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The role of monoamines in the immune system regulation during infection

Role monoaminů při regulaci imunitní odpovědi v průběhu infekce

Bachelor thesis

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Prohlašuji, že jsem závěrečnou práci zpracovala samostatně a že jsem uvedla všechny použité informační zdroje a literaturu. Tato práce ani její podstatná část nebyla předložena k získání jiného nebo stejného akademického titulu.

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ABSTRACT

Monoamines (norepinephrine, epinephrine, dopamine, serotonin, melatonin and histamine) have been extensively studied for their ability to regulate the activity of the immune system during infection in mammals and birds. Monoamines can induce a response in immune cells through their receptors and on the other hand, immune cells can affect the central nervous system through the release of cytokines. The effect on the immune system mediated by monoamines is stimulatory or inhibitory, tuned for the appropriate immune response to ensure a higher probability of the animal survival. Any weakening of this interaction leads to impaired immune function or deficient development of immune organs.

Keywords: monoamines, immune system, infection, mammals, birds

ABSTRAKT

Monoaminy (noradrenalin, adrenalin, dopamin, serotonin, melatonin a histamin) jsou ve veliké míře studovány pro jejich schopnost regulace imunitního systému během infekce, a to jak u savců, tak u ptáků. Monoaminy mohou svými receptory ovlivňovat aktivitu buněk imunitního systému, zatímco imunitní buňky uvolňují cytokiny, které posléze regulují mozkovou aktivitu. Monoaminy mohou imunitní systém stimulovat, ale zároveň i tlumit jeho aktivitu, což je nezbytné pro správný průběh imunitní odpovědí a zvýšení šance zvířete na přežití. Jakékoli oslabení tohoto vzájemného působení vede zároveň i k oslabení imunitní odpovědi nebo nedostatečnému vývoji imunitních orgánů.

Klíčová slova: monoaminy, imunitní systém, infekce, savci, ptáci

LIST OF ABBREVIATIONS

5-HT – Serotonin

6-OHDA – 6-hydroxydopamine

ADCC – Antibody-dependent cellular cytotoxicity

BMDCs – Bone marrow-derived dendritic cells

Con A – Concanavalin A

CNS – Central nervous system

DNP – Dinitrophenyl

HCLP-EC – High performance liquid chromatography with electrochemical detection

IFN – Interferon

Ig – Immunoglobulin

IL – Interleukin

KLH - Keyhole limpet hemocyanin

LPS – Lipopolysaccharide

MHC II – Major histocompatibility complex II

NDV – Newcastle disease virus

NK cells – Natural killer cells

pDCs – Plasmacytoid dendritic cells

PCPA – Para-chlorphenylalanin

PHA - Phytohemagglutinin

SNS – Sympathetic nervous system

SRBC – Sheep red blood cells

Th cells – T-helper cells

TLR – Toll-like receptor

TGF - Tumor growth factor

TNF – Tumor necrosis factor

TNP – Trinitrophenyl

VTA – Ventral tegmental area

CONTENT

1 INTRODUCTION

1.1 Mammalian and avian immune systems

The immune system in mammals and birds is grouped into innate and adaptive response. The innate immune system represents the first-line defence of the organism and is composed of different types of immune cells including phagocytic macrophages, cytotoxic nature killer cells (NK cells), granulocytes (including neutrophils, eosinophils and basophils), mast cells and dendritic cells, which are the major antigen-presenting cells to lymphocytes. These cells release signalling molecules called cytokines, for example interleukins (IL), interferons (IFN) and tumour-necrosis alpha (TNF-α) (Abbas *et al*., 2012; Chaplin, 2010).

The adaptive immune system consists of T and B lymphocytes. T lymphocytes migrate from the bone marrow into the other primary lymphoid organ, thymus, where they develop. After that, they move to secondary lymphoid organs, spleen or lymph nodes, where they wait for the antigen presentation. Before they are exposed to an antigen, they are called naive CD4+ or CD8+ T lymphocytes. As soon as they meet the antigen, they differentiate to the effector CD4+ T-helper cells (Th1, Th2 or Th17), cytotoxic CD8+ cells or CD4+ T-regulatory cells. B lymphocytes develop in bone marrow and migrate to secondary lymphoid organs. These cells produce and secrete antibodies (immunoglobulins - Ig) which neutralize and eliminate the pathogens (Abbas *et al*., 2012; Chaplin, 2010).

Although the general mechanisms of the avian immune system assimilate those of mammals, some differences exist. The major difference is the location of the differentiation of B lymphocytes in an organ unique to birds, the bursa of Fabricius, which is located near the cloaca and is also called cloacal bursa (Figure 1). Furthermore, structural lymph nodes are absent from birds but found in mammals (Tizard, 1979; Everly *et al*., 1979; Sharma, 1991).

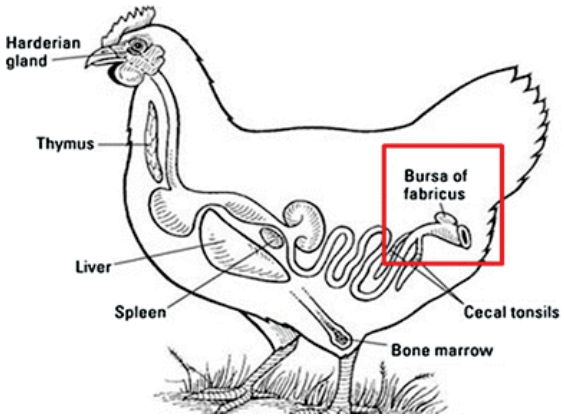


Figure 1: This picture demonstrates a scheme of some of the avian organs including lymphoid tissues, such as thymus, spleen, bone marrow and the bursa of Fabricius (in the red square) which is the organ of the differentiation of B lymphocytes located near the cloaca and is unique to birds (adapted from Ribatti, 2015).

1.2 Interactions between the nervous and immune systems

In the past, there was a widespread belief that the functions of nervous and immune systems are separated, but nowadays it is extensively evidenced that both systems interact in many ways and that the connection between them is bidirectional (Kipnis, 2016). When infection is present in the organism, the immune cells start to release cytokines that change the levels of neurotransmitters in the brain (Zalcman *et al*., 1994). On the other hand, neurotransmitter signalling can modulate the immune response through wide projections of efferent nerves. Lymphoid organs are innervated by the autonomic nervous system which regulates the activity of immune cells (Abbas *et al.*, 2012; Bellinger *et al*., 1992). In addition, various immune cells have the ability to store and synthetize neurotransmitters and release them upon the stimulation acting in autocrine or paracrine manner (Nakano *et al.*, 2009; Josefsson *et al.*, 1996; Blalock, 1992).

1.2.1 Methods to study neuro-immune interactions during peripheral infections

Two categories of methods are described that investigate processes during peripheral infection, involving changes in behaviour and cognition or connections between the neural and immune systems. First is the use of live infectious bacteria, viruses or parasites whose application leads to immune activation (Kusnecov and Anisman, 2013). Second is the

administration of substances that mimic these pathogens. These substances include polysaccharides, such as lipopolysaccharides (LPS) or antigens (such as sheep red blood cells). Cytokines, such as IL-6, can be also used to induce immune system activation (Zhang *et al.*, 2001; Kusnecov and Anisman, 2013).

The LPS experimental model is extensively used to examine processes during peripheral infection in animals (Catorce and Gevorkian, 2016). LPS is a component of the gram-negative bacterial cell wall and acts as a strong endotoxin (Galanos and Freudenberg, 1993). It is known for its ability to activate immune system response (Catorce and Gevorkian, 2016).

Sheep red blood cells are also used to evoke the immune response. SRBC are a T-dependent harmless antigen that stimulates an intense immune response without any tissue injury (del Rey and Besedovsky, 2017).

