may affect the activity of phagocytes, the principal cells of the innate immunity involved in killing *Salmonella typhimurium* (Mittrucker and Kaufmann 2000; Kirby, Yrlid et al. 2002). It has been demonstrated that peritoneal macrophages from HYPOX rats have an impaired tumor necrosis factor alpha response to *in vitro* lipopolysaccharide stimulation and are less effective in killing *Salmonella typhimurium* than those derived from rats with intact pituitaries (Edwards, Lorence et al. 1991). GH injections enhanced resistance of both intact and HYPOX rats following a challenge with *Salmonella typhimurium* (Edwards, Lorence et al. 1991; Edwards, Ghiasuddin et al. 1992). The enhanced resistance is correlated with the ability of peritoneal macrophages from these animals to generate toxic oxygen metabolites, such as superoxide anion and hydrogen peroxide (Edwards, Ghiasuddin et al. 1992). In addition, GH activates human monocytes for enhanced reactive oxygen intermediate production *in vitro* (Warwick-Davies, Lowrie et al. 1995; Warwick-Davies, Lowrie et al. 1995; Navolotskaya, Malkova et al. 2002).

An analysis of the secretion of intestinal IgA specific to outer membrane proteins of *Salmonella* shows that the titers of the specific intestinal IgA response was significantly lower in HYPOX and NIL animals than in the sham-operated group ($P < 0.001$, Fig. 2), and was also lower in the HYPOX than NIL rats ($P < 0.001$)(Campos-Rodriguez, Quintanar-Stephano et al. 2006).The fact that HYPOX induced a more marked decrease in the humoral immune responses to outer membrane proteins of *Salmonella typhimurium* than NIL suggests that the hormones melanocyte stimulating hormone (MSH), AVP, and oxytocin from the neurointermediate pituitary lobe may affect adaptive immune responses. The direct anti-inflammatory effects of MSH on immunocytes have been described previously (Catania and Lipton 1993; Blalock 1999; Luger, Scholzen et al. 2003; Taylor 2003). Since NIL eliminates the intermediate lobe— the main source of pituitary -MSH— an increased inflammatory response to *Salmonella typhimurium* infection may be expected. However, our results show that -MSH from the intermediate pituitary lobe is not involved in the immune response to *Salmonella typhimurium* infection. Further experiments are required to test this possibility.

Furthermore, in the aforementioned study levels of IgG and IgM were also significantly lower in the HYPOX and NIL animals than in the sham-operated group (Fig. 2), and in HYPOX rats than in the NIL group (Campos-Rodriguez, Quintanar-Stephano et al. 2006). The cause of these reduced humoral immune responses may be the decreased secretion of the neurointermediate pituitary hormones. In previous experiments, we found that in NIL rats there are decreased humoral and cell-mediated immune responses, including: (i) decreased hemagglutination, IgG and IgM responses to sheep red blood cells (Organista-Esparza, Tinajero-Ruelas et al. 2003; Quintanar-Stephano, Kovacs et al. 2004), (ii) decreased contact hypersensitivity to dinitrochlorobenzene (Quintanar-Stephano, Kovacs et al. 2004), and (iii) protection against EAE (Quintanar-Stephano, Chavira-Ramirez et al. 2005). In

agreement with these previous findings, our results suggest that the higher colonization of the Peyer's patches and spleens and the decreased IgG, IgM, and IgA responses to *Salmonella typhimurium* may be due to AVP deficiency in the NIL animals. In another study we found that in both HYPOX and NIL rats, there was a decrease in the IgM response to the LPS of *Salmonella typhimurium* (Quintanar-Stephano, Abarca-Rojano et al. 2010). These results support the view that hormones from both pituitary lobes play an important stimulatory/modulatory role in both humoral and cell-mediated immune responses.

