BIOCHEMISTRY RESEARCH TRENDS SERIES

Biochemistry and Histocytochemistry Research Developments

Stefan Fuchs
Max Auer
Editors

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AND
MAX AUER
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PREFACE

Biochemistry is the organic chemistry of compounds and processes occurring in organisms. Histocytochemistry is the study of intracellular distribution of chemical, reaction sites, enzymes, etc. by means of staining reactions, radioactive isotope uptake, selective metal distribution in electron microscopy, or other methods. This book focuses on the role of norepinephrine in neuroinflammation, discusses the contribution of norepinephrine to Alzheimer's (AD) and Parkinson's Disease (PD) and provides an overview of potential therapeutical options targeting this neurotransmitter. Using methodologies such as questionnaires and laboratory tasks, experimental results showing specific effects related to noradrenaline in both clinical and experimental studies are described. This book also provides the current findings on the relationships between sympathetic nerve activity, B-adrenoceptor polymorphisms, and renal function. Recent methodologies that are useful for advanced immunohistochemistry (IHC) analysis in pathological research into therapeutic agents is also analyzed. Other chapters in this book discuss the unresolved areas of plasma cell research, an analysis of a new technology based on B-Cell targeting and its advantages over conventional methods for selective generation of novel monoclonal antibodies, as well as a review of the regulation of proteases and their role during the biocontrol process. Recent advances in the isolation and characterization of glycosidases from hyperthermophilic microorganisms and the methods used for their application in oligosaccharide synthesis are explored as well.

Chapter 1 - Neuroinflammation emerges as a driving force in chronic neurodegenerative processes like Alzheimer's (AD) or Parkinson's disease (PD). Neuroinflammatory mediators such as cytokines, reactive oxygen species and molecules of the arachidonic acid pathway are generated and released by microglia, astrocytes and neurons upon stimulation and activation. In general, enhanced release of these substances has been considered to be detrimental.

Different neurotransmitters participate in the regulation of the production of these inflammatory mediators. The adrenergic system seems to play an important role in neuroinflammation and neurodegeneration. For example, norepinephrine has been considered to be immunosuppressive and adrenergic agonists attenuate the release of potentially toxic molecules. In AD and PD, degeneration of the locus coeruleus, an assembly of aminergic nuclei and major source for norepinephrine, is part of the disease process. In both diseases, a reduction in norepinephrine levels accelerates disease progression and pathology as well as worsening of clinical symptoms. Therefore, an increase in the content of norepinephrine may therefore be beneficial in reducing inflammatory damage in the brain.

This review focuses on the role of norepinephrine in neuroinflammation, discusses the contribution of norepinephrine to AD and PD and provides an overview of potential therapeutical options targeting this neurotransmitter.

Chapter 2 - The aim of this chapter is to examine the role of noradrenaline in interpersonal functioning. Healthy interpersonal functioning is important for the development of relationships in both work and personal situations. Many psychiatric disorders including depression are associated with poor interpersonal functioning and less social activity but improvement in interpersonal functioning can be independent of symptom resolution. Noradrenaline may be involved in the adaptive function of human social behaviours.

Concepts relevant to interpersonal behaviours leading to interpersonal rejection and the relationship between social skills and depression will be briefly reviewed. Then the methodology involved in this type of research will be described. This will involve both techniques developed to measure interpersonal functioning, from questionnaires to laboratory tasks, and psychotropic drugs which have been used to study noradrenergic function.

Using these methodologies, experimental results showing specific effects related to noradrenaline in both clinical and experimental studies will be described. Reboxetine has been shown to be associated with increased cooperative behaviour and other socially adaptive behaviours.

It is concluded that noradrenaline modulates cooperation and other socially adaptive behaviours and this action may promote friendship formation and facilitate social support.