Another substance used to study peripheral infection is phytohemagglutinin (PHA) which is a glycoprotein from seeds of red kidney beans (*Phaseolus vulgaris*) (Kjemtrup *et al*., 1995). PHA binds to T-lymphocyte receptors (Schneider *et al*., 2012), and induces their proliferation and activation (Gibbs *et al*., 1982).

1.3 Monoamines

The monoamines are biogenic amines that contain a single amine group and act as neuromodulators. The biosynthesis of monoamines is settled only in a few of nuclei in the CNS, but the axons of their neurons project to almost every part of the brain and spinal cord thus affecting all tissues (Nestler *et al*., 2009). This allows them to influence all physiological and behavioural functions (Flügge, 2000).

Monoamines can be divided into three groups – catecholamines, indolamines and histamine (Flügge, 2000). Catecholamines are characterized by a nucleus catechol group. Catecholaminergic monoamines include norepinephrine, epinephrine and dopamine and all of them are synthetized by the amino acid tyrosine (Gnegy, 2012; Nestler *et al*., 2009). The indolamines contain an indole ring and consist of serotonin and melatonin. Both are synthetized from the amino acid tryptophan. Histamine does not belong in any of these two groups and its biosynthesis begins from the amino acid histidine (Nestler *et al*., 2009). The activity of monoamines is mediated through receptors belonging to G-coupled receptor

family, except one, the 5-hydroxytryptamine receptor 3 (5-HT3) (Barnes and Sharp, 1999). The action of monoamines is terminated by cellular re-uptake and enzymatic catabolism (Nestler *et al*., 2009).

1.4 Aim of the thesis

The aim of this thesis is to summarize the existing knowledge on the importance of monoamines in the regulation of the immune response during peripheral infection and compare the findings from mammals to those of bird studies. The thesis will focus on the role of each monoamine in the neuroimmune interactions and their immune-stimulatory or -inhibitory activities during infection.

2 NOREPINEPHRINE AND EPINEPHRINE

2.1 Norepinephrine

Norepinephrine, also called noradrenaline, is produced in brain nuclei located in the medulla and pons. More than half of all noradrenergic neurons in the CNS are located in the nucleus called locus coeruleus. Noradrenergic neurons then project widely throughout the whole CNS including cerebral cortex, brainstem, cerebellum and spinal cord (Figure 2). Norepinephrine is also synthetized peripherally by the medulla of adrenal gland (Nestler *et al*., 2009).

Two noradrenergic types of receptors have been detected – the alpha-adrenergic receptors, classified in α1-AR and α2-AR subtypes and the beta-adrenergic receptors, β1-AR, β2-AR, and β3-AR (Malenka, 2009). These receptors have been detected on various immune cells including lymphocytes and macrophages (Gabanyi *et al*., 2016).

Norepinephrine regulates the activity of the immune system during infection in both activating and inhibitory manner. The connection between norepinephrine and the immune response is characterized by changes in the release of norepinephrine, the adrenergic innervation of lymphoid organs and its direct impact on immune cells via adrenergic receptors (Kohm and Sanders, 2000).

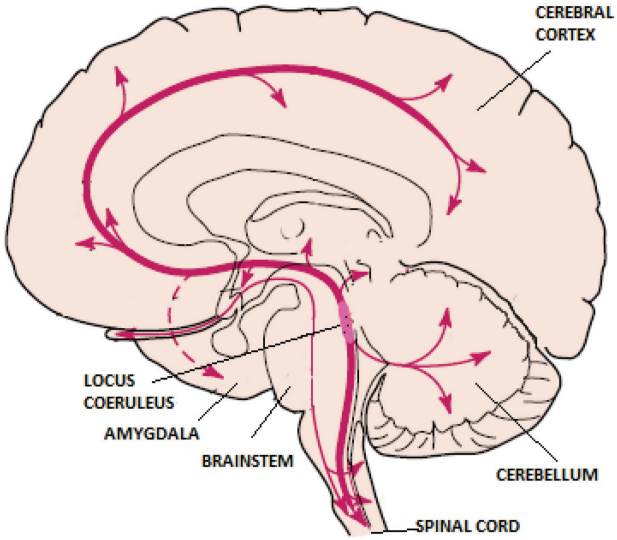


Figure 2: This figure shows a sagittal view of a human brain with the main noradrenergic pathways in the CNS including the localization of the locus coeruleus (pale red line) where the biosynthesis of norepinephrine is settled. The solid arrows indicate projects to cerebral cortex from the locus coeruleus, spinal cord and cerebellum. Dashed arrows show the projection into amygdala (adapted from Nestler *et al*., 2009).

2.1.1 Innervation of lymphoid tissues

Norepinephrine has been reported as the primary neurotransmitter involved in regulation of the immune system through the sympathetic nervous system (SNS) (Bellinger *et al.*, 2008). Noradrenergic nerve fibres innervate the primary lymphoid tissues such as thymus or bone marrow and also the secondary lymphoid tissues such as lymph nodes or spleen (Felten, 1993). Using histofluorescence in four strains of mice, Williams and Felten, (1981) showed that their thymus is innervated by norepinephrine nerve fibres. Histofluorescence was also used in another study which showed the presence of sympathetic nerves in lymph nodes of rat (Giron *et al.*, 1980). Norepinephrine modulates the activity of immune cells through adrenergic receptors.

According to studies on lymphoid organs, the turnover of norepinephrine during the immune response is enhanced. For example, the turnover of norepinephrine in the spleen and bone marrow was increased in response to an antigen. Rats injected with LPS from *Salmonella enteritidis* at the dose of 2 mg or 5.7- 6.7 mg/kg showed enhanced turnover of norepinephrine

in the spleen (Pardini *et al*., 1983). Similar results were obtained after the injection of *Pseudomonas aeruginosa* to adult mice using isotopic and non-isotopic methods. The dose was 1 -1.5x10^{-6} colony-forming units in 0,5 ml saline. LPS caused elevated turnover of norepinephrine in the bone marrow (Tang *et al*. 1999). Another study showed that *in vivo* stimulation of antigen specific B and T lymphocytes elevates the rate of norepinephrine release and turnover in spleen and bone marrow. Severed combined deficient (*scid*) mice, reported to have less, if any, of T and B lymphocytes, were reconstituted with keyhole limpet hemocyanin (KLH)-specific Th2 lymphocytes and trinitrophenyl (TNP)-specific B lymphocytes from the spleen of healthy mice. One week after the cell receipt, the *scid* mice were immunized with TNP-KLH specific antigen. The rate of norepinephrine release was enhanced when measured after 18-25 h following immunization, whereas no significant difference was detected after 1-8 h (Kohm *et al*., 2000).

2.1.2 Norepinephrine and innate immune response

Norepinephrine regulates the innate immune response following infection by modulating the release of cytokines from innate immune cells, such as macrophages or dendritic cells. Norepinephrine induces a reduction of TNF-α release by macrophages via β2-AR. Hu *et al.*, (1991) stimulated previously isolated spleen macrophages from Lewis rats with 10 μg/ml of LPS to investigate the effect of norepinephrine on the activity of macrophages, and particularly the release of TNF-α. It was found that macrophages co-incubated with norepinephrine showed reduced release of TNF-α. Treatment with a β2-AR-antagonist lowered this inhibitory effect suggesting a β2-AR mediation (Hu *et al.*, 1991).

Other innate immune cells reported to be affected by norepinephrine are dendritic cells. Dendritic cells express on their surface Toll-like receptors (TLR) which are capable of recognizing pathogens (Hemmi and Akira, 2005). After TLR stimulation, norepinephrine mediates the IL-10 and IL-12 cytokine production from dendritic cells. Upon stimulation of TLR2 and TLR4 with their agonists, norepinephrine induced secretion of IL-10 which lowers the production of IL-12. IL-12 directs the naïve T cells to differentiate to Th1 cells and stimulates the secretion of pro-inflammatory cytokines like TNF-α and IL-6 (Maestroni, 2005). Since IL-6 reduces the suppressive effect of T-regulatory cells which then cannot control the activity of Th1 cells (Pasare, 2003), this can lead to an increased risk of self-damage of

organism due to uncontrolled immune response. However, stimulation of murine dendritic cells together with the influence of norepinephrine caused reduced IL-12 and enhanced IL-10 secretion (Maestroni, 2002). IL-10 decreases the production of pro-inflammatory cytokines (Fiorentino *et al.*, 1991) and T-regulatory cells are then able to modulate Th1 immune response which might serve as a prevention of the immunopathological damage (Figure 3) (Maestroni, 2005).