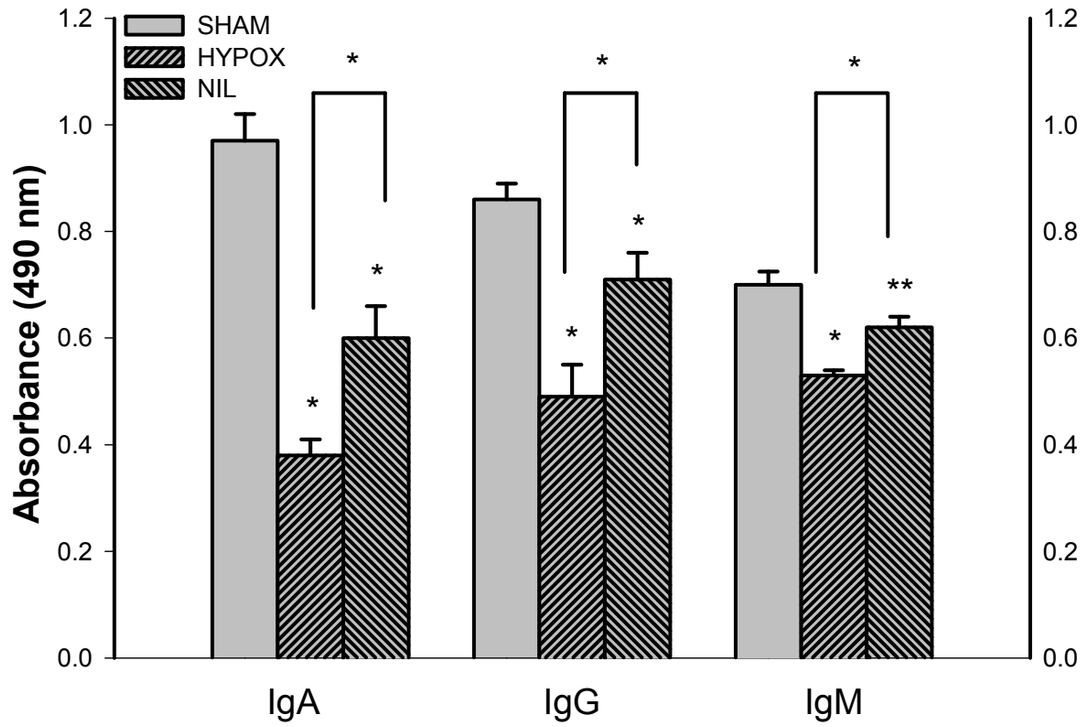

Fig. 2. Intestinal IgA and serum IgG and IgM response to *Salmonella typhimurium*. Intestinal IgA or serum IgG and IgM antibodies were quantified by ELISA using *Salmonella typhimurium* surface antigens. Serum and gut samples were obtained 9 days postinoculation. The samples were assayed in triplicate, and the titers were expressed as the absorbance at 490 nm. Data are expressed as means SD of results from four to six rats per group. The immunoglobulin levels were significantly lower in HYPOX and NIL groups than in the sham operated group (*, $P < 0.001$; **, $P < 0.01$) and significantly lower in the HYPOX group than in the NIL group (*, $P < 0.001$). (From Campos-Rodriguez et al. Hypophysectomy and Neurointermediate Pituitary Lobectomy Reduce Serum Immunoglobulin M (IgM) and IgG and Intestinal IgA Responses to *Salmonella enterica* Serovar Typhimurium Infection in Rats. Infect Immun. 2006; 74(3):1883-1889).

Finally, intestinal elimination of *Salmonella typhimurium* HYPOX and NIL rats was similar to that seen in sham-operated animals. However, it is known that HYPOX animals develop an increased susceptibility to intraperitoneal *Salmonella typhimurium* infection, and that GH and PRL treatments protect the rats against the disease (Edwards, Yunger et al. 1991; Edwards, Ghiasuddin et al. 1992). Similarly, PRL increases resistance to infection in normal mice after intraperitoneal inoculation of *Salmonella typhimurium* (Di Carlo, Meli et al. 1993; Meli, Raso et al. 1996).

Since the immune responses are PRL and GH dependent and no pituitary hormones are produced in the HYPOX animals, how can the formation of anti-*Salmonella typhimurium* IgG, IgM, and IgA immunoglobulins be explained? Perhaps part of the answer lies in an unpublished study with HYPOX animals. After surgery a gradual increase was observed in the plasma PRL levels, which after 7 to 9 weeks post-operation reached 50% of the levels of this hormone found in intact animals (Nagy and Berczi 1991; Quintanar-Stephano and A. Organista- Esparza, unpublished). Although the source of this non-pituitary PRL is not known, one possibility is from T lymphocytes (Draca 1995; Stevens, Ray et al. 2001). The fact that HYPOX rats had a higher number of *Salmonella typhimurium* cells in Peyer's patches and spleen than sham operated and NIL rats suggests that the low serum IgG and IgM and intestinal IgA immunoglobulin levels in HYPOX rats may be due to the insufficient immune-stimulating effect of the non-pituitary PRL (Nagy and Berczi 1991). However, further studies are needed to evaluate this suggestion.

In summary, it can be concluded that through different mechanisms, hormones from both the anterior and neurointermediate pituitary lobes play an important role in the control of systemic and gastrointestinal immune responses to *Salmonella*. However, more experiments are needed to establish the interactions between the hypothalamo-neurohypophysial (AVP) and immune systems.

3. Striatum modulates the humoral immune response to LPS and outer membrane proteins of *Salmonella enterica* serovar Typhimurium

The striatum is implicated in movement and learning (Costall, Naylor et al. 1972; Pycock 1980; Graybiel 1995), and there is increasing evidence that it is involved in the modulation of immune responses, although such evidence is contradictory. Bilateral electrolytic lesions of the caudate nucleus of rats do not reduce the intensity of cell-mediated immune responses or the production of antibodies to bovine serum albumin (BSA) (Jankovic and Isakovic 1973). On the other hand, such lesions result in a reduction of the antibody immune response to sheep red blood cells (SRBC) (Devoino, Alperina et al. 1997; Devoino, Cheido et al. 2001; Nanda, Pal et al. 2005; Rivera-Aguilar, Querejeta et al. 2008). In addition, the destruction of dopaminergic neurons in the substantia nigra or dopaminergic terminals in the caudate nucleus by in situ injection of 6-hydroxydopamine decreases the antibody response and impairs cell-mediated immunity (Deleplanque, Vitiello et al. 1994; Devoino, Alperina et al. 1997; Devoino, Cheido et al. 2001; Filipov, Cao et al. 2002).Furthermore, bilateral lesions of nigrostriatal pathways induced by systemic injections of the neurotoxin 1-methyl-4-phenyl-1,2,3,6- tetrahydropymidine reduce the number of leukocytes, alter lymphocyte populations,decrease proliferation of T lymphocytes induced bymitogens or alloantigens, and modify the synthesis of cytokines (Renoux, Biziere et al. 1989; Bieganowska, Czlonkowska et al. 1993; Shen, Hebert et al. 2005; Engler, Doenlen et al. 2009).

These findings suggest that the nigrostriatal dopaminergic system has an immunostimulatory effect on the humoral and cell-mediated immune response. To test the hypothesis that GABAergic medium-sized spiny neurons in the striatum modulate the humoral immune response, in rats with a bilateral lesion of the striatum provoked by the injection of quinolinic acid we analyzed this response to several antigens (both T-independent and T-dependent antigens), including LPS and outer membrane proteins of *Salmonella typhimurium*. Quinolinic acid produces axon-sparing lesions that result in a loss of GABAergic medium-sized spiny neurons (MSP) in the striatum, while the dopaminergic

terminal network originating from cell bodies in the substantia nigra remains unchanged (McGeer and McGeer 1976; Schwarcz, Whetsell et al. 1983; Beal, Kowall et al. 1986).

