

The Autonomic Nervous System

Summary

This document arises from a WHO meeting held in Bethesda, MD, USA, on 10-12 December, 1998. It considers current research on the autonomic nervous system, directions for future investigation, and implications for clinical medicine and public health.



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This document results from a WHO meeting on the autonomic nervous system, held in Bethesda, MD, USA., on 10-12 December, 1998. The following experts participated:

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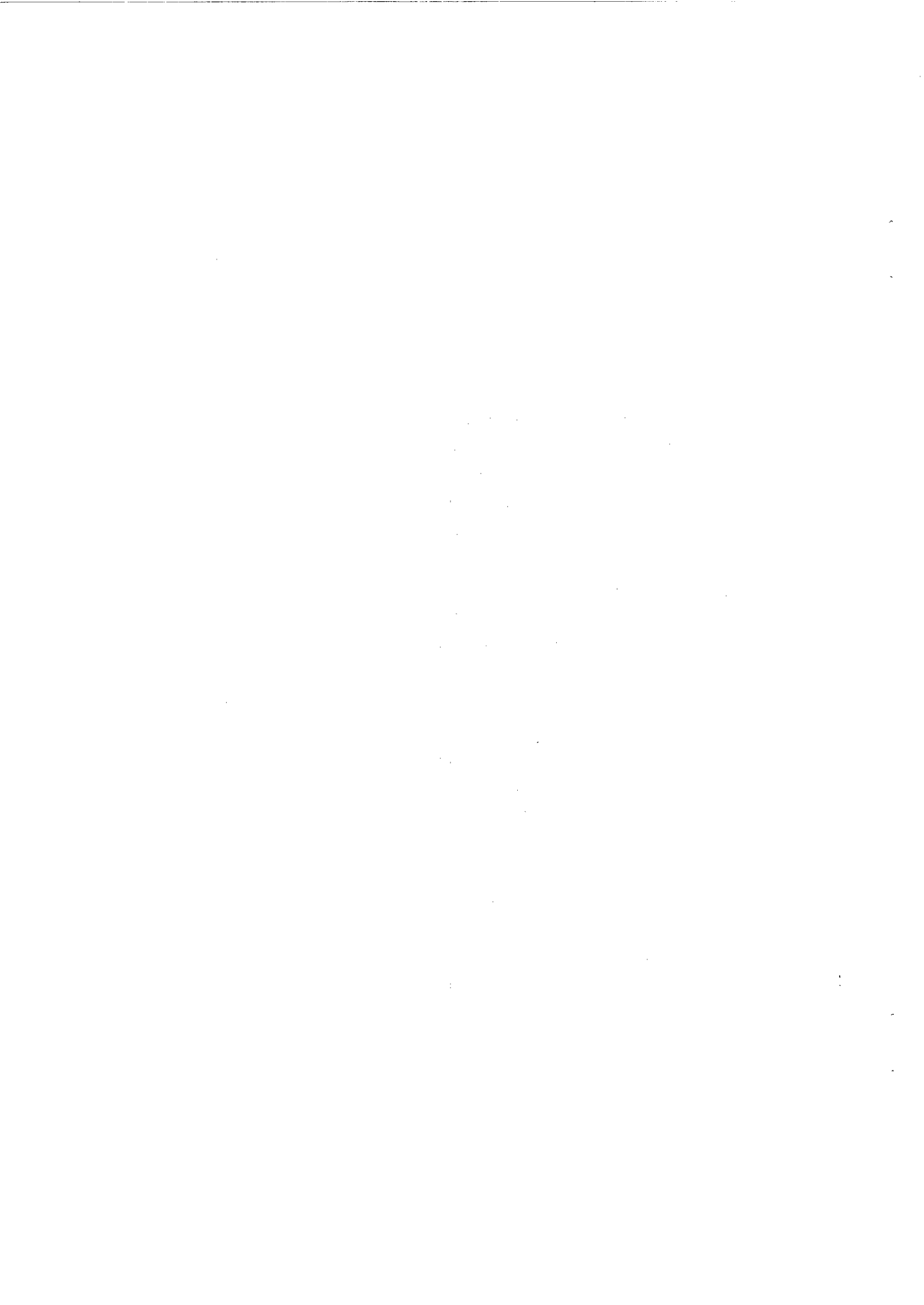
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The Autonomic Nervous System

1. INTRODUCTION

A WHO Informal meeting on the Autonomic Nervous System was held at the National Institutes of Health, Bethesda, Maryland, USA on 10-12 December, 1998. An opening statement was given by Professor C. Liana Bolis on behalf of the WHO and the Office of Research Policy and Cooperation.