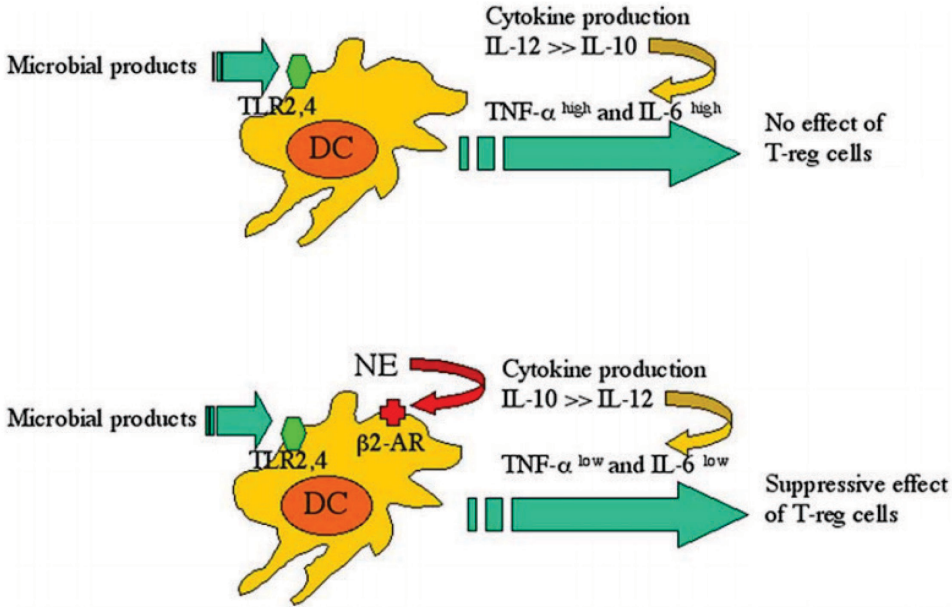


Figure 3: Following infection, the products of pathogens are recognized by Toll-like receptors (TLR) on the surface of dendritic cells. Without the effect of norepinephrine, this recognition leads to lower production of IL-10 and enhanced production of IL-12 which results in higher secretion of pro-inflammatory cytokines TNF-α and IL-6. These cytokines then reduce the activity of T-regulatory cells which can cause immunopathological damage. However, norepinephrine regulation of dendritic cells through β-AR induces the production of IL-10 and reduces the IL-12 secretion. The production of TNF-α and IL-6 is then also reduced and T-regulatory cells promote their suppressive effect which prevents immunopathology (adapted from Maestroni, 2005).

2.1.3 Norepinephrine and adaptive immune response

Since the lymphoid organs are the site where the production and development of lymphocytes is settled, norepinephrine regulates lymphocyte activity. Both T and B lymphocytes express adrenergic receptors (Kohm and Sanders, 2001), which allows

norepinephrine to act directly on these cells. In LPS-stimulated (25 g/ml) mice, norepinephrine at a dose of 5 x 10^{-6} M to 5 x 10^{-5} M has been reported to increase proliferation and differentiation of B lymphocytes. This enhancement seems to be mediated via β-AR, since the β-adrenergic antagonist propranolol completely blocked it (Kouassi *et al*., 1988).

Also, the secretion of immunoglobulins is affected by norepinephrine. In a study by Cross *et al*., (1986), mice at the age of 55-70 days were given an injection of 6-hydroxydopamine (6-OHDA), which is a catecholaminergic neurotoxin used to destroy sympathetic nerve terminals (Joers *et al.*, 2014; Kondo and Togari, 2003). Animals injected with 6-OHDA showed reduced levels of IgM and IgG-producing B lymphocytes compared to controls (Cross *et al*., 1986). However, the study of Besedovsky *et al*., (1979) described the opposite effect of norepinephrine on the antibody response. Rats in this study were given daily doses of 6-OHDA for the first 5 days after birth to destroy the peripheral adrenergic nerve terminals. At the age of 2-3 months, they were immunized with SRBC. These animals showed increased antibody response to SRBC when measured 5 days after immunization (Besedovsky *et al*., 1979). The reason why these two studies are not in agreement is unclear. A possible explanation could be the different age of the tested animals during the 6-OHDA administration, and the fact that the neuro-immune network of new born rats is immature.

2.2 Epinephrine

Epinephrine, also called adrenaline, is synthetized in the brain in a small number of neurons located in the medulla. Peripherally, like norepinephrine, it is secreted in the gland of adrenal medulla (Nestler *et al*., 2009). Epinephrine acts via the same adrenergic receptors as norepinephrine and is involved in analogous processes in the body (Gnegy, 2012; Pravosudov, 2010). Epinephrine also participates in the regulation of immune response. During infection, the levels of epinephrine released from the adrenal medulla change. This was initially studied by Egdahl et al. (1959) who injected eleven dogs with *E.coli* endotoxin at dosages ranging from 0.01 mg to 0.5 mg. The 0.01 mg dosage did not induce epinephrine bioavailability in most tested animals, whereas the 0.2 mg or 0.5 mg dosages showed highly increased epinephrine levels secreted from the adrenal medulla (Egdahl *et al.*, 1959).

2.2.1 Epinephrine and innate immune response

2.2.1.1 Epinephrine-mediated cytokine release

Following infection, epinephrine affects the response of the innate immune cells. For example, macrophages from Sprague-Dawley rats were investigated *in vitro.* After 1-hour stimulation with LPS, the cells were treated with epinephrine. It was found that epinephrine modulated the macrophage activity by enhancing phagocytosis and the release of cytokines, such as TNF-α, IL-1β or IL-10. Interestingly, the effect of epinephrine differed depending on its concentration: the 10 ng/mL dose of epinephrine increased the activity of macrophages, whereas the 50 and 100 ng/mL doses promoted a reducing effect (Zhou *et al.* 2014). In another study, epinephrine, at 10^{-5} M, induced a decrease in the production of nitric oxide and TNF-α release by mice macrophages stimulated with LPS. In contrast, IL-10 secretion was enhanced (Zinyama *et al*., 2001).

In agreement with these studies, alteration in cytokine release mediated by epinephrine was shown in whole human blood stimulated with LPS. Epinephrine not only reduced the TNF-α secretion, but also enhanced the release of IL-10. Administration of the β-antagonist propranolol completely suppressed the effect of epinephrine on TNF-α production, but only the combination of propranolol with the α-antagonist phentolamine inhibited the release of IL-10, which suggests the involvement of both adrenergic receptors. Also, LPS stimulation with the presence of epinephrine caused enhanced release of IL-8 and decreased secretion of IL-1β in the whole human blood. In both cases, propranolol alone completely inhibited the epinephrine-mediated elevation or reduction in cytokine release (Van Der Poll and Lowry, 1997a; Van Der Poll and Lowry, 1997b).