3.1 Bilateral lesion of the striatum decreases the humoral immune response to TNP-LPS

The serum levels of IgG and IgM antibodies anti-trinitrophenol-lipopolysaccharide (TNP-LPS)(Fig. 3, panel A and B), and the IgA antibodies anti-TNP-LPS in intestinal fluid (Fig. 3, panel C) were significantly lower in rats with a bilateral lesion of the striatum compared with the control group ($P < 0.01$). These results show that the lesions of the striatum had a prolonged effect on the immune response to this T-independent antigen, indicating that the striatum modulates this type of humoral immune response. On the contrary, a bilateral lesion of the striatum increased the humoral immune response to T-dependent antigens (ovoalbumin, lysozyme and bovine serum albumin).

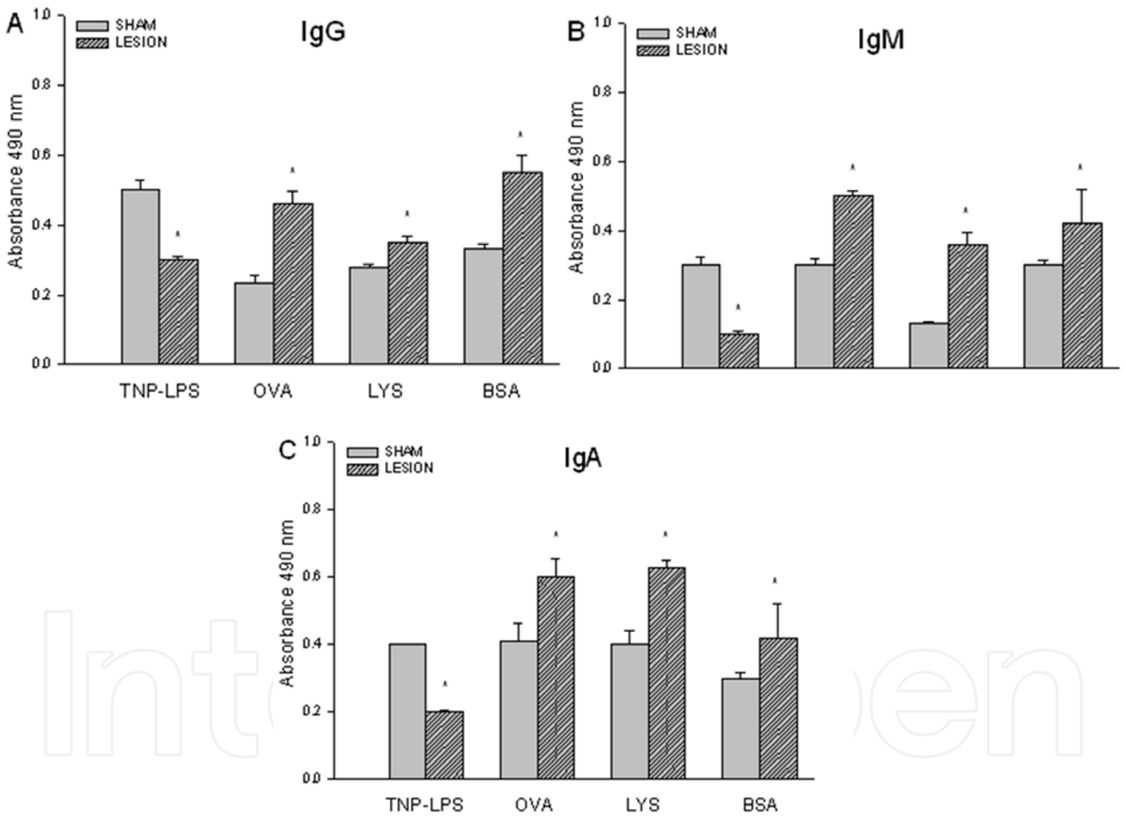

Fig. 3. IgG, IgM and IgA response to T-independent and T-dependent antigens in rats with bilateral lesion of striatum. The antibody response to TI and TD antigens was analyzed in rats that had been lesioned 25 days before immunization. The serum IgM and IgG levels as well as the intestinal IgA levels to the T-independent antigen (TNP-LPS) were significantly lower in lesioned rats than in the sham-operated rats (*$P < 0.01$). On the contrary, the antibody levels to all the T-dependent antigens (OVA, lysozyme, and BSA) were significantly higher in the lesioned group than in sham operated group (*$P < 0.01$). (From Rivera-Aguilar et al. Role of the striatum in the humoral immune response to thymus-independent and thymus-dependent antigens in rats. ImmunolLett 2008;120:20-28).

Although themechanisms by which the lesion of the striatal MSP neurons leads to a decrease in the immune response to TNP-LPS (TI type 1 antigen) are not known, it is likely that they are related to defects in B lymphocyte activation. In fact, the number of IgM+ B cells in the marginal zone of the spleen was significantly lower in lesioned rats than in the control group.However, the mechanisms by which striatal lesions reduce the population of B cells in the spleen are at the present unknown, as are the mechanisms involved in the maturation, selection and long-term survival of immature peripheral B cells (Thomas, Srivastava et al. 2006).

We also found that striatal lesions caused a reduction in the expression of the gene for caveolin-1 and in the number of lymphocytes caveolin-1+ in the spleen (Fig. 4). Caveolin-1, expressed on B-lymphocytes, down-regulates tyrosine phosphorylation of Btk, a molecule that participates in B-cell activation and signaling (Vargas, Nore et al. 2002; Medina, Williams et al. 2006). Caveolin-1 deficient mice have a reduced response to both type 1 and type 2 thymus-independent antigens, but have a normal response to thymus-dependent antigens (Medina, Williams et al. 2006). Therefore, it is possible that the reduced response to TNP-LPS is caused by the decreased expression of caveolin-1 in B cells that respond to TI antigens.