After reviewing the recent activities of the WHO in the field of stress, Professor Bolis gave a general overview of the historical and comparative aspects of autonomic function. Because the autonomic nervous system (ANS) regulates key physiological functions of most organs and systems, it is important at this point to review the work that has been conducted in this field, to prepare new directions for further investigation, and to identify the implications of this work for clinical medicine and for public health. The structure and function of the ANS were among the earliest topics of study in neurology and neuroscience. Rapid progress in neuroscience research has led to considerable advances in molecular neurobiology and functional brain imaging. It is now possible to dissect physiology and pathophysiology at the molecular, cellular and integrative levels. It is therefore important to identify new opportunities for hypothesis-driven research on ANS that are provided by the tools of contemporary biology. Such developments in research will lead to improvements in our understanding of human disease and should facilitate novel therapeutic and preventive strategies. The autonomic nervous system integrates information that comes from the environment, from physiological processes, and from the genome. This system is therefore an ideal model for the study of the effects of the environment on homeostasis.

2. SCOPE OF THE MEETING

The scope of the meeting was defined as follows:

1. To review the state of the art of research and clinical relevance of ANS function.
2. To communicate recent developments in the molecular mechanisms that regulate

central and peripheral autonomic function.

3. To identify promising new areas of research on ANS function in physiology and medicine.
4. To integrate new scientific developments with public health approaches for disease prevention and treatment.
5. To evaluate the role of environmental factors, including socioeconomic factors, on ANS function and human health.
6. To examine the role of ageing in ANS function.

3. THE AUTONOMIC NERVOUS SYSTEM

3.1 The Autonomic Nervous System

The earliest recorded reference to the visceral nervous system was made by Galen in the second century. He gave the first account of the paravertebral sympathetic chains, but he made the mistake of describing the sympathetic and vagal trunks as one structure originating within the cranium. This gave rise to an error which persisted for fifteen hundred years. Stephanos (1545) and later Eustachius (1563) were the first to distinguish the two separate systems. In the seventeenth century Willis (1664) published a remarkably clear account of the ganglionated chains and their connections with the intercostal nerves. He described the cardiac branches and stated that the great mesenteric plexus sent its nerve fibres like rays in all directions; hence, it came to be called the solar plexus. He considered that its function was to place the heart and viscera in connection with the brain so that they should act in harmony. The modern nomenclature of the cranial nerves originated with Willis. In addition, he gave an accurate description of the vagus or "wandering nerve" with a true understanding of its apparent union with the cervical sympathetic in some of the lower mammals and its separate course in man. He even noted the branch given off to the aortic arch "so it may react to changes in the pulse". In 1732 the Danish anatomist Winslow gave the name "sympathetic" to nerves which he demonstrated by dissection to lie outside the main cerebrospinal pathways. Neubauer (1772) published an illustration of the vagus and sympathetic nerves in the neck and thorax which ranks as one of the best anatomical plates that have been produced to date.

As in the other fields of medical science, anatomical knowledge developed far ahead of physiological experimentation. In 1669 Lower published the earliest observations on stimulation of the vagus. Further experiments by Ens (1745) and by the Webers a century later (1846) finally established the role of the vagus in inhibition of the heart. The discovery that the sympathetic trunks originate below the cranium and not from the brain stem, as described by Galen and all subsequent anatomists, was made by Du Petit in 1727. He was likewise the first to observe the pupillary paralysis which follows cervical sympathectomy, thus antedating Bernard and Horner by over a hundred years.