Chapter 3 - There are number of lines of evidence that the neurotransmitter norepinephrine (NE) might be very important in pathophysiology of anxiety and mood disorders. Firstly, NE projections innervate the limbic system, suggesting the involvement of NE in the regulation of emotions and cognition. Secondly, NE interacts with serotonin (5-HT) and dopamine (DA) systems, which also play very important roles in the regulation of mood. Thirdly, it has been shown that various agents for increasing NE availability, such as NE reuptake inhibitors, are also effective antidepressant drugs. And fourthly, the depletion of NE can result in the relapse of depression after successful treatment with antidepressant drugs. All these pieces of evidence suggest that the stimulation of NE transmission can be beneficial in the treatment of affective disorders. However, different psychiatric medications have distant effects on NE transmission. The current chapter analyses the effect of psychiatric medications on NE system and proposes how the treatment outcome might be improved.

Chapter 4 - Renal injury, chronic renal disease and end-stage renal disease are often associated with obesity, hypertension, and diabetes mellitus. Heightened sympathetic nerve activity is observed in patients with renal injury, renovascular hypertension, chronic renal disease and end-stage renal disease (ESRD). Further, heightened sympathetic nerve activity as observed in plasma norepinephrine concentrations predicts survival and the incidence of cardiovascular events in patients with end-stage renal disease, and future renal injury in normotensive healthy subjects with a normal range of renal function. Hypertension, obesity and diabetes are currently among the World Health Organization's top 10 global health risks. Hypertension and diabetes mellitus, which occur often with obesity, together account for approximately 70% of end-stage renal diseases in the United States and Japan. Obesity also leads to increases in the incidence of cardiovascular diseases including renal injury. Many clinical and epidemiological studies have also documented that heightened sympathetic nerve activity plays an important role in obesity and hypertension. Thus, one could speculate that heightened sympathetic nerve activity might be an important mechanism of the onset and

maintenance of renal injury, and that obesity and hypertension might emphasize the relationship between heightened sympathetic nerve activity and renal injury.

Human obesity and hypertension have strong genetic as well as environmental determinants. Several observations show associations of β2- and β3-adrenoceptor polymorphisms with hypertension and obesity, although these findings have not been confirmed. In addition, relationships between adrenoceptor polymorphisms, plasma norepinephrine levels, and renal function have not been fully studied. Understanding the contribution of plasma norepinephrine and β-adrenoceptor polymorphisms with the onset and maintenance of renal injury might aid in the prevention of renal injury, chronic renal disease and end-stage renal disease in obesity and hypertension. It may theoretically help rational, pharmacological treatments for renal injury in obesity and hypertension.

The purpose of this review is to provide the current findings on the relationships between sympathetic nerve activity, β-adrenoceptor polymorphisms and renal function. Also, to further understand the precise roles of sympathetic nerve activity in renal injury in the context of obesity and hypertension, which may lead to the prevention and treatment of renal injury in these patients.

Chapter 5 - As immunohistochemistry enters its fourth decade as a diagnostic tool this analytical procedure continues to experience poor reproducibility, albeit in specific situations. The problem becomes more important with the mounting pressure to employ the assay in a quantitative manner for the assessment of therapeutic and prognostic markers in a number of neoplasms. Qualitative applications of immunohistochemistry are well established and continue to increase with the range of sensitive antibodies and detection systems available, however, numerous variables that influence the immunoexpression of proteins in formalin-fixed tissue continue to exist in the pre-analytical and analytical phases of the test procedure. Many pre-analytical variables are currently beyond the control of the laboratory. Tissue fixation is critical but the exposure to fixative prior to accessioning by the laboratory is not controlled. Antigen retrieval, another pivotal procedure in immunohistology, continues to be employed in an empirical manner with the actual mechanism of action remaining elusive. There is great variation in reagents, method, and duration of tissue processing and immunostaining procedure, and detection system employed is not standardized between laboratories. While many of these variables are offset by the application of antigen retrieval, which enables the detection of a wide variety of antigens in fixed tissue, the method itself is not standardized. This myriad of variables makes it inappropriate to provide meaningful comparisons of results obtained in different laboratories and even in the same laboratory as in current practice each specimen experiences different pre-analytical variables. Importantly, it calls into question the use of immunohistochemistry as a quantitative assay. Furthermore, variables in interpretation exist and cutoff thresholds for positivity differ. Failure to recognize false positive and false-negative stains leads to further errors of quatitative measurement. Many of the problems relating to the technology and interpretation of immunostaining originate from failure to recognize that this procedure is different from other histological stains and involves many more steps that cannot be monitored until the end result is attained. While several remedial measures can be suggested to address some of these problems, accurate and reproducible quantitative assessment of immunostains presently remains elusive as important variables that impact on antigen preservation in the paraffin-embedded biopsy cannot be standardized.