3.2 Bilateral lesion of striatum increased the humoral immune response to outer membrane proteins (OMP) of *Salmonella enterica* serovar Typhimurium

To evaluate whether the increase in the humoral immune response to protein antigens was a general effect in rats with striatal lesions, we analyzed the IgG immune response to outer membrane proteins of *Salmonella typhimurium*. The levels of IgG in serum were significantly higher in rats with a bilateral lesion than in sham-operated animals (Table 1, $P < 0.001$). These results support the idea that a bilateral lesion of striatum increases the humoral immune response to T-dependent antigens.

Group	SHAM	Lesion of CN	P
Saline	0.100 ± 0.050	0.091 ± 0.060	
10^7*	0.282 ± 0.008	0.519 ± 0.023	< 0.001 ‡
10^8*	0.524 ± 0.020	0.650 ± 0.050	0.004 ‡

* 10^7 or 10^8 CFU of *Salmonella enterica* Serovar Typhimurium were administered i.p 7 days before the serum was collected and the titers were determined by ELISA. The data are presented as mean ± standard deviation of the absorbance at 490 nm (n = 4-6 rats per group).
‡ Difference in IgG levels between sham-operated and rats with lesion of striatum were significant as determined by the non-paired Student *t* test. Representative results from two independent experiments are shown.

Table 1. IgG antibody response to proteins of *Salmonella enterica* Serovar Typhimurium rats with bilateral lesion of striatum

The mechanisms involved in the increase of the immune response to OMP and other TD antigens in rats with a bilateral lesion in striatum are not clear. One possibility is that cytokines produced by the inflammatory cells in the injured area of the brain increase the antibody production. However, we did not find inflammatory cells in these areas and the expression of mRNA for cytokines did not increase (Fig. 4, panel A). Another possibility is

that alterations in the HPA axis contribute to the observed changes in the humoral immune response. Nevertheless, we did not find any increase in the expression of mRNA for prolactin in the hypophysis of rats with a bilateral lesion.

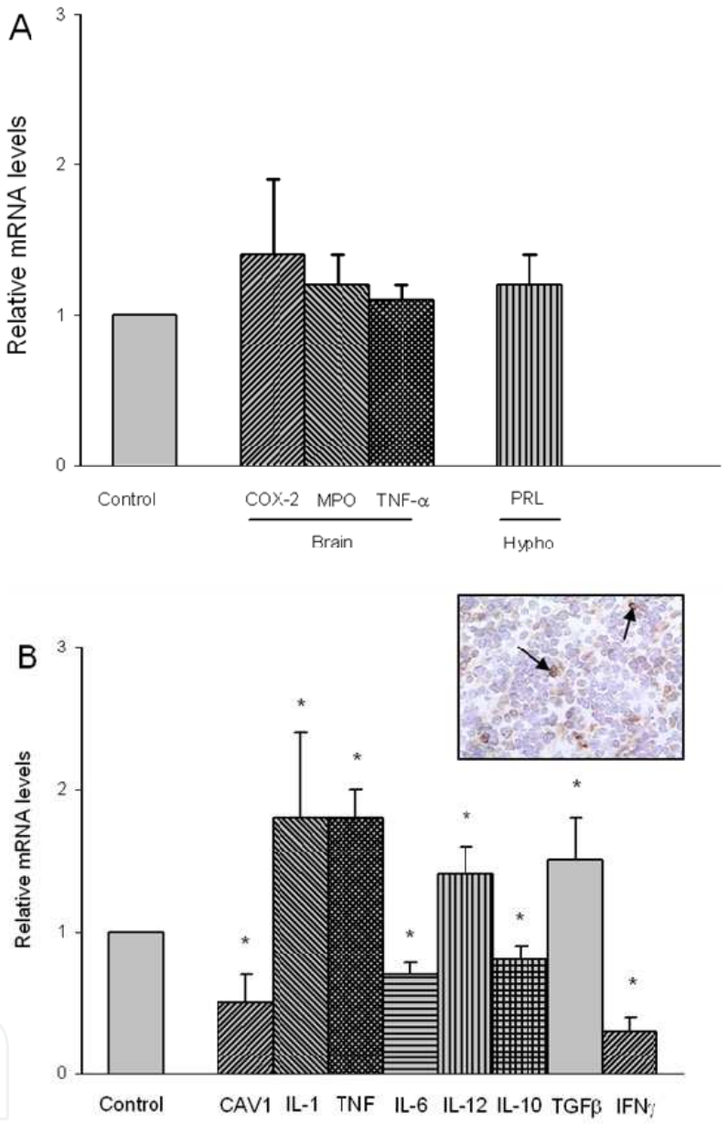

Fig. 4. Real-time RT-PCR analysis: (A) expression of genes in brain and hypophysis. Samples were collected 15 days after bilateral lesion of striatum and the mRNA expression of cyclooxygenase (COX)-2,myeloperoxidase (MPO), tumor necrosis factor-alpha (TNF-α), and prolactin (PRL) was measured by real-time RT-PCR. (B) expression of genes in spleen. The expression of caveolin-1 (CAV1), TNF-α, Interleukin (IL)-6, IL-12, IL-10, Transforming growth factor-beta (TGF-β), Interferon-gamma (IFN-γ) was measured by real-time RT-PCR, as detailed in materials and methods. Data represent the mean ± S.D (n = 6). *P < 0.05 compared with sham rats. Insert: immunolocalization of caveolin-1 positive cells in the splenic marginal zone, 400×. (From Rivera-Aguilar et al. Role of the striatum in the humoral immune response to thymus-independent and thymus-dependent antigens in rats. ImmunolLett 2008;120:20-28).