Langley's final establishment of the two great divisions of the involuntary nerves depended on Hirschmann's discovery in 1863 that moderate doses of nicotine prevent pupillary dilatation when the cervical sympathetic trunk is stimulated. In fact the term "autonomic nervous system" was proposed by Langley in 1898 to describe "... the sympathetic system and the allied nervous system of the cranial and sacral nerves, and for the local nervous system of the gut" (Langley, 1898). Early work on the functional anatomy of the autonomic nervous system included studies on tetrapods and other mammals. There were other very interesting studies on amphibians and birds. Young studied both teleost and elasmobranch fish, describing the morphology of the autonomic innervation of the iris and viscera.

The comparative approach makes it possible to understand how animals can adjust various physiological parameters in response to changing environmental or internal cues.

Neurotransmitters: comparative aspects

Cholinergic neurons

Acetylcholine has been considered the transmitter of old preganglionic neurons, and of most postganglionic, parasympathetic neurons of the autonomic nervous system in old vertebrate groups. The earliest experiments leading to the biochemical identification of acetylcholine were made by Loewi in 1921 on the amphibian heart.

Adrenergic Neurons

Adrenergic neurons use the catecholamines noradrenaline and adrenaline as transmitters.

Catecholamines are synthesized in adrenergic nerves and in the adrenal medulla. Noradrenaline is formed from tyrosine and adrenaline is formed from noradrenaline. Adrenaline is synthesized intraneuronally and can act as a transmitter in some species. Assays have shown that adrenaline in fact dominates over noradrenaline in many organs of amphibians, holosteans and teleosts. Noradrenaline is the dominating catecholamine in mammalian adrenergic nerves. But analyses of perfusates from the mammalian intestine after stimulation and mesenteric nerves showed that 5-25% of the catecholamines were adrenaline.

Neuropeptides

Peptides were recognized as neurotransmitters of the autonomic and sensory nervous systems at a relatively late stage. Several of the humoral substances released from endocrine cells were peptides. The demonstration of the peptide - like substance P in the intestine of both an elasmobranch, the spiny dog fish, *Squalus acanthias*, and a teleost, the cod, *Gadus morhua*, was the first finding of a regulatory peptide in a non-mammalian vertebrate. Like its mammalian counterpart the non-mammalian peptide occurred in both brain and gut. Several properties of the fish polypeptide were similar to those of the mammalian peptide substance P. It was established at an early stage that brain-gut peptides existed in non-mammalian species as well as in mammals. Indeed, neuropeptides occur in the nervous system of all animal groups possessing a nervous system, from the most simple of coelenterates. Compared to other known types of transmitters there is an enormous potential diversity for the individual in using peptides as neuronal messengers.

3.2 Structural and Chemical Organization of the Autonomic Neuroeffector System

The autonomic nervous system contains the parasympathetic and sympathetic systems. The parasympathetic system consists of sets of nerves, derived from the brainstem (cranial parasympathetic outflow) and from the intermediolateral columns of the sacral spinal cord (sacral parasympathetic outflow). Sympathetic nerves emanate from the thoracic and lumbar spinal cord. In general, when sympathoneural activity increases, parasympathetic activity decreases. Parasympathetic nerves release acetylcholine as the neurotransmitter. Acetylcholine appears to produce vasodilation by increasing local generation of nitric oxide. Sympathetic nerves derive from cells in ganglia rather than from cells in the spinal cord or brainstem and therefore consist mainly of post-ganglionic neurons. Sympathetic fibres supply the heart, vasculature, and glands. Because of the dominance of sympathetically mediated vasoconstriction in preservation of blood pressure during orthostasis, orthostatic hypotension constitutes a