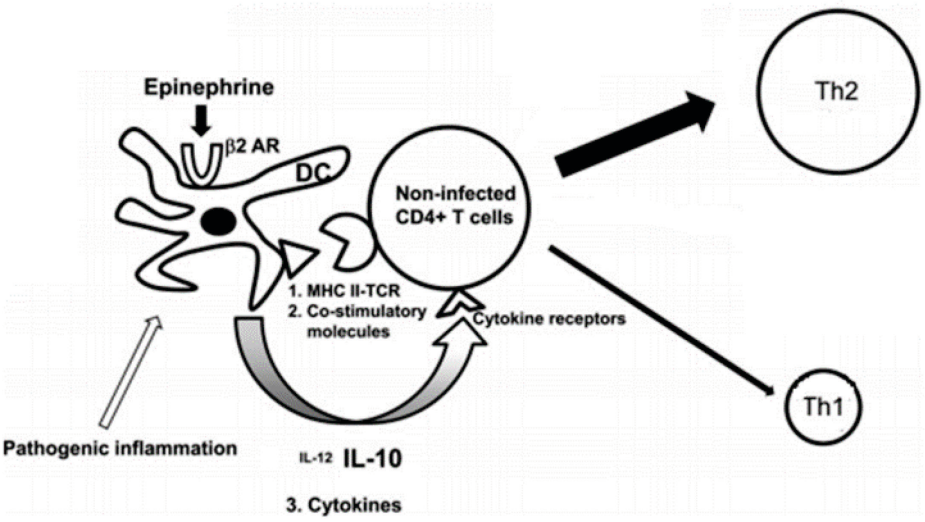
In addition, since IL-8 has been described as a neutrophil chemoattractant, epinephrine is indirectly involved in neutrophil chemotaxis (Baggiolini and Clark-Lewis, 1992).

2.2.1.2 Impact of epinephrine on dendritic cells and indirect mechanism of regulating T-lymphocyte differentiation

Epinephrine promotes the activation of dendritic cells and eventually affects T-lymphocyte differentiation following infection. The *in vitro* study of Kim and Jones (2010) showed that exposure to epinephrine for 2 hours before stimulation with LPS led to bone marrow-derived dendritic cells (BMDCs) expressing significantly increased major

histocompatibility complex II (MHC II) molecules which are expressed on antigen-presenting cells and recognized by antigen-specific T lymphocytes (Roche and Furuta, 2015) and the co-stimulatory CD80 and CD86 on their surface when co-incubated with CD4+ T lymphocytes. The MHC class II and the co-stimulatory molecules CD80 and CD86 participate in the interactions between dendritic cells and T lymphocytes (Lim *et al.*, 2012; Holling *et al.*, 2004).

In addition, epinephrine regulated the BMDCs mediated release of cytokines driving CD4+ T-lymphocyte differentiation through the β2-adrenergic receptor (Kim and Jones, 2010). Epinephrine enhanced the release of IL-10 involved in the development of Th2 response by a direct act on surface receptors on naïve T cells (Laouini *et al.*, 2003). Furthermore, IL-12, which has been reported to drive naïve T cells into Th1 subtype, was suppressed by epinephrine. Thus, epinephrine is capable to drive CD4+ T lymphocytes into Th2 subtype through its effect on dendritic cells via β-AR, while reduces the Th1-mediated response (Figure 4) (Kim and Jones, 2010).



F**igure 4**: The figure shows a diagram of the effect of epinephrine on dendritic cells during infection. During peripheral infection, epineprine binds to β-AR on the surface of dendritic cells and stimulates the expression of MHC II-TCRs and co-stimulatory molecules which are necessary for the interaction between dendritic cells and naive T cells. Furthermore, epinephrine increases the secretion of the cytokine IL-10, which promotes the differentiation of naive T cells to Th2 subtype and decreases the IL-12 production, which results in reduced Th1 polarization of naive T cells (adapted from Kim and Jones, 2010).

2.3 Norepinephrine and epinephrine and avian immune system

Norepinephrine modulates the immune response in birds similarly to mammals. For example, following infection in poultry, the release of norepinephrine in lymphoid tissues is reduced. In a study by Edens *et al*., (1987), the inoculation of turkeys with the bacterium *Bordetella avium* led to decreased norepinephrine release in thymus and bursa of Fabricius, the avian immune tissue where the differentiation of B lymphocytes is settled (Ratcliffe, 2006).

Avian immune cells express adrenergic receptors. Motobu *et al*., (2003) showed in chicken that lymphocytes in bursa of Fabricius, spleen and thymus express β-AR. β-AR were detected in chicken embryos and their number was elevated during the embryonal maturation. This study further showed that the proliferation of chicken lymphocytes induced by a mitogen was decreased after 6-OHDA administration proposing that norepinephrine released from the sympathetic nerve terminals increases lymphocyte proliferation in birds (Motobu *et al*., 2003).

Apart from the proliferation of B lymphocytes, norepinephrine and epinephrine control the production of antibodies in birds. This effect of both catecholamines was investigated *in vivo* and *in vitro* in chicken. The birds were injected with norepinephrine and epinephrine (500 and 100 μg/kg respectively). After that, 1 mL of 5% SRBC in 9% saline was administrated. In the *in vitro* study, the birds were injected with 1 mL of 5% SRBC in 9% saline and after five days they were euthanized, and their spleens were collected. Splenocytes were then co-incubated with norepinephrine and epinephrine with the same doses as in the *in vivo* study. It was found that norepinephrine suppressed both the IgM and IgG *in vivo*, but the *in vitro* results were slightly different. IgM levels were decreased but IgG did not, suggesting a possibility of an implicated indirect mechanism. Epinephrine administration caused an increase in IgM following SRBC antigen administration in chicken *in vivo* and also *in vitro,* compared to controls. In contrast, the IgG levels were reduced *in vivo* and *in vitro* (Denno *et al*., 1994).

Taken together, these data demonstrate that norepinephrine and epinephrine regulate the innate and adaptive immune system during infection in mammals and birds. Both monamines act through β-AR, which are detected on both mammalian and avian immune cells. Following infection, the norepinephrine bioavailability changes in avian and mammalian lymphoid tissues and furthermore, norepinephrine and epinephrine modulate the activity of

lymphocytes in both, mammals and birds.

3 DOPAMINE

In the CNS, dopaminergic neurons are settled in two areas in the midbrain – the substantia nigra pars compacta and the ventral tegmental area (VTA). Dopamine is also synthetized in hypothalamus and the retina. Dopaminergic axons then project to other areas in the brain through three major dopaminergic pathways. The mesostriatal pathway begins in substantia nigra and extends to the dorsal striatum. The mesocortical pathway projects from VTA to the ventral striatum and other parts of the brain including the prefrontal cortex. From hypothalamus, the tuberoinfundibular pathway projects to the anterior pituitary (see Figure 5) (Nestler *et al*., 2009).

Dopamine receptors are classified into two families: the D1-like family consisting D1 and D5 receptors, and the D2-like family, involving D2,D3 and D4 receptors (Nestler *et al*., 2009). Dopamine is implicated in various functions, such as cognition, movement, reward and mood (Vaughan and Foster, 2013).

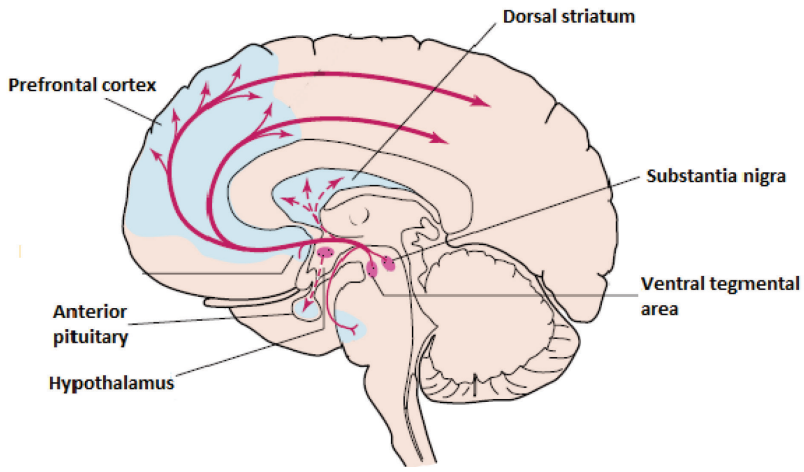


Figure 5: The picture illustrates the main dopaminergic pathways on a scheme of human brain viewed sagittally. The biosynthesis of dopamine occurs in the substantia nigra, ventral tegmental area, and hypothalamic nuclei (red dots). From the nuclei of the aforementioned areas, three major dopaminergic pathways project to dorsal striatum (upward dashed arrows), ventral striatum, hippocampus, olfactory bulb, amygdala, prefrontal cortex (solid arrows) and anterior pituitary

(downward dashed arrows). The parts in blue indicate the brain areas innervated by these pathways (adapted from Nestler *et al*., 2009).