Chapter 6 - It is important to establish the biological basis of immunohistochemical characteristics of mandibular bone and cartilage, as well as periodontal tissue reaction to mechanical stress for orthodontic treatment.

The mandible is composed of mandibular bone and cartilage. This cartilage is classified as secondary, together with condylar, coronoid and angular cartilages. The mandibular bone formation pattern attracts many researchers because it suggests large possibilities for orthodontic treatment. Mandibular condylar cartilage has bone characteristics which are more significant than cartilaginous characteristics. In general, Runx2 is a transcription factor necessary for osteoblast differentiation and bone formation. Therefore, we focused on Runx2 and investigated the distribution of Runx2 in developing mouse mandibular condylar cartilage, with Jagged-Notch signaling, using immunohistochemistry (IHC) and in situ hybridization (ISH) techniques. These IHC and ISH results suggest that Runx2 plays an essential role for mandibular condylar cartilage development, especially that Runx2 is essential for the onset of secondary cartilage differentiation.

In addition, to establish an immunohistochemical basis for orthodontic treatment, we examined early changes of Runx2 and Msx2 immunohistochemical expressions by immunohistochemistry in mouse periodontal ligament exposed to mechanical stress. At 20 minutes, 1 hour, 3 hours, 9 hours and 24 hours, relevant parts of the mouse tissues were histopathologically evaluated, and they were examined for Runx2, Msx2 and alkaline phosphatase (ALP) expressions. Strong expressions of Runx2 and Msx2 were seen in periodontal fibroblasts of the tension side at 20 minutes after mechanical stress. Expressions of Runx2 and Msx2 became stronger in parallel with time, and at 24 hours after mechanical stress, the periodontal fibroblasts, cementoblasts, and osteoblasts showed strong expression. Moreover, ALP has also demonstrated similar strong expression. All these results strongly suggested that Runx2 promoted differentiation of osteoblasts at an early stage and Msx2 worked as an activator of Runx2 function. Furthermore, because Heat Shock Proteins (HSPs) serve as molecular chaperones to maintain homeostasis in tissues, we examined the immunohistochemical profile change of one such protein, HSP70, in periodontal ligament cells after receiving mechanical stress during orthodontic treatment in the course of up to 24 hours. We thought that the mechanical stress for orthodontic treatment might cause dynamic histological change occurred within a short time and might also cause expression of HSP70 in periodontal ligament tissue.

Chapter 7 - With the development of highly specific antibodies and improvements in detection systems, immunohistochemistry has become a common analytical technique, and detection techniques such as the avidin/biotin- and polymer-based methods are widely used in pathological research and diagnosis. Meanwhile, the development of molecular-targeted agents that make attacks against proteins and their sites via kinase activity has led to increasing demand for a next generation IHC approach. Here, we outline recent methodologies that are useful for advanced IHC analysis in pathological research into therapeutic agents.

Chapter 8 - Processing biological specimens for light microscopy (LM) and electron microscopy (EM) requires a critical amount of samples. We report a pre-embedding technique for processing scarce biological specimens for LM and EM. The technique is based on immobilizing the samples in bovine serum albumin (BSA) and bis-acrylamide (BA), cross-linked and polymerized. The preparation is compatible with a broad range of histological and electron microscopy protocols and procedures. It presents several advantages

over other pre-embedding techniques; it is rapid, simple, and permits efficient and reproducible analysis of scarce biological specimens by LM and EM. The technique may be particularly useful for processing specimens, like biopsies, cystic and amniotic-fluid cells.