cardinal sign of sympathetic neurocirculatory failure. The main sympathetic neurotransmitter is norepinephrine. Binding of norepinephrine to adrenoceptors on cardiovascular smooth muscle cells causes them to contract. In contrast with sympathetic nerves, adrenomedullary cells secrete catecholamines—in humans mainly epinephrine—directly into the bloodstream. The adrenomedullary system therefore is hormonal. Epinephrine affects the function of most body organs. Exogenously administered epinephrine rapidly increases the rate and force of cardiac contraction; increases myocardial cell; dilates bronchioles and increases the rate of breathing; redistributes blood volume toward the heart, brain, and skeletal muscle and away from the skin, kidneys, and gut; enhances the aggregability of platelets; relaxes smooth muscle of the uterus and gut; increases blood glucose by a variety of means including glycogenolysis and antagonizing insulin; dilates pupils; increases activity of the renin-angiotensin-aldosterone system; decreases serum potassium concentrations; increases the metabolic rate; and produces psychological effects such as increased alertness, decreased fatigue, and intensification of emotions. These effects would be expected usually to enhance survival in emergencies such as traumatic haemorrhage, hypoglycaemia, asphyxiation, cardiac collapse, or emotional distress, when the individual senses an overall threat to well-being or survival.

Norepinephrine biosynthesis begins with conversion of tyrosine to dihydroxyphenylalanine by tyrosine hydroxylase, the enzymatic rate-limiting step in catecholamine synthesis. Phenylalanine hydroxylase, tryptophan hydroxylase, tyrosine hydroxylase, and nitric oxide synthase all require tetrahydrobiopterin as a cofactor. Norepinephrine undergoes inactivation mainly by cellular uptake, with subsequent intracellular metabolism or storage. Reuptake into nerve terminals via a specific membrane transporter is the predominant means of terminating the actions of released norepinephrine. Norepinephrine removed from the extracellular fluid is subject to two fates—translocation into storage vesicles and deamination by monoamine oxidase-A. Catechol-*o*-methyltransferase catalyzes the conversion of norepinephrine to normetanephrine and epinephrine to metanephrine. The myriad different effects exerted by only three endogenous catecholamines in different organs depend on the numerous types and subtypes of adrenoceptors and intracellular mechanisms.

Accumulating evidence indicates the existence of three types of peripheral catecholamine systems—the sympathetic nervous system, an adrenomedullary hormonal system, and a non-neuronal, dopaminergic, autocrine-paracrine system. The heterogeneity and stressor-specificity of parasympathetic, pituitary-adrenocortical, sympathoneural, and adrenomedullary responses to different stressors casts doubt on the validity of Selye's doctrine of non-specificity, wherein stress is defined as the non-specific response of the body to any demand, and favours "primitive

specificity" of neuroendocrine responses. The recent development of 6-[¹⁸F]fluorodopamine positron emission tomographic scanning has enabled detailed clinical studies of sympathetic innervation in the heart, nasopharyngeal mucosa, thyroid, salivary glands, and limbs. This approach holds great promise for examining sympathetic neuroeffector function in patients with neurocardiological disorders. Future research should consider the central neural anatomic and chemical pathways responsible for differential sympathoneural and adrenomedullary activation, elucidate neurogenetics of catecholaminergic systems, test hypotheses derived from the "homoeostatic theory" of stress, and learn from patients with disautonomias about the normal functions of the autonomic nervous system.

3.3 Neuropeptides and Autonomic Nervous Function

There is little doubt that neuropeptides constitute the bulk of the transmitters within the central nervous system and they are also strongly represented in the periphery. Neuropeptides are particularly concentrated in areas of the brain involved in central autonomic control. There are few autonomic responses that have not been shown to be affected by peptide application directly to the brain. While limited availability of antagonists to the neuropeptides has resulted in slow progress in revealing roles for endogenous neuropeptides in autonomic function, studies utilizing antisense oligonucleotides, *in situ* hybridization and microdialysis and perfusion methodologies have revealed involvement of some endogenous brain peptides in autonomic control. Because particular neuropeptides are often associated with specific physiological functions, they represent potential targets for directed drug action. Studies have been conducted on the role of the peptides arginine vasopressin (AVP) and oxytocin (OXY) as neurotransmitters involved in central autonomic control. These studies have benefited from early access to receptor antagonists to these peptides, availability of genetic mutants and an early elucidation of the genes coding for their precursor peptides. Studies related to the understanding of the roles of these peptides in two important autonomic functions - central control of blood pressure and central control of body temperature and fever - will be detailed.