Because the response to OMP requires CD4+ T cells and cytokines,we analyzed that population aswell as the expression of genes for cytokines in the spleen. The number of CD4+ T cells in the spleen was significantly higher in lesioned rats than in the control group, and that increase could explain the augmented immune response to TD antigens (Table 2). Although the mechanism by which striatal lesions increase the number of naïve CD4+ T cells in the spleen is unknown, one possibility is that high corticosterone levels promote the migration of lymphocytes from the blood to the spleen, as occurs from the blood to other tissues (Dhabhar 2001). The other possibility, that the population of CD4+ T cells was activated by antigens and costimulators, is ruled out by the fact that CD4+ T cells did not express the gene for interleukin (IL)-2 , since this cytokine is produced by activated CD4+ T cells (Jenkins, Khoruts et al. 2001).On the other hand, the increase in their number can be explained by a greater migration of CD+ T cells from the blood into the spleen, although the mechanism of this possible migration remains unclear.

Splenicell	SHAM	Lesion of Striatum	P
IgM +	34 ± 3	25 ± 3	< 0.001‡
IgG +	5 ± 0.4	5 ± 0.6	1.0
CD4+	5 ± 0.4	8 ± 1.2	< 0.05‡

The data are presented as mean ± standard deviation of the number of positive cells for IgM, IgG, Caveolin-1, and CD4+ (n = 4-6 rats per group).
‡ Differences in number of cells between sham-operated and rats with lesion of striatum were significant as determined by the Student *t* test. Representative results from two independent experiments are shown.

Table 2. Lymphocytes and Caveolin-1+ cells in the spleen of rats with bilateral lesion of striatum

Whereas in lesioned rats the expression of genes for IL-1, tumor necrosis factor (TNF), IL-12 and transforming growth factor-beta (TGF-β) increased, the expression of genes for IL-6, IL-10 and interferon-gamma (IFN-γ) decreased (Fig. 4, panel B). Although this pattern of cytokine production could contribute to the activation of the immune system (Trinchieri 1998; Pestka, Krause et al. 2004), further studies are needed to elucidate the role of cytokines in these changes. However, the fact that CD4+ T cells did not express the gene for IL-2, and that an increased expression of the gene for TGF-β was foundprobably explains the higher synthesis of IgA antibodies observed in lesioned rats, since TGF-β stimulates the production of IgA antibodies (Li, Wan et al. 2006).

Finally, the higher corticosterone levels found in lesioned rats compared with the control group (221. 8±53 ng/ml versus 24.6±12 ng/ml; mean ± S.D.; P < 0.001) could contribute to the changes observed in the immune response. Since glucocorticoids have opposite effects on the TI and TD antibody responses (Addison and Babbage 1981; Garvy and Fraker 1991), high corticosterone concentrations may depress TI responses and stimulate TD responses. In addition, given that physiological glucocorticoid concentrations enhance immunoglobulin production *in vitro* and *in vivo* (Ambrose 1964; Halliday and Garvey 1964; Fauci, Pratt et al. 1977; Gonzalez-Ariki and Husband 1998), the rise in corticosterone levels that we found might explain the increase in the immune response to TD antigens. However, pharmacological studies are required to elucidate the role of glucocorticoids in mediating the effects of striatal lesions on immune function.

In summary, our results indicate that striatal GABAergic medium-sized spiny neurons probably modulate the humoral immune response to *Salmonella* outer membrane proteins (OMP) through mechanisms related to the function of B and T cells, the expression of caveolin-1, and andchanges in serum levels of corticosterone.

4. Pathways for the CNS regulation ofthe immune response to *Salmonella* in the intestinal mucosa

In the intestinal mucosa, main site of entry of *Salmonella*, the CNS may regulate the immune response to *Salmonella* by modulating the activity of the HPA axis and the activity of the autonomic nervous system.

4.1 Role of the HPA axis in the immune response to *Salmonella*

The activity of the hypothalamus-pituary-adrenal axis results in the release of the corticotropin-releasing factor (CRF), the adrenocorticotropin hormone (ACTH) and glucocorticoidsinto the circulatory system (Wilder 1995; Webster, Tonelli et al. 2002; Charmandari, Tsigos et al. 2005; Gunnar and Quevedo 2007). Glucocorticoids released from the adrenal gland are delivered to the intestinal mucosa through blood circulation. Glucocorticoids inhibit mucosal inflammation through activation of glucocorticoid receptors present on epithelial cells and intestinal lymphocytes (Boivin, Ye et al. 2007; Jarillo-Luna, Rivera-Aguilar et al. 2008; Fujishima, Takeda et al. 2009; Resendiz-Albor, Reina-Garfias et al. 2010). Also, GCs increase bacterial translocation from the gastrointestinal tract to the mesenteric lymph nodes (Jones, Minei et al. 1990; Fukuzuka, Edwards et al. 2000; Dunn, Ando et al. 2003).

4.2 Role of the autonomic nervous system in the immune response to *Salmonella*

The CNS can modulate the activity of the autonomic nervous system (the adrenergic and cholinergic nervous system) and evoke the neuronal release of norepinephrine (NE), acetylcholine (ACh) and other neurotransmitters in peripheral tissues, including the intestinal mucosa (Felten, Felten et al. 1987; Kulkarni-Narla, Beitz et al. 1999; Kohm and Sanders 2001; Tracey 2002; Green, Lyte et al. 2003; Pavlov, Wang et al. 2003; Sternberg 2006; Sanders and Kavelaars 2007; Schmidt, Xie et al. 2007; Chrousos 2009; Kvetnansky, Sabban et al. 2009). These mediators may influence the function of the intestinal mucosa and its associated surface bacterial populations.

4.2.1 Sympathetic nervous system and the immune response to *Salmonella*

The sympathetic or adrenergic division of the autonomic nervous system is associated with a dual mode of regulation of inflammatory responses (Hasko and Szabo 1998; Elenkov, Wilder et al. 2000). Epinephrine (adrenaline), secreted from the adrenal medulla, and norepinephrine (noradrenaline), which is both secreted from the adrenal medulla and released from sympathetic nerve axons, modulate the release of cytokines and inflammation through adrenoceptors on immune cells (Hasko and Szabo 1998; Elenkov, Wilder et al. 2000).