Chapter 9 - Autoimmune diseases, such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) are facilitated by B cells that have lost self-tolerance. B cells contribute to autoimmune diseases by production of autoantibodies, by presenting autoantigens or by secreting proinflammatory cytokines. For that reason, it is important to understand the origin of autoreactive B cells and their role in the pathogenesis of autoimmune disease. Many autoreactive B cell receptors (BCR) are normally generated during B cell development, but in healthy individuals most of the B cells carrying an autoreactive BCR are silenced by deletion, receptor editing, inclusion or anergy. Interestingly, in humans a unique self-reactive $VpreB^{+}LC^{+}$ B cell subset was identified, which comprises 0.5-1% of circulating B cells and co-expresses conventional immunoglobulin light chain (Ig LC) and the non-rearranging surrogate light chain (SLC), which was previously thought to be exclusively expressed during early B cell development. These $VpreB^{+}LC^{+}$ B cells are present in healthy individuals and accumulate in the joints of some patients with RA. They manifest an unusual Ig heavy chain (HC) and LC repertoire, which displays evidence for receptor editing and is associated with autoimmunity. To elucidate the role of these autoreactive $VpreB^{+}LC^{+}$ B cells in the development of autoimmunity, we have recently generated a novel SLC-transgenic mouse model in which all B cells coexpress SLC components. Here we review the characteristics of the unique subset of $VpreB^{+}LC^{+}$ B cells identified in human and discuss our findings in the SLC-transgenic mouse model in the context of the involvement of $VpreB^{+}LC^{+}$ B cells in the etiology of autoimmune disease.

Chapter 10 – The most widely used organisms are fungi, and several enzymes and organic acids are synthesized by species of *Aspergillus*. Over than the past 1,000 years the use of hydrolytic enzymes from fungi has become more prevalent in Japanese fermentation industries. The molds *Aspergillus oryzae*, *A. sojae*, *A. awamori*, and *A. saitoi* are of great practical importance in the fermentation industries, enzyme technologies, food industries, and civilization in Japan. In the eastern world rice is used instead of malt or mashed grapes for fermentation. Here a mold, usually *A. oryzae*, initiates the fermentation process by hydrolyzing rice starch to fermentable sugars. Later on the sugar is converted to change by spontaneous fermentation by either yeast or bacteria leading to products such as 'Sake', Japanese rice wine. Other examples of the traditional use of fungi in food production are in the making of soy sauce and miso paste. In the fermented vegetable protein, soy sauce, the cooked soybeans are mixed with equal amounts of roasted wheat and then inoculated with a pure cultured 'Koji' starter or 'seed mold'.

Another important field for the early industrial application of fungi was the production of enzymes, and enzymes are now being used in a wide variety of processes. The invention and production of 'Takadiastase' for *A. oryzae* by Takamine J. in 1894 became an enzyme industry from the late nineteen century. After Takadiastase was discovered it was produced in appreciable amounts during the Second World War, initially with *A. oryzae*, *A. sojae*, *A. awamori*, and *A. niger*. *Aspergillus saitoi*, which is a food microorganism, a black *Aspergillus* used in 'Shochu', a traditional Japanese spirit, was described taxonomically by Sakaguchi *et al.*. An acid stable proteolytic enzyme 'Molsin' from *A. saitoi* produced on an industrial scale by us used in the preparation of a human digestant (Fujisawa Pharmaceutical Co., Osaka).

The genome of *Aspergillus oryzae* has been sequenced in 2005. The ability to secrete large amounts of proteins and the development of a transformation system have facilitated the use of *A. oryzae* in modern biotechnology. In 2006, the Brewing Society of Japan gave its seal of approval to the decision: '*Aspergillus oryzae* and related food *Aspergilli* are the national microorganisms of Japan'.