3.1 Modulation of dopaminergic system by cytokines

As mentioned earlier, interactions between the immune and nervous systems work in both directions. Cytokines secreted by immune cells also influence the dopaminergic activity during response to a pathogen. Using *in vivo* brain microdialysis, 7-8-weeks old mice were injected with IL-1β directly into the hypothalamus. Dopamine levels were then measured with high-performance liquid chromatography (HPLC). According to the findings of this study, IL-1β administration evoked augmented production of dopamine in the brain. In addition, after IL-1β was administrated to murine hypothalamus slices *in vitro,* increased production of dopamine was evidenced, indicating a direct effect of IL-1β on stimulation of dopamine release in the brain (Shintani *et al*., 1993). In another study, 3-months old mice were injected with 200 ng of IL-1, IL-2 or IL-6. After two hours, the animals were euthanized, their brains were separated, and monoamine levels were measured by HPLC. All of the three cytokines caused elevated dopamine turnover in the prefrontal cortex (Zalcman *et al*., 1994).

3.2 Dopamine and innate immune response

Not only cytokines regulate the activity of dopamine, but dopamine also regulates the innate immune response through its effect on macrophages, dendritic and NK cells (Pinoli *et al.*, 2017).

Macrophages store dopamine and release it in response to a pathogen. According to an *in vitro* study using a macrophage cell line, the Raw264.7, LPS-treated cells (50 ng/ml) showed increased intracellular levels of dopamine two days after administration, as shown by high performance liquid chromatography with electrochemical detection (HCLP-EC) (Brown *et al*., 2003). Dopamine also altered cytokine release by macrophages *in vitro*. In primary human monocyte derived macrophages treated with LPS, dopamine induced an increase in IL-6, CCL2, CXCL8 and IL-10 release, but decrease in TNF-α, whereas in untreated cells, dopamine just elevated IL-6 and CCL2 release (Gaskill *et al.*, 2012). It was proposed that dopamine may have anti-inflammatory effects mediated or not by beta adrenoreceptors. In accordance to the findings discussed above, macrophages (J774.1 and mouse peritoneal macrophages)

stimulated with LPS and treated with dopamine released significantly higher amount of IL-10, whereas production of IL-12 was reduced *in vitro* (Haskó *et al.*, 2002).

Dopamine also regulates dendritic cells, which not only express dopamine receptors, but also are able to synthesize and store dopamine. Findings of light and electron microscopy provide evidence of dopamine stored in vesicles of human dendritic cells. Moreover, at the presence of T lymphocytes, dendritic cells started to release dopamine in granules. Flow cytometry findings showed that the amount of dopamine in dendritic cells was reduced 2 hours after contact with lymphocytes (Nakano *et al*., 2009). Prado *et al*., (2012) also used flow cytometry and found that both, immature and mature murine dendritic cells express D1, D2, D3 and D5 receptors (Prado *et al*., 2012).

NK cells are another type of cells described to express dopamine receptors. Zhao *et al.*, (2013) isolated NK cells from mouse spleen and, using western blot analysis, showed that these cells express all of the five dopamine receptor subtypes. Furthermore, activation of the D1-like receptors with the agonist SKF-38393 resulted in elevated cytotoxic activity of NK cells, whereas a D2-like agonist haloperidol administration led to suppressive effect. Based on these findings, it is implied that dopamine modulates the activity of NK cells differently, depending on what kind of dopamine receptor is implicated (Zhao *et al.*, 2013).

3.3 Dopamine and adaptive immune response

Dopamine modulates the adaptive immune response. This may occur directly through dopaminergic receptors on T and B lymphocytes detected in humans (Santambrogio *et al*., 1993). Murine T and B lymphocytes also store and produce dopamine acting in paracrine and autocrine way. The concentration of dopamine in these cells varies from $7x10^{-7}$ to $2x10^{-17}$ (Josefsson *et al.*, 1996).

Dopamine may have activating or inhibitory role on T lymphocytes. Watanabe *et al.,* (2006) reported that dopamine induced migration of murine and human CD8+ naïve T lymphocytes into secondary lymphoid organs through the D3 receptor, detected on these cells. On the other hand, Saha *et al.*, (2001) showed that dopamine at the dose of 48 pg/ml reduced the proliferation of both activated CD4+ and CD8+ human T lymphocytes and the cytotoxic activity of T lymphocytes was suppressed by dopamine action. These contradictory

results suggest that the effect of dopamine on naïve lymphocytes is stimulatory, whereas activated T lymphocytes are suppressed by dopamine (Sarkar *et al*., 2010). T-regulatory cells incubated with 10^{-5} M dopamine showed impaired suppressive effect on T-effector cells. Since SCH-23390, antagonist of D1-like receptor family, completely blocked this effect, this activity of dopamine seems to be mediated through D1-like receptors (Kipnis *et al.*, 2004). Dopamine was also found to reduce the release of human IL-10 and TGF-β, which are the major suppressive cytokines produced by T-regulatory cells (Consentino *et al*., 2007).

Dopamine has a suppressive effect on the activity of B lymphocytes *in vitro*. Murine B lymphocytes isolated from spleen, mesenteric lymph nodes and Peyer's patches were stimulated by LPS and showed suppressed B-lymphocyte proliferation and production of antibodies when co-treated with dopamine (Kouassi *et al.*, 1988).

Apoptosis has been proposed as the most probable mechanism by which dopamine suppresses the adaptive immune cells following evidence from a study in which co-incubation with dopamine promoted apoptosis in murine lymphocytes after 24 hours (Josefsson *et al*., 1996).

3.4 Dopamine and avian immune system

In birds, like in mammals, dopamine modulates the immune response. The dopamine-mediated migration of avian leukocytes has been investigated in chicken. In a study from McCorkle *et al*., (1994), birds received different doses of dopamine (100 ng, 1 or 10 µg) administrated every hour for 1, 2 or 3 days through osmotic pumps. It was found that the first dose did not affect the migration of leukocytes at any time, but the 1 µg/hr dose increased leukocyte migration in the 2 and 3 days groups and the 10 µg/hr significantly augmented leukocyte migration at all observed times, suggesting a dose-dependent effect of dopamine on mobilization of leukocytes in birds (McCorkle *et al*., 1994).

Depending on the dose, dopamine also increases the phagocytosis activity of macrophages in birds. Chicken macrophages treated with dopamine at a concentration of .1 or 25 µg showed highly increased phagocytosis of *E. coli*. However, the concentration of .01 µg did not cause any effect (Ali *et al*., 1994).

Similar to mammals, dopamine modulates the adaptive immune cells through regulation of antibody secretion. In chicken injected with SRBC, dopamine reduced the number of cells secreting both IgG and IgM *in vitro* and *in vivo*. The fact that i*n vitro* findings also showed a reducing effect, suggests a direct effect of dopamine on avian antibody-producing B lymphocytes (Gray *et al*., 1991).

In summary, dopamine appears to promote mostly inhibitory effect on the immune system regulation. However, it depends on the dose of dopamine which can turn the suppressive effect into activating. The regulatory role of dopamine is comparable in birds and mammals, since the regulation of antibody secretion and macrophage activity has been detected in both.