Animals and people exposed to pyrogens (lipopolysaccharide, interleukin, prostaglandins, etc.) develop fevers characterized by a regulated increase in body temperature. The reduction in febrile temperature following the termination of the pyrogenic stimulus or administration of a drug such as aspirin is known as antipyresis. There is now good evidence that the peptide arginine vasopressin (AVP) acts, in a wide variety of animals, as a neurotransmitter in the ventral septal area (VSA) to reduce fever. During fever, it is released from fibres and terminals in this area, where it acts on receptors of the V1 subtype to reduce heat production

and increase heat loss. Stimulation of endogenous AVP release reduces or prevents fever, whereas interference with the release of, or action of AVP in the VSA prolongs fever. A number of physiological and pathophysiological states in animals are associated with a reduced ability to develop fever; these include states of tolerance to pyrogens, some types of hypertension, the immediate neonatal period and the mother at parturition. There is evidence that altered AVP transmission in the brain may be responsible for some of these states of "endogenous antipyresis".

AVP has long been known to have pressor actions through actions at receptors on vascular smooth muscle; we now know that it also has pressor effects via receptor-mediated actions on central neurons controlling blood pressure and water balance. Because of redundancy of transmitters and of pathways controlling blood pressure it has been difficult to demonstrate an obligatory role for endogenous AVP in central cardiovascular control. Nonetheless, it appears that AVP, like a number of other central neuropeptide transmitters, displays a complementary action upon homeostatic function through actions both in the periphery and in the central nervous system.

The action of AVP upon V1 receptors in the brain is characterized by a peculiar "sensitization" phenomenon; that is, both cardiovascular and antipyretic responses to AVP in the brain are greatly enhanced and the threshold dose is reduced upon a second exposure. This sensitization can be induced by endogenously released AVP and may play a role in dynamic alterations in autonomic responses seen under pathological conditions.

3.4 Autonomic Nervous System and its Neuroendocrine Regulation

The sympathetic nervous system and the hypothalamic pituitary-adrenal-axis (HPA) are key elements of the response to stress. The interactions between these two systems is crucial for adaptation, survival, and evolution. The term "stress" was borrowed from physics and introduced in medicine by Selye, who proposed that a variety of noxious agents could elicit a general adaptive response. Selye's concepts were a progression of line of thought originating in antiquity that postulated that the organism existed in a healthy and stable state that would be disrupted in response to threats from the environment or to perturbations in the internal milieu. When the organism is exposed to a threat to its basal state of health a variety of adaptive neurobiological and neuroendocrine responses takes place. In addition to rapid activation of the sympathetic nervous system, there is rapid activation of the hypothalamic-pituitary-adrenal (HPA) axis. In conjunction with the HPA axis the sympathetic system provides a rapid and

integrative response to stress. The neurobiology and neuroendocrinology of the response to stress should consider that activation of the HPA axis originates in the central nervous system (CNS). The subgenual prefrontal cortex and the hippocampus provide negative feedback to the paraventricular nucleus of the hypothalamus (PVN). PVN neurons synthesize corticotropin-releasing hormone (CRH). CRH reaches the anterior pituitary gland, where it promotes proopiomelanocortin (POMC) gene transcription, translation, and the secretion of the POMC fragment ACTH (adrenocorticotrophic hormone). ACTH binds to receptors in the adrenal gland, eliciting the production of the steroid hormone cortisol or corticosterone. Cortisol circulates and reaches both the pituitary and the brain, providing an important negative feedback signal that contributes to cease HPA activation. Disorders in which there is persistent HPA hyperactivity, such as major depression, are conceptualized as conditions in which persistent negative feedback provided by glucocorticoids fails to normalize the excessive activity of the HPA axis.