In this chapter, catalytic and molecular properties of unique and characteristic enzymes obtained from *Aspergillus* fungi used in Japanese bioindustries are described.

Chapter 11 - During the infection of entomopathogenic fungi, extracellular hydrolytic enzymes are important for the degradation of the insect cuticle, facilitating penetration and providing nutrients for further growth. A common feature between different insect pathogenic fungi is the involvement of extracellular proteolytic enzymes in these processes.

Regarding proteases, the most extensively studied entomopathogenic fungal genera are *Metarhizium* and *Beauveria*. The majority of the protease enzymes described from these genera belong to the family of serine proteases, however, the expression of metalloproteases and aminopeptidases under biocontrol-related conditions was also demonstrated. Detailed knowledge on protease genes and enzymes involved in fungal biological control will assist further strain improvement enabling the overexpression of genes encoding effective proteases.

The aim of this chapter is to summarize the information available about the extracellular proteases of entomopathogenic fungi, focusing on *Metarhizium* and *Beauveria* species. A large number of protease enzymes have been purified, cloned and characterized from these beneficial organisms. These results will be reviewed and data about the regulation of proteases as well as their role during the biocontrol process will be discussed.

Chapter 12 - Hyperthermophilic microorganisms thrives at temperatures higher than 80°C and proteins and enzymes extracted from these sources are optimally stable and active in the presence of temperatures close to the boiling point of water and of other denaturants, i.e. chaotropic agents, pH, organic solvents, detergents, etc. Therefore, hyperstable enzymes are considered attractive alternatives in biocatalysis and in chemo-enzymatic synthesis. In addition, the molecular bases of the extreme stability to heat and to the ability to work optimally at high temperatures are not completely understood and intrigued biochemists, enzymologists, and biophysics in the last twenty years. In particular, hyperstable glycosidases, enzymes catalysing the hydrolysis of *O*- and *N*-glycosidic bonds, have been studied in detail as they are simple model systems promoting single-substrate reactions, and, more importantly, can be exploited for the enzymatic synthesis of oligosaccharides. The importance of these molecules increased enormously in recent years for their potential application in biomedicine. Hyperstable glycosidases, working in transglycosylation mode, can be excellent alternatives to the classical chemical methods helping in the control of regio- and stereoselectivity as conventional enzymes, but also resisting to the organics used in chemical synthesis. We will review here recent advances in the isolation and characterization of glycosidases from hyperthermophilic microorganisms and the methods used for their application in oligosaccharide synthesis.

Chapter 13 - L-Asparaginase (E.C.3.5.1.1, L-ASNase) catalyzes the hydrolysis of L-Asn, producing L-Asp and ammonia. This enzyme is an anti-neoplastic agent; it is used extensively in the chemotherapy of acute lymphoblastic leukemia (ALL). L-asparaginase from *Erwinia carotovora* (*Eca*L-ASNase) was cloned and expressed in *E. coli*. The enzyme was purified to homogeneity by a two-step procedure comprising cation-exchange chromatography and

affinity chromatography on immobilized L-asparagine. The purified enzyme was subjected to thermal inactivation studies. Thermodynamic parameters (E_a, $\Delta H^{\neq}$ and $\Delta S^{\neq}$) for the thermal inactivation process of the enzyme were determined. It was concluded that the low thermal stability of the enzyme is of entropic origin and is most likely due to structural determinants that cause a higher degree of local disorders at specific locations.

CONTENTS

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Chapter 1

FUNCTION OF NOREPINEPHRINE IN NEUROINFLAMMATION AND CHRONIC NEURODEGENERATIVE DISEASES

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ABSTRACT

Neuroinflammation emerges as a driving force in chronic neurodegenerative processes like Alzheimer's (AD) or Parkinson's disease (PD). Neuroinflammatory mediators such as cytokines, reactive oxygen species and molecules of the arachidonic acid pathway are generated and released by microglia, astrocytes and neurons upon stimulation and activation. In general, enhanced release of these substances has been considered to be detrimental.