4 SEROTONIN

Serotonin, also named 5-hydroxytryptamine (5-HT) is a monoamine associated with mood, emotions and happiness (Nestler *et al*., 2009; Dfarhud *et al*., 2014) but it can also modulate arousal or appetite (Olivier, 2015). In brain, serotonin is produced in the raphe nuclei located in the brainstem. Serotonergic neurons innervate almost the whole CNS. Their axons project to cortex, brainstem, cerebellum and spinal cord (Figure 6) (Nestler *et al.*, 2009). The most important peripheral source of 5-HT are enterochromaffin cells of the gastrointestinal tract. After its synthesis, 5-HT is released to circulation and taken-up by platelets which are capable of storing but not producing 5-HT (Duerschmied *et al*., 2013).

Seven families (5-HT1 – 5-HT7) of serotonergic receptors have been identified. Unlike other monoamine receptors, 5-HT3 is the only receptor which is a ligand-gated ion channel (Barnes and Sharp, 1999).

5-HT plays an important immunomodulatory role during infection (Ahern, 2011; Jackson *et al.*, 1985). Various immune cells have been reported to express serotoninergic receptors (Herr *et al*., 2017) and ability to store 5-HT which also represents another peripheral source of this monoamine (Arreola *et al*., 2015).

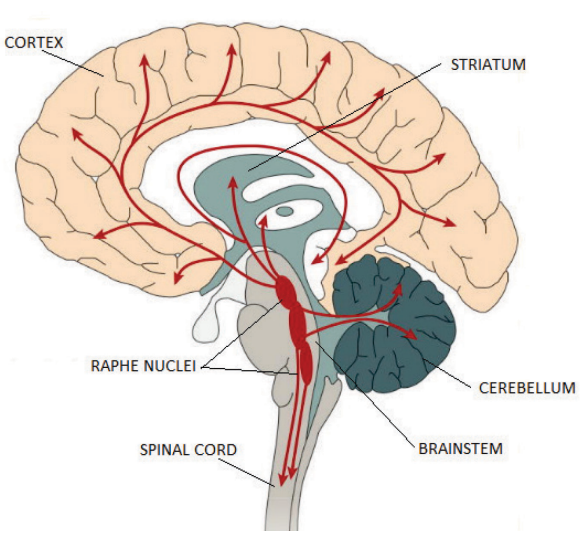


Figure 6: The figure represents the main serotonergic pathways in the human brain as viewed sagittally. The three connected red points show the anatomical location of the biosynthesis of serotonin in the brainstem, the raphe nuclei. From raphe nuclei, serotonergic pathways project to the spinal cord (downward arrows), cortex and striatum (upward arrows) and to the cerebellum (right arrows) (adapted from Berger *et al*., 2009).

4.1 5-HT and innate immune response

During the innate immune response, 5-HT functions as an important chemoattractant and is essential for the appropriate neutrophil and mast cell-mediated immune response in mammals. The migration of neutrophils associated with platelets-derived 5-HT has been studied. Acute peritonitis was stimulated in non-neural 5-HT deficient mice and wild types, which were used as controls. It was demonstrated that in mutants, the migration of neutrophils to the site of inflammation (extravasation) was decreased in comparison to wild types (Duerschmied *et al*., 2013).

Kushnir-Sukhov *et al.*, (2006) further showed that 5-HT acts as a chemoattractant for murine mast cells activated with dinitrophenyl (DNP)-human serum albumin. Murine and human mast cells not only express serotonergic receptors, but they also store and synthetize 5-HT which can be released when mast cells are activated (Ringvall *et al*., 2008; Kushnir-Sukhov *et al*., 2007).

4.2 5-HT and adaptive immune response

During infectious challenge, serotonin also affects the adaptive immune system in mice and rabbits by inhibiting the production of antibodies, such as IgM and IgG (Eremina and Devoino, 1973; Jackson *et al.*, 1985). The administration of the 5-HT precursor 5-hydroxytryptophan (5-HTP) to mice resulted to decreased antibody production in response to immunization by SRBC. The level of inhibitory activity depended on the dose, since the highest tested 5-HTP concentration of 200 mg/kg promoted the most inhibitory impact. Moreover, after inhibition of serotonergic activity by para-chlorphenylalanin (PCPA; inhibitor of tryptophan hydroxylase in 5-HT biosynthesis), the antibody release was increased (Jackson *et al.*, 1985).

In rabbits, the removal of serotonergic neurons in raphe nuclei in the midbrain by electrolytic lesion, led to augmented antibody release following immunization with bovine serum albumin (Eremina and Devoino, 1973).

4.3 5-HT and avian immune system

During the avian immune response, 5-HT has been reported to regulate leukocyte migration and humoral immunity. Similarly to what applies to dopamine *in vitro*, the continuous *in vitro* administration of 5-HT to leukocytes isolated from chicken (*Gallus domesticus)* led to increased migration of these cells suggesting the presence of 5-HT receptors on their surface, implying an analogous mechanism following infection *in vivo* (Mccorkle *et al*., 1989).

5-HT modulates antibody release and the number of antibody secreting cells. In the study of Gray *et al.*, (1991), chickens were administered 5-HT (100 µg/kg) 5 days before the injection of SRBC. The number of IgM secreting cells increased following *in vivo* 5-HT administration, whereas IgG producing cells tended to decrease. Consistently with the *in vivo* findings, the *in vitro* results showed low enhancement of IgM secreting cells and mild reduction of IgG forming cells (Gray *et al.*, 1991).

In conclusion, following infection in birds and mammals, 5-HT influences similar processes, such as the migration of leukocytes or antibody production. In contrast to what occurs in mammals, IgM secreting cells were found to increase. This might have occurred due to different doses of 5-HT used in the studies. Since in mammalian study, the dose was significantly higher, it is possible that serotonin promotes its inhibitory effect on IgM secreting cells only in higher doses.

5 MELATONIN

Melatonin is synthetized in the pineal gland (Figure 7) (Nestler *et al*., 2009). The peak of the concentration of melatonin in the blood is detected at night (Reiter, 1991), which is associated with the ability of melatonin to regulate the cycle of sleep and have a sleep-promoting effect. Melatonin can be used as a treatment for insomnia or unsynchronized biological clock (Zhdanova and Tucci, 2003). Besides the pineal gland, melatonin is synthetized also in retina and gastrointestinal tract (Fukuhara, 2004; Bubenik, 2002). The activity of melatonin is mediated through its receptors MT1 and MT2 (Nestler *et al*., 2009).

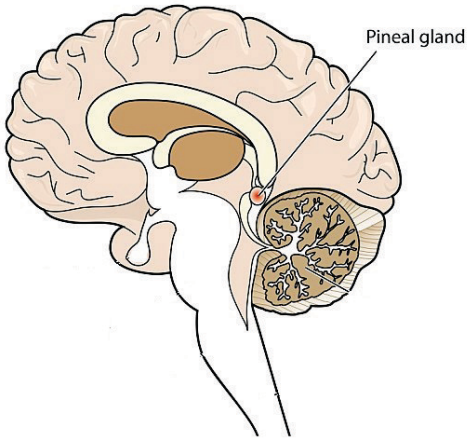


Figure 7: This picture shows a sagittal view of a human brain with the localization of pineal gland (red spot) where the biosynthesis of melatonin in the brain is settled (adapted from Borkhataria, 2017).

Besides sleep regulation, melatonin enhances the activity of cell-mediated and humoral immunity in both mammals and birds. In general, the effect of melatonin has been characterized as immunostimulatory (Terrón *et al*., 2009, Majewski *et al*., 2012).