There is strong immunohistochemical evidence for catecholaminergic innervation of Peyer's patches, the inductive sites for mucosal immunity and the main entry site for *Salmonella*. In

addition, adrenergic receptors are expressed on neurons, epithelial cells and other cellular components of the intestinal mucosa (Kulkarni-Narla et al. 1999) (Nijhuis, Olivier et al. ; Kulkarni-Narla, Beitz et al. 1999; Green, Lyte et al. 2003; Chiocchetti, Mazzuoli et al. 2008; Lyte, Vulchanova et al. 2011).

Norepinephrine (NE), released within the intestinal wall during activation of the sympathetic nervous system, has a wide variety of actions at the intestinal mucosa. Norepinephrine participates in the host-S*almonella* interaction by enhancing the growth of Salmonella *enterica* and other enteropathogens, such as enterohemorrhagic *Escherichia coli* O157:H7 (EHEC) and *Yersinia enterocolitica* (Freestone, Haigh et al. 2007; Green and Brown 2010; Lyte, Vulchanova et al. 2011). This same neurotransmitter substancealters mucosal attachment, and therefore the invasiveness, of serovars of *Salmonella enterica* by acting on cells of the intestinal mucosa that express adrenoreceptors (Green and Brown 2010). In this same study, the electrical stimulation of enteric nerves increased *Salmonella typhimurium* internalization in ileal mucosa explants from swine (Schreiber, Price et al. 2007). These results suggest that enteric catecholaminergic nerves modulate *Salmonella* colonization of Peyer's patches at the earliest stages of infection, in part by altering epithelial uptake of bacteria(Brown and Price 2008).Furthermore, NE apparently activates the expression of virulence-associated factors in *Salmonella typhimurium*, including flagella-mediated motility (Bearson and Bearson 2008; Moreira, Weinshenker et al. 2010), and Type III protein secretion (Rasko, Moreira et al. 2008; Moreira, Weinshenker et al. 2010).Currently, the cellular mechanisms underlying these neurally mediated effects on *Salmonella* internalization in the intestinal mucosa are undefined.It has been proposed that catecholamines may regulate the sampling function of Peyer's patches in the control of the entry of pathogenic microbes or immune processing of the same at these intestinal sites (Green and Brown 2010).

4.2.2 The parasympathetic nervous system and the immune response to *Salmonella*

Efferent vagus nerve fibers innervate the small intestine and proximal colon of the gastro intestinal tract(Altschuler, Ferenci et al. 1991; Altschuler, Escardo et al. 1993),suggesting the possibility that cholinergic activity may modulate immune cells residing in, or recruited to, the densely innervated bowel wall(Van Der Zanden, Boeckxstaens et al. 2009). In fact, current knowledge indicates that the vagus nerve provides an important bi-directional communication circuit by which the brain modulates inflammation (Tracey 2002; Pavlov, Wang et al. 2003).

The presence of bacterial infection and inflammation can be detected by the sensory (afferent) vagus nerve and communicated to the nucleus tractus solitarus in the brainstem medulla oblongata. Neural communication between this other brainstem nuclei and "higher" brain structures, including the hypothalamus, are associated with the generation of brain-derived anti-inflammatory output through the efferent vagus nerve, which inhibits pro-inflammatory cytokine release and protects against systemic and mucosal inflammation. As acetylcholine is the principle parasympathetic neurotransmitter,this vagal function has been termed "the cholinergic anti-inflammatory pathway" (Borovikova, Ivanova et al. 2000; Tracey, Czura et al. 2001; Tracey 2002; Pavlov, Wang et al. 2003; Pavlov and Tracey 2005; Pavlov and Tracey 2006; Bonaz 2007; Gallowitsch-Puerta and Pavlov 2007; Tracey 2007; Tracey 2010).

Information about the role of the parasympathetic system and the immune response to S*almonella* is scarce. In one study, in *Salmonella typhimurium*-stimulated groups, inflammatory pathological changes were seen in ileum and the mesenteric lymph node. Whereas *Salmonella* induced a decrease in the level of CD4+ T cells in peripheral blood, such levels were restored to normal by a subdiaphragmatic vagotomy. The vagus nerve is involved in the transmission of abdominal immune information to the brain during *Salmonella typhimurium* infection, and it plays an important role in the maintenance of the immune balance of the organism (Wang, Wang et al. 2002). In another study, the specific inhibition of acetylcholinesterase (AChE), the enzyme that degrades ACh, rendered animals more resistant to infection by a virulent strain of *Salmonella typhimurium*, which correlated with the efficient control of bacterial proliferation in spleen. Immunologically, inhibition of AChE enabled the animals to mount a more effective systemic (inflammatory and anti-microbial) response, and to secrete higher levels of interleukin-12, a key T helper type 1-promoting cytokine. Thus, in one model of Gram-negative bacterial infection, cholinergic stimulation was shown to enhance the anti-microbial immune response leading to effective control of bacterial proliferation and enhanced animal survival (Fernandez-Cabezudo, Lorke et al.).

Currently, there is no evidence that the cholinergic anti-inflammatory pathway inhibits or enhances the immune response to *Salmonella* in the intestinal mucosa. However, taking into account that the anti-inflammatory activity of the cholinergic nervous system is based on cholinergic signals that are linked to macrophages and other innate immune cells, whichare central to the control of *Salmonella* infection, it is likely that the cholinergic nervous system attenuates the inflammatory response to *Salmonella* (Jones and Falkow 1996; Mittrucker and Kaufmann 2000; Wick 2004).