Different neurotransmitters participate in the regulation of the production of these inflammatory mediators. The adrenergic system seems to play an important role in neuroinflammation and neurodegeneration. For example, norepinephrine has been considered to be immunosuppressive and adrenergic agonists attenuate the release of potentially toxic molecules. In AD and PD, degeneration of the locus coeruleus, an assembly of aminergic nuclei and major source for norepinephrine, is part of the disease process. In both diseases, a reduction in norepinephrine levels accelerates disease progression and pathology as well as worsening of clinical symptoms. Therefore, an increase in the content of norepinephrine may therefore be beneficial in reducing inflammatory damage in the brain.

This review focuses on the role of norepinephrine in neuroinflammation, discusses the contribution of norepinephrine to AD and PD and provides an overview of potential therapeutical options targeting this neurotransmitter.

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1. Introduction

The brain and the immune system are accepted as the two major body's adaptive systems (Elenkov et al., 2000). The brain can modulate immune functions and the immune system also sends messages to the brain. The communication between these two systems is done mainly by the hypothalamic-pituitary-adrenal axis and the autonomic nervous system (ANS). The sympathetic nervous system (SNS), which is part of the ANS, innervates the lymphoid organs (Elenkov et al., 2000) (Flierl et al., 2007). Catecholamines, like dopamine, serotonin, epinephrine and norepinephrine, are the end products of the SNS.

Norepinephrine (NE) is a classical neurotransmitter of the central nervous system (CNS). NE is a catecholamine belonging to the group of biogenic amines. Like other biogenic amines, NE is produced in distinct neuronal populations within the CNS, from which axons project widely throughout the CNS. Therefore, alterations in NE levels and/or adrenergic receptor levels lead to ample changes in brain homeostasis. Classically, the NE system has been studied for its involvement in human behaviour and psychiatric diseases. Recent studies have even further widened possible functions of NE. NE has gained widespread attention because it seems to modulate neuroinflammation and thereby contributes to disease pathogenesis. The scope of this review is to give insights into *in vitro* and *in vivo* findings contributing to the role NE in the CNS.

2. The Locus Coeruleus

NE is mainly synthesized in the neurons of the locus coeruleus (LC), but also in the lateral tegmental field. In this review, we focus on the LC because of its implication in neurodegenerative diseases and cognition (Friedman et al., 1999).

Neurons of the LC constitute the largest and most important aggregation of NE cells within the brain. LC is latin for "blue place" and was named so because of its high neuronal content of melanin, formed by polymerization of norepinephrine. The LC is located below the floor of the fourth ventricle in the rostrolateral part of the pons (Figure 1). Neurons of the LC project through the medial forebrain bundle to the cerebral cortex including the frontal and entorhinal cortices, the limbic system (amygdala, hippiocampus, cingulate gyrus, fornix, hypothalamus, and thalamus) and to the cerebellum, brain stem, and spinal cord. The LC also receives input from the above mentioned brain areas (Nieuwenhuys, 1984). Thus, the NE system has a widespread effect on various brain regions and thereby on cognition and behaviour.

The number of neurons within in the LC range from 45 000 to 60 000 cells in normal young adult human brains and this number declines up to 50% in the normal aging human brain (Mann et al., 1983). NE levels also seems to be reduced in the aging population compared to younger subjects (Yates et al., 1983).