New developments in molecular biology, integrative physiology, and metabolism have led to considerable progress in our understanding of the neurobiology and neuroendocrinology of the diverse elements of the response to stressors. The response to stress is mediated by a network of molecules that are expressed in the CNS in specific temporal and spatial patterns and are secreted into the circulation in complex rhythms. The interactions of central control systems with peripherally secreted molecules such as leptin determines the final outcome of the response to stress. Moreover, an understanding of the molecular mechanisms by which CRH elicits gene transcription has led us to develop a testable hypothesis for stress-induced alterations in disease susceptibility. According to that hypothesis CRH - related transcription factors might bind to unexpected genomic targets regulating oncogenes, viruses, and the gene encoding for inflammatory mediators. Advances in the understanding of the neurobiology and neuroendocrinology of the stress response have permitted the conceptual integration of events occurring at the molecular, cellular, integrative, and clinical levels. Our ability to bridge the gap between molecular medicine and clinical investigation in this area has placed this field at the forefront of contemporary biology. To expand the frontiers of existing knowledge in stress research we need to continually examine at the molecular and clinical levels the role of stress mediators in pathogenesis, pathophysiology, and therapeutics. Such work is of particular importance in the light of the recent development of non-peptide CRH antagonists, which can provide conceptually novel therapeutic strategies for human disease such as major depression which is associated with sympathetic system activation.

The pulsatile, adipocyte hormone leptin modulates HPA function, ANS activity, and energy expenditure. Leptin provides a bridge between nutrition HPA function and ANS activity.

Patients with a mutation in the leptin gene, exhibit decreased sympathetic tone, similar to what has been described in the *ob/ob* mouse. Thus, leptin represents a peripherally secreted pulsatile signal of nutritional status which has profound effects on ANS regulation.

3.5 The Endocrine Heart and the Clinical Impact of the Natriuretic Peptides

In the past decade considerable work has led to the identification and characterization of hormones of the natriuretic peptide family. These peptides are primarily involved in the regulation of blood pressure and electrolyte/body fluid homeostasis. The prototype of the natriuretic hormones is cardiodilatin/atrial natriuretic peptide (ANP), which is primarily expressed in the heart. It is synthesized as a precursor molecule ANP-1-126 and packed in specific granules in atrial myoendocrine cells. Cleavage into the C-terminus ANP-99-126 and excretion into the circulation is caused by appropriate stimuli for release. Further members of the natriuretic peptide family were isolated such as brain natriuretic peptide (BNP) and C-type natriuretic peptide (CNP). All the members of this family share many common features, including tissue distribution of gene expression, biosynthetic pathways, and pharmacological effects in target organs. The main interactions with the functions of the autonomic nervous system exerted by these hormones are natriuresis, diuresis, and vasodilation but varying among the individual peptides. Urodilatin (URO) is a further member of the natriuretic peptide family synthesized in the kidney and exerting potential paracrine renal effects.

The discovery of the natriuretic peptide family resulted in further research showing that primary disturbances of synthesis, secretion, or response to these peptides may underly some disorders of electrolyte/body fluid homeostasis, blood pressure regulation, and modulation of smooth muscle tone. Research in the last years has been conducted on the development of URO for various clinical indications based upon the physiological and pharmacological properties of this peptide hormone. At the present time the pharmacological potential of URO is studied in phase II clinical trials for therapeutic use in acute renal failure, in phase III trials for the therapeutic use in acute exacerbations of bronchial asthma, and in phase I trials for the treatment of congestive heart failure.

The physiological and pharmacological impact of the natriuretic peptides and the most recent clinical developments of URO, indicate promising perspectives as well as the limitations and problems for its therapeutic use.