5.1 Melatonin and cytokine release

During infection, melatonin promotes the release of cytokines from immune cells. These cytokines may therefore affect other immune cells, and in this way, melatonin can affect them indirectly. The role of melatonin-regulated cytokine release was proposed in a study which showed that melatonin protects mice against Venezuelan equine encephalomyelitis virus. According to the findings of this study, the administration of melatonin to infected mice significantly reduced virus levels in blood and brain as well as the mortality of the infected animals (Bonilla *et al*., 1997). In another study on infected mice with the same virus, animals treated with melatonin showed increased IFN-γ and TNF-α and IL-1β secretion compared to controls. To find out through which cytokine melatonin acts, blockers of IL-1β, IFN-γ and TNF-α were administrated. It was found that blockade of IL-1β release caused death in all infected animals, thus IL-1β was suggested as a major melatonin-regulated cytokine in the protection against viral disease (Valero *et al*., 2002).

Sze *et al*., (1993) also found melatonin-mediated release of cytokines. In this study, mice were treated with melatonin added to a drinking water at a dose of 100 μg/ml for two weeks. After this melatonin treatment, mice were euthanized, and their spleen immune cells were co-incubated with Concanavalin A (Con A) or LPS, T or B-lymphocyte mitogen, respectively. Cells from melatonin treated animals showed higher release of IL-2 and IFN-γ compared to controls. Additionally, Pioli *et al*., (1993) described higher TNF-α and IL-1 release of antigen-stimulated murine macrophages after the injection of melatonin. These findings indicate an indirect effect of melatonin on the activity of T lymphocytes through its involvement in the enhanced release of cytokines. IL-1 has been reported to take a part in the activation of Th2 cells (Lichtman *et al*., 1988) and TNF-α has been detected as a co-stimulator in IL-2-mediated IFN-γ production and proliferation of T lymphocytes (Scheurich *et al*., 1987).

5.2 Melatonin and humoral immune response

During the humoral response in mammals, melatonin increases the antibody production of murine spleen B lymphocytes. For example, in the *in vivo* study of Caroleo *et al*., (1992), mice injected subcutaneously with melatonin (10 mg/kg daily for 4 days) and immunized with horse red blood cells showed significantly increased antibody response compared to controls

(Caroleo *et al*., 1992). Due to its promoting impact on humoral response, melatonin was proposed as immunostimulatory treatment for animals with depressed humoral immunity due to ageing. Evidence for this effect derive from a study in aged rats immunized against SRBC and injected with melatonin at the afternoon for seven days. It was found that melatonin increased the levels of IgG and IgM compared to controls (Akbulut *et al*., 2001).

Furthermore, during the humoral response, various immune cells such as macrophages, lymphocytes, monocytes, and neutrophils can promote lysis of targeted cells marked as antigens coated with antibodies. This mechanism is called antibody-dependent cellular cytotoxicity (ADCC) (Hashimoto *et al*., 1983; Fanger *et al*., 1989). The effect of melatonin on this mechanism has been studied. Mice were injected intravenously with different doses of melatonin. After the last melatonin injection, splenocytes were isolated and co-incubated with red blood cells from chicken that were used as target cells in ADCC. It was found that melatonin-treated splenocytes showed higher ADCC activity optimally at 1 mg/kg/day. Thus, at adequate concentration, melatonin enhanced the lysis of recognized cells by the immune system through ADCC in mice (Giordano and Palermo, 1991).

5.3 Melatonin and avian immune system

As well as in mammals, melatonin promotes an immunoenhancing effect during the adaptive immune response. Moore and Siopes (2002) examined the impact of melatonin treatment on humoral and cellular immune response in Japanese quail (*Coturnix coturnix japonica*). The birds in this study were divided into two experimental groups given the same dose of melatonin (50 μg/ml) but different duration of melatonin administration. The first group received melatonin for 24 h, the second for 3 h and a last group was used as control. After that, they were immunized with phytohemagglutinin or with Chukar red blood cells to induce cell-mediated or humoral response, respectively. The experimental group of the longer administration period of melatonin significantly increased the cellular immune response compared to the shorter period although both groups were affected. Similar findings were presented for humoral response (Moore and Siopes 2002). Moreover, aged ringdoves (*Streptopelia risoria*) were pre-treated with melatonin and its precursor tryptophan and then immunized against SRBC. Pre-treatment with either melatonin or tryptophan raised the

depressed humoral response in aged birds as shown by elevated levels of IgM. On the other hand, the IgA levels were reduced after treatment with both, melatonin and tryptophan. The IgG amount did not show any significant difference after the administration (Terrón *et al*., 2009).

Melatonin also increases the proliferation of lymphocytes in birds. For example, melatonin elevated the total white blood cell (WBC) number and heterophil/lymphocyte (H/L) ratio. In the study of Brennan *et al*. (2002), chicken exposed to 16/8 h light-dark cycle, were divided into two groups. Melatonin was administrated to first group during the light period and to the second group during the dark period at 5, 10, 20 and 40 mg/kg/day for one week. Chicken treated the highest melatonin had significantly increased total WBC count and enhanced proliferation of B and T lymphocytes compared to controls. H/L ratio was elevated in chicken injected during the dark period implying that melatonin activity is conditioned by the time of administration (Brennan *et al*., 2002).

The findings presented show that melatonin acts as an immunostimulant in infected mammals and birds. During the avian and mammalian immune response, melatonin elevates the production of antibodies and possibly could be used to restore the depressed humoral response of aged animals. Although in birds, melatonin was not found to increase the IgG levels as was detected in mammals, the immunoenhancing effect of melatonin in IgM production was found in both, mammals and birds.

6 HISTAMINE

The biosynthesis of histamine in CNS is settled in the tuberomammillary nucleus in hypothalamus. Histamine neurons then project throughout the whole brain to areas such as cerebral cortex, hippocampus, amygdala, cerebellum and spinal cord (Figure 8). Histamine regulates diverse functions such as sleep, arousal, memory or learning (Nestler *et al*., 2009; Haas and Panula, 2003).

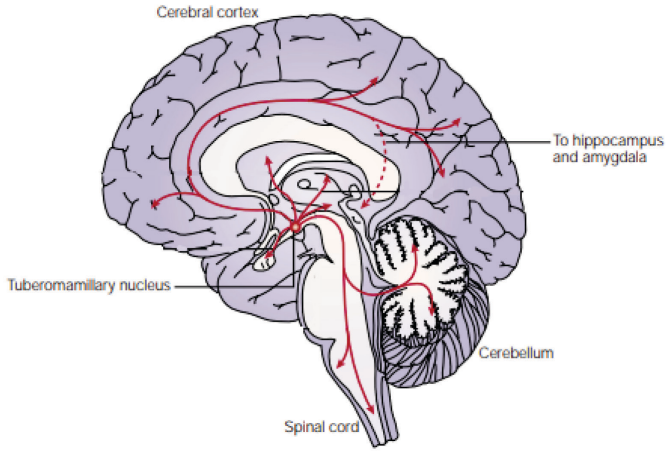


Figure 8: This figure represents the main histaminergic pathways in the human brain (sagittal view). The red circle illustrates the biosynthesis of histamine anatomically located in the tuberomammillary nucleus. Histaminergic pathways then project widely into cerebral cortex (solid upward arrows), hippocampus and amygdala (dashed arrows), cerebellum (right solid arrows) and spinal cord (downward arrows) (adapted from Haas and Panula, 2003).

Histamine acts as an immunomodulator during infection through its receptors grouped into HR1-HR4 subtypes (Branco *et al.*, 2018). For example, *Yersenia enterocolitica*, an intestinal pathogenic bacterium, induced upregulation of histidine decarboxylase, enzyme involved in histamine synthesis in infected mice. Although the administration of the H1R antagonist pyrilamine did not alter the response to *Y. enterocolitica,* the blocking of H2R with its antagonist cimetidine was associated with shorter animal survival and increased proliferation and colonization of *Y. enterocolitica* in the intestine (Handley *et al.,* 2006).