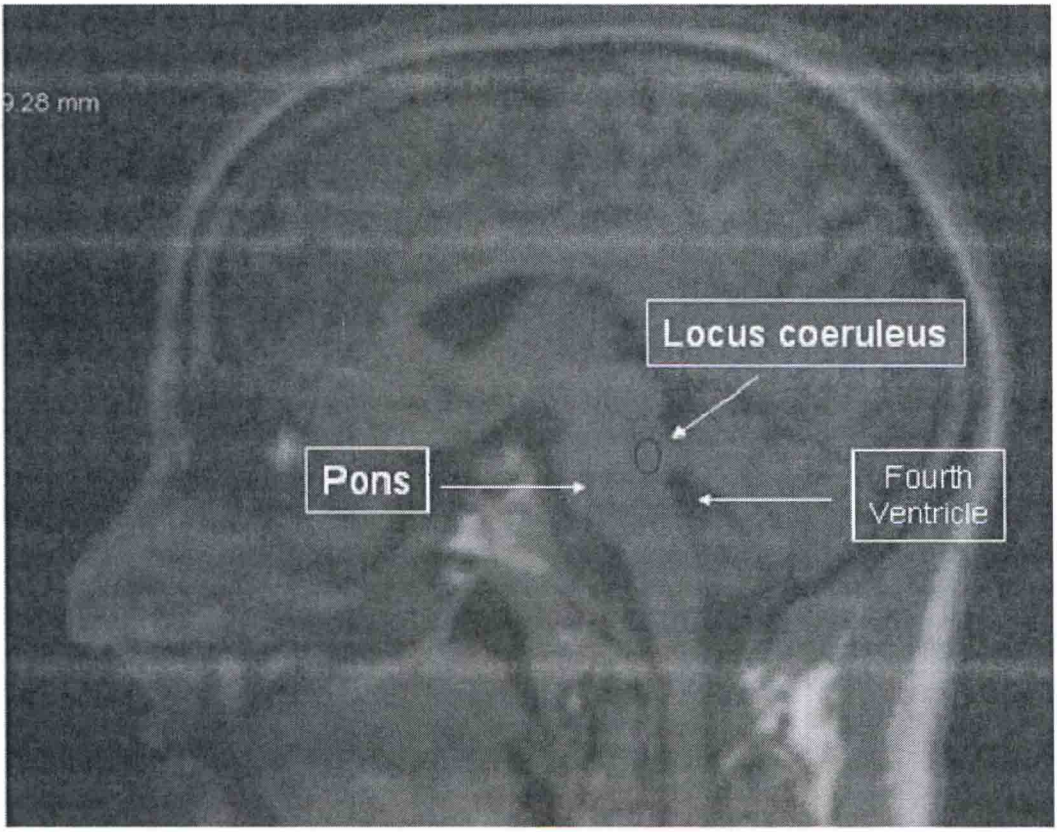

Figure 1. Courtesy of Dr. Lars Frings.

3. Classical Functions of Norepinephrine in the CNS

NE is derived from the essential amino acid L-tyrosine. The tyrosine hydroxylase converts L-tyrosine into L-dihydroxyphenylacetic (L-DOPA), which is then transformed into dopamine by dopa-decarboxylase. The β-hydroxylase converts dopamine into NE. NE is then released into synaptic cleft and exerts its effects via binding adrenergic receptors, which can be divided into α- and β-adrenergic receptors, as discussed later. A role has been described for NE in cognition, emotions, and behaviour (Figure 2). The classical psychiatric disease, in which modulation of NE has been postulated to be of pivotal role, is the major depressive disorder (MDD). The monoamine deficiency hypothesis holds a deficiency in serotonin and NE levels accountable for the pathogenesis of MDD. This is supported by the usage of tricyclic antidepressant drugs or monoamine oxidase inhibitors, which are highly effective in alleviating symptoms of depression (Belmaker and Agam, 2008).

However, there is a strong interplay between the different neurotransmitter systems in the CNS. E.g., NE not only mediates other neurotransmitter system, but also gets modified by others. NE interacts with acetylcholine, serotonin, and dopamine (Beani et al., 1978) (Vizi and Pasztor, 1981) (Bianchi et al., 1979) (Murphy et al., 1998) (Gresch et al., 1995). In addition, NE modulates neurotrophic factors like corticotropin-releasing hormone (Melia and