3.6 Stress and the Cardiac Response

The traditional medical approach dictates treatment of patients because of a disease, implicitly of an acute nature, in order to induce a recovery from illness. The paradigm is that of a doctor-patient relationship, on a one - to - one basis. This approach, however, is being largely superseded by a new style that could be exemplified by disease management strategies. In this context, specific paradigms and algorithms are implemented in the therapeutic chain, with the declared goal of increasing both efficiency and quality of the health system. Accordingly, the emphasis is shifting from specific components of the multifaceted reality of medical care, to a more global approach, focusing on overall performance. This new approach considers explicitly the various aspects of medical care, and in particular medical costs. These latter ones should not be simply equated to the overall direct and indirect monetary expenses, or missed gains, related to illnesses, but comprise as well other, less quantifiable aspects, such as quality of life. Treatments depend also upon the personal choices of patients, and reflect not only scientific, but also other more undefined ingredients of the complex reality of the health system. An emerging new strategy seems to take into consideration the observation that medical costs are unevenly distributed throughout the population. This could relate either to the concentration of medical costs in the last months of individuals' life span, or to the observation that populations with specific genetic, behavioural and environmental risks might consume a much larger fraction of medical resources. Accordingly, it might be wise to address not so much the treatment of diseases after they are manifest, but rather to influence risk factors, in order to compress the disease in a smaller fraction of the population at risk. This might have beneficial effects, such as to change "ageing" into "successful ageing", i.e. an ageing process which maintains a high standard of quality of life and of health, or to a modification of life-styles, leading to a better risk profile, in short to reduce morbidity and mortality. The critical aspect of this approach is that it is targeted at populations rather than to individuals. In brief, we are witnessing a change in treatment modality: from curing existing diseases in given individuals, to reducing the risk of a disease in given populations at risk. Successful treatment however must also consider the individual, in spite of the general population approach. The ensuing emphasis is on prevention, rather than on cure, with the assumption that the former is not only more efficacious, but also leads to a better quality of life. Preventive strategies seem to offer an optimal usage of resources, in the face of increasing public demands and shrinking budgets: rationalizing rather than rationing medical interventions. It is in this context of a changing medical scenario, that the concept of stress, or rather its physiopathological counterpart, the role of the autonomic nervous system, might provide a convenient approach to address in practice the paradox of better medicine at a smaller cost.

3.7 Neural and Peptidergic Control of Water Balance

The role played by the central nervous system (CNS) in the control of body fluid homeostasis has been demonstrated by several authors. The anteroventral third ventricle region (AV3V) plays a key role in central control of sodium excretion as evidenced by the findings that cholinergic, adrenergic, angiotensinergic and osmotic stimulation of the AV3V enhances and its destruction blocks sodium excretion in rats and goats. Cholinergic stimulation of the AV3V induced an increase in plasma atrial natriuretic peptide (ANP) as well as a marked elevation in content of the peptide in the medial basal hypothalamus, neuro - and adenohypophysis. On the other hand, a decline in plasma ANP after AV3V lesions was accompanied by dramatic declines in content of ANP in these same structures. The AV3V region and its ANPergic neurons have an essential role in the control of ANP release in response to blood volume expansion (BVE); adrenergic and muscarinic receptors are critical in mediating these responses. Lesions destroying the perikarya or caudally projecting axons of the ANP neurons in the AV3V region, the median eminence or posterior lobe of the pituitary gland blocked the increase in plasma ANP concentration in response to BVE. That this effect is related to blockade of the activity of the brain ANPergic neurons is supported by findings in sheep and in rats that the injection of antiserum directed against ANP into the AV3V region at least partially blocked the BVE-induced release of ANP. It has previously been shown that denervation of baroreceptors inhibits ANP release induced by BVE. Activation of the ANP neurons also causes release of ANP from the anterior and neural lobe of the pituitary gland. Since oxytocin (OT) is also released by BVE, ANP neurons may activate oxytocinergic neurons in the supraoptic and paraventricular nuclei, that project to the neural lobe. Oxytocin would circulate to the right atrium and directly activate release of ANP from the atrial myocytes, since intravenous or intraperitoneal injection of oxytocin elevates plasma ANP and also increases sodium excretion. The ANP released from cardiac atria myocytes by OT circulates to the kidneys and evokes natriuresis to return circulating blood volume to normal. Recently, OT-receptors were demonstrated on cardiomyocytes. When OT is directly applied to the atria *in vitro* or perfused through denervated heart it has an inhibitory effect on the rate and force of contraction of the heart. When OT was incubated *in vitro* with rat atria it induced a dose-related increase in the ANP release from the incubated atrial quarters. This OT-induced release of ANP from the rat atria was blocked by an OT antagonist. The negative ino- and chronotropic effects of OT via ANP would produce a rapid compensation for increased blood volume by decreasing cardiac output. The released ANP would have a rapid compensatory effect by evoking vasodilation. It has also been shown that OT acts on its renal receptors on NOergic cells (macula densa and proximal tubule cells) to stimulate release of NO that activates guanylyl cyclase releasing cGMP that probably activates