5. Neuroendocrine regulation of intestinal IgA and protection against *Salmonella*

Glucocorticoids, catecholamines and acetylcholine regulate the secretion of Intestinal IgA, which in turn plays a key role in protecting against *Salmonella* infection.Therefore; this molecule may mediate the effects of the CNS on the immune response to this bacterium.

Secretory immunoglobulin A (S-IgA) is the most abundant intestinal immunoglobulin. By binding to antigens, such as microbes and toxins, S-IgA prevents them from attaching to or penetrating the mucosal surface (Mowat 2003; Fagarasan and Honjo 2004; Kaetzel 2005; Cerutti and Rescigno 2008; Macpherson, McCoy et al. 2008; Brandtzaeg 2009). IgA is secreted into the intestinal lumen due to the cooperation of local plasma cells with epithelial cells. The polymeric IgA (pIgA) secreted by plasma cells diffuses through the stroma and binds to the polymeric immunoglobulin receptor (pIgR) on the basolateral surface of the epithelial cells to form the pIgA–pIgR complex, which in turn is translocated to the apical surface of epithelial cells, where it is cleaved and secreted into lumen as S-IgA (Norderhaug, Johansen et al. 1999; Kaetzel 2005).

In the intestinal lumen, S-IgA protects against infection by inhibiting *Salmonella* adhesion to epithelial cells and M cells and the penetration of this bacterium into deeper tissues (Michetti, Mahan et al. 1992; Michetti, Porta et al. 1994; Mittrucker and Kaufmann 2000; Matsui, Suzuki et al. 2003). However, little is known about the neuroendocrine regulation of intestinal IgA (Schmidt, Eriksen et al. 1999; Schmidt, Xie et al. 2007; Reyna-Garfias, Miliar et al. 2010).

5.1 Glucocorticoids and IgA

Glucocorticoids have several diverse effects on the production and secretion of IgA in the intestine. They have been shown to increase or decrease intestinal IgA levels, effects which may be species-dependent (Alverdy and Aoys 1991; Spitz, Ghandi et al. 1996; Reyna-Garfias, Miliar et al. 2010; Lyte, Vulchanova et al. 2011). Other studies have demonstrated that GCsreduce the number of IgA-producing cells in Peyer's patches of mice (Martinez-Carrillo, Godinez-Victoria et al. 2011), decrease the number of intraepithelial lymphocytes (IEL) in the proximal small intestine of mice (Jarillo-Luna, Rivera-Aguilar et al. 2007; Jarillo-Luna, Rivera-Aguilar et al. 2008; Reyna-Garfias, Miliar et al. 2010),andincrease the levels of mRNA for pIgR in the proximal duodenum of suckling rats (Li, Wang et al. 1999).Thus,it may be through the liberation of GCs that the CNS regulates the production and secretion of intestinal IgA specific to *Salmonella*.

5.2 Noradrenaline and IgA

Although the intestinal tract is a major site for mucosal immunity and is extensively innervated, little is known about the adrenergic regulation of enteric S-IgA secretion.Norepinephrine stimulates S-IgA secretion by acting through alpha-adrenergic receptors in the colonic mucosa, and in this way may enhance mucosal defense *in vivo* (Schmidt, Xie et al. 2007)]. This neurotransmitter also significantly increases pIgR mRNA expression and intestinal IgA concentration (Reyna-Garfias, Miliar et al. 2010). The increased expression of pIgR might contribute to an increasedsecretion of S-IgA in the gut, andthus a greater protectionagainst pathogens including *Salmonella*. A sympathectomy decreases the number of IgA-positive lamina propria cells in the weanling rat (Gonzalez-Ariki and Husband 2000). Furthermore, NE has been found to slightly increase the number of IgA-immunoreactive cells in the intestinal wall of marathon runners (Nilssen, Oktedalen et al. 1998).Finally, we have found that catecholamines reduce the number of IgA-producing cells in Peyer's patches of mice(Martinez-Carrillo, Godinez-Victoria et al. 2011), decrease the number of IEL in the proximal small intestine of mice (Jarillo-Luna, Rivera-Aguilar et al. 2008), increase the IgA concentration in rat small intestine(Reyna-Garfias, Miliar et al. 2010), and reduce the intestinal IgA concentration in mice (Jarillo-Luna, Rivera-Aguilar et al. 2007).

Although the effect of noradrenaline or adrenaline (catecholamines) on the production of IgA antibodies specific to *Salmonella* has not been studied, it is possible that the release of these molecules by the activation of the sympathetic-adrenal medullary axis may modify the production and secretion of intestinal IgA specific to *Salmonella*.

5.3 Acetylcholine and IgA

Some data indicate that intestinal secretion of immunoglobulin A is stimulated by the muscarinic effect of cholinergic agonists, which suggest that the basal secretion of immunoglobulin A may be influenced by the parasympathetic nervous system (Wilson, Soltis et al. 1982; Freier, Eran et al. 1987; Freier, Eran et al. 1989; Schmidt, Xie et al. 2007). However, there is no information about the role of the parasympathetic nervous system in the secretion of IgA during infections by *Salmonella*.

6. Neurotransmitters and neuroendocrine molecules: Substance P, cholecystokinin, Somatostatin and the Macrophage migration inhibitory factor (MIF)

Apart from the immune regulatory role of the classic neurotransmitters, acetylcholine and norepinephrine, both the sympathetic and parasympathetic subdivisions of the autonomic nervous system include several subpopulations of neurons that express several neuropeptides related to the modulation of the immune response. In this sense,corticotropin-releasing hormone (CRH), neuropeptide Y (NPY), somatostatin, and galanin are found in postganglionic noradrenergic vasoconstrictive neurons, whereas vasoactive intestinal peptide (VIP), Substance P (SP), and calcitonin gene-related peptide are found in cholinergic neurons (Charmandari, Tsigos et al. 2005; Kvetnansky, Sabban et al. 2009).