6.1 Histamine and innate immune response

6.1.1 Storage of histamine in mast cells and basophils

Histamine is detected in basophils and mast cells, which have been described as the major storage of histamine in the body (Eckert *et al*., 1988). Histamine is stored in cytoplasmatic granules, which, when basophils and mast cells are activated, merge with the plasma membrane and their content is secreted with exocytosis (Stone *et al*., 2010). This was studied by Norn *et al*., (1986) who administrated LPS to human basophils. LPS activated the complement system which stimulated basophils to release histamine, as shown by

spectrofluorometry (Norn *et al*., 1986). This method was also used in another study which showed that pathogens such as *Staphylococcus aureus* caused elevated release of histamine from human basophils and rat mast cells (Espersen *et al.,* 1984).

Not only pathogenic agents, but also cytokines can evoke histamine secretion from immune cells. In human basophils and mast cells, IL-33 significantly increased the histamine release measured by ELISA (Rivellese *et al*., 2014; Rivellese *et al.*, 2015).

6.1.2 Effect of histamine on dendritic cells

As described previously, monoamines can modulate the activity of dendritic cells and indirectly affect T lymphocytes. Histamine alters cytokine secretion from dendritic cells, induces mobilization of dendritic cells to the lymph nodes and, since the antigen presentation of dendritic cells to T lymphocytes is settled in the lymph nodes, histamine can participate in activation of T lymphocytes (Itano and Jenkins, 2003).

The modification of dendritic cells by cytokine release was examined with plasmacytoid dendritic cells, which are involved in the antiviral response and are the primary source of IFN-α, a cytokine promoting antiviral activity (Tang *et al.*, 2010; Abbas *et al.*, 2012). Administration of live flu virus (strain A/Puerto Rico/8/34) to human plasmacytoid dendritic cells and concurrent effect of histamine caused reduced IFN-α secretion. Further investigation elucidated the role of H2R in this process (Mazzoni *et al.*, 2003).

The histamine-mediated mobilization of dendritic cells was showed by a study from Dawicki *et al.*, (2010) who stimulated mice with peptidoglycan from Staphylococcus aureus causing migration of various types of dendritic cells, such as CD11b+ and plasmacytoid dendritic cells (pDCs) to the lymph nodes. To examine whether histamine was involved in this process, histamine receptors H1 and H2 were blocked with pyrilamine or ranitidine, respectively. According to the findings of this study, the blockade of H2 receptor suppressed the migration of CD11b+ and pDCs (Dawicki *et al.*, 2010).

6.2 Histamine and adaptive immunity

Histamine is also indirectly involved in the differentiation of T lymphocytes. For example, the production of IL-12 of human dendritic cells was reduced by histamine through

H1 and H2 receptors (Caron *et al.,* 2001). Since IL-12 is the cytokine that drives the differentiation of naïve T lymphocytes into Th1 effector cells, histamine suppresses the polarization of T lymphocytes into Th1 cells and drive naïve T lymphocytes to develop Th2 response (Caron *et al.,* 2001). In addition, histamine administration to LPS-stimulated human whole blood led not only to reduced levels of IL-12, but also to increased release of IL-10 (Elenkov *et al.*, 1998), which promotes the differentiation of naïve T lymphocytes into Th2 subtype (Coomes *et al.*, 2017).

6.3 Histamine and avian immune system

Avian mast cells synthetize and release histamine during infection, like in mammals. The presence of histamine in mast cells was investigated in different avian body parts, such as proventriculus and oviduct. Sun *et al.,* (2009) inoculated 20 chickens with Newcastle disease virus (NDV). Then, the birds were euthanized and their proventriculus tissues were harvested. The number of mast cells and the content of histamine were examined by quantitative analysis of fluorescent assay. The results showed that the quantity of mast cells and the content of histamine were significantly increased in the infected chicken compared to controls (Sun *et al.*, 2009).

Another study showed that mast cells containing histamine are also found in the oviduct of birds. Laying hens were euthanized after the oviposition, their oviducts were collected and examined for the localization of mast cells and the concentration of histamine. It was found that the number of mast cells and the histamine concentration differ in the various parts of the oviduct. The largest amount of both mast cells and histamine was detected in the infundibulum part (Figure 9). In addition, histamine was detected in diffusible as well as in granular form, which suggests that in birds, mast cells also store histamine in granules, and release it similarly to mammals (Hrabia *et al*., 2001).

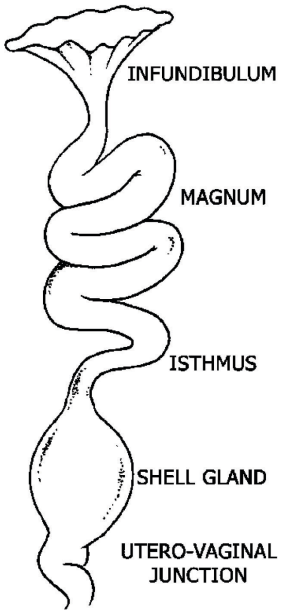


Figure 9: This figure shows a scheme of the avian oviduct with its parts indicated: infundibulum, magnum, isthmus, shell gland and utero-vaginal junction. The oviduct segment known as infundibulum is the major source of mast cells containing histamine in birds (adapted from Holm *et al.,* 2001).

In summary, histamine acts as an inhibitor but also as activator of immune processes following infection, especially the migration and release of cytokines from dendritic cells which are associated with T-lymphocyte differentiation. In both mammals and birds, the main source of histamine is in basophils and mast cells which synthetize and store histamine allowing them to release histamine in response to infection.

7 CONCLUSION

Monoamines orchestrate the immune response in mammals and birds. Their regulatory role is essential for the appropriate functioning of the immune system following infection. In cases of disruption of the monoamine bioavailability due to, for example, psychopathology or pharmacotherapy, the immune response is impaired possibly causing immunopathology and psychopathology (for example depression or other psychiatric diseases) (Steinman, 2004; Leonard, 2010).

Interesting findings were obtained about all of the three catecholamines (norepinephrine, epinephrine and dopamine) which showed reduced release of Th1 cytokines, such as IL-12 and also, enhanced secretion of Th2 cytokines, such as IL-10. These findings suggest that during stress, when the levels of catecholamines are elevated (Finlay *et al*., 1995; Majewski *et al*., 1986), Th1/Th2 balance is switched towards Th2 response, whereas Th1 response is suppressed (cytokine shift model). This could explain the higher susceptibility to infection (reduced Th1 response) and also risk of an autoimmune disease or allergy (increased Th2 response), both associated with stress (Marshall *et al*., 1998; Segerstrom and Miller, 2004).

Almost all of the studies presented in this thesis showed that monoamines regulate the immune system in a similar manner in mammals and birds. The only exceptions found were the effects of norepinephrine, serotonin and melatonin on antibody response, where the results of studies slightly differed between mammals and birds. Norepinephrine in birds showed either suppressive or no effect on IgM and IgG antibody response. In mammals, one study showed also the inhibitory effect, but according to another study, norepinephrine can also act as an activator of the antibody response in mammals. Serotonin in mammals reduced the number of IgM secreting cells, whereas increased it in birds. Also, melatonin caused elevated IgG secretion in mammals and in a contrast did not have an effect on IgG amount in birds. These inconsistencies possibly occurred due to different doses of monoamines used in these studies or the age of the tested animals.

An interesting possibility for treatment of depressed or enhanced immune response for example in aged animals is through pharmacotherapy aiming at the modulation of monoamine bioavailability. For example, melatonin has been found to restore the humoral

response of aged mammals and birds, which proposes its future application in medicine as a cure for the weaken humoral immunity.

Finally, despite large numbers of observations, the role of monoamines during infection needs to be further investigated, especially for understanding the underlying mechanisms, which in many studies remained unclear and were only guessed. However, in most of the cases, the studies reviewed in this thesis used chicken as an experimental model. Since species of birds such as parrots or songbirds (for example crows) show cognitive abilities comparable to mammals (Emery and Clayton, 2005; Olkowicz *et al*., 2016), studies on these birds could explain the neuro-immune interactions modulated by monoamines in more detail.

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