There are even some gut neuropeptides, including SP, neuropeptide Y and neurotensin, that possess inherent antimicrobial activity (Brogden, Guthmiller et al. 2005). The role of neuropeptides and their receptors in the inflammatory response to *Salmonella* and other invasive pathogens has scarcely been analyzed.

6.1 Substance P

Substance P participates in the intestinal immune response to *Salmonella* in several ways. Oral infection with *Salmonella* increases SP and neurokinin A mRNA precursors, and the expression of substance P receptors in Peyer's patches, lymph nodes and spleen (Bost 1995; Kincy-Cain and Bost 1996; Pothoulakis and Castagliuolo 2003). Substance P increases resistance to *Salmonella* by improving the activity of macrophages, and increases the production of IFN-γ and IL-12, which are part of the initial response to *Salmonella* that helps limit bacterial growth and dissemination (Kincy-Cain, Clements et al. 1996; Kincy-Cain and Bost 1997; Weinstock 2003). Thus, it is postulated that SP and its receptor may contribute to the mounting of a coordinated early immune response against *Salmonella* infection (Pothoulakis and Castagliuolo 2003; Weinstock 2003).

6.2 Somatostatin

Somatostatin (SOM) exerts an active role in the regulation of mucosal inflammatory responses (Pothoulakis and Castagliuolo 2003). SOM released from neuronal and non-neuronal cells distributed throughout the gastrointestinal tract may modulate la inflammatory response to *Salmonella* infection by inhibiting the release of pro-inflammatory cytokines such as IL-10 and IL-8 from intestinal epithelial cells (Chowers, Cahalon et al. 2000; Pothoulakis and Castagliuolo 2003).

6.3 Macrophage migration inhibitory factor (MIF)

The cytokine macrophage migration inhibitory factor (MIF) exerts a multitude of biological functions. Notably, it induces inflammation at the interface between the immune system and the HPA axis (Flaster, Bernhagen et al. 2007). The role of MIF in infectious diseases has scarcely been studied. MIF-deficient (MIF(-/-) knockout mice do not control an infection with wild-type *Salmonella typhimurium*. Increased susceptibility is accompanied by decreased levels of IL-12, IFN-γ, and tumor necrosis factor alpha, and markedly increases of IL-1β levels. Additionally, compared with control animals, infected MIF (-/-) mice show

elevated serum levels of nitric oxide and corticosterone. These results suggest that MIF is a key mediator in the host response to *Salmonella typhimurium*. Not only does MIF promote development of a protective Th1 response, but it also ameliorates disease by altering levels of reactive nitrogen intermediates and corticosteroid hormones, which both exert immunosuppressive functions (Koebernick, Grode et al. 2002). Epithelial MIF from cultured cells was found to be released predominantly from the apical side after *Salmonella* infection (Maaser, Eckmann et al. 2002).

6.4 Effect of these molecules on the production and secretion of IgA

The aforementioned molecules, in addition to their functions in the innate and cellular immune responses, affect the production and secretion of intestinal IgA. For example, the intravenous or intra-arterial injection of gut neuropeptides cholecystokinin, substance P and somatostatin increase S-IgA secretion in isolated loops of the rat small intestine and vascularly-perfused segments of the swine ileum (Wilson, Soltis et al. 1982; Freier, Eran et al. 1987; Freier, Eran et al. 1989; Schmidt, Xie et al. 2007).

7. Conclusion

CNS can regulate the immune response to *Salmonella* by the activation of both the HPA axis and the autonomic nervous system (including the sympathetic, parasympathetic and enteric divisions). Hormones, neurotransmitters, neuropeptides and neuroendocrine molecules mediate the effects of the CNS on the systemic and intestinal immune responses. In the intestinal mucosa, the CNS may modify the synthesis and secretion of IgA, which protects against the invasion by *Salmonella*.

8. Acknowledgment

We thank Bruce Allan Larsen for reviewing the use of English in this manuscript. This work was supported in part by grants from SEPI-IPN and from COFAA-IPN.

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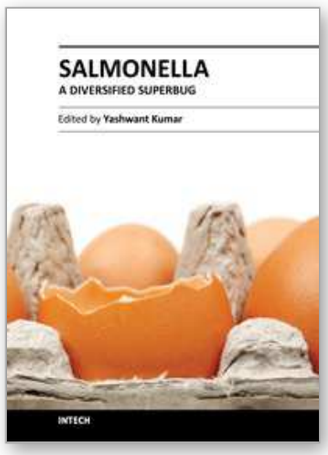

Salmonella - A Diversified Superbug
Edited by Mr. Yashwant Kumar

ISBN 978-953-307-781-9
Hard cover, 576 pages
Publisher InTech
Published online 20, January, 2012
Published in print edition January, 2012

Salmonella is an extremely diversified genus, infecting a range of hosts, and comprised of two species: enterica and bongori. This group is made up of 2579 serovars, making it versatile and fascinating for researchers drawing their attention towards different properties of this microorganism. Salmonella related diseases are a major problem in developed and developing countries resulting in economic losses, as well as problems of zoonoses and food borne illness. Moreover, the emergence of an ever increasing problem of antimicrobial resistance in salmonella makes it prudent to unveil different mechanisms involved. This book is the outcome of a collaboration between various researchers from all over the world. The recent advancements in the field of salmonella research are compiled and presented.

How to reference
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Rafael Campos-Rodríguez, Andres Quintanar Stephano, Maria Elisa Drago-Serrano, Edgar Abarca-Rojano, Istvan Berczi, Javier Ventura-Juárez and Alexandre Kormanovski (2012). The Central Nervous System Modulates the Immune Response to Salmonella, Salmonella - A Diversified Superbug, Mr. Yashwant Kumar (Ed.), ISBN: 978-953-307-781-9, InTech, Available from: http://www.intechopen.com/books/salmonella-a-diversified-superbug/the-central-nervous-system-modulates-the-immune-response-to-salmonella

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