protein kinase g that closes Na⁺ and K⁺ channels, limiting Na⁺ and K⁺ reabsorption and evoking increase in salt excretion; these effects are almost completely inhibited by blocking NO synthesis. Thus, both ANP and OT-induced natriuresis and kaliuresis appear to be mediated by cGMP.

3.8 Autonomic Nervous System and Adrenocortical Function: What Can be Learned from Transgenic Models and Knockout Mice?

The autonomic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis both play a central role in the regulation of a wide range of physiological processes and are substantially involved in the maintenance of homeostasis and the adaptation of the organism to stressful conditions. The appropriate functioning of the systems to meet this demand largely depends on the intact and finely tuned regulatory mechanisms which act on several levels.

The adrenal gland combines essential components of the autonomic nervous system and the HPA axis in close contact. From morphological, immunohistochemical and ultrastructural studies it became evident that the chromaffin cells of the adrenal medulla and the steroid producing cortical cells are extensively intermingled, which is in contrast to previous contentions regarding the adrenal medulla and cortex as two distinct tissues with respect to location and function. Moreover, evidence from recent studies clearly demonstrates that the cells of the two tissues intensely communicate and furthermore exert regulatory actions on each other's function to form complex intra-adrenal regulatory circuits. Several experimental *in vitro* and *in vivo* approaches have been attempted to provide substantial evidence for those interactions. In *in vitro* studies a variety of regulatory factors produced and released by the adrenal medulla have been identified as playing an important role in modulating adrenocortical function.

Recent advances in generating transgenic models and knockout mice provide an excellent opportunity to analyse the impact of specific changes in the autonomic nervous system and the HPA axis on the integrative control in each other's function in the intact functional organism. With respect to the sympathetic nervous system, overexpression of phenylethanolamine-*n*-methyl transferase (PNMT) in transgenic mice resulted in a decrease of PNMT in extra - adrenal tissues following adrenalectomy, possibly as a consequence of glucocorticoid deficiency. In PNMT transgenic mice, corticosterone levels are elevated and strongly correlated with plasma epinephrine levels, whereas in tyrosine hydroxylase knockout mice corticosterone levels are severely suppressed. On the other hand, some animal models with disrupted function of several components of the HPA axis display alterations which are to be explained in the context of an

accompanying effect on the sympatho - adrenal system in these mice. CRH receptor knockout mice exhibit an atrophied adrenal medulla accompanied by a greater decrease in corticosterone levels compared to ACTH. Glucocorticoid receptor knockout mice do develop an adrenal medulla which is, however, incapable of epinephrine synthesis due to the lack of PNMT expression. Finally, mice deficient in 21 - hydroxylase reveal a marked decrease of adrenomedullary PNMT expression.

In conclusion, animal models of overexpression and depletion in catecholaminergic enzymes as well as of altered function of components of the HPA axis provide evidence that the mutual interdependence of the sympatho - adrenal system and the HPA axis at the level of the adrenal gland is functional and of physiological relevance *in vivo*, and that this relationship may also be involved in the pathophysiology of adrenal disease. In the light of all these findings it is apparent that along the line from the classical *in vitro* cell culture systems to the application of transient transfection of cells and peaking in the use of transgenic and knockout models, there is substantial support for the presence of an intricate communicative system in the adrenal gland. In addition to pituitary ACTH, the autonomic nervous system as well as the endocrine and the immune system are important effectors in the integrated control of adrenal function. The detailed analysis of the physiological relevance of these extrapituitary mechanisms may further extend our knowledge of pathogenic mechanisms of adrenal diseases and related disorders and may finally reach clinical relevance in the development of more specific and more efficient therapeutic strategies for such diseases.

3.9 Nonlinear Dynamics and Autonomic Control of the Heartbeat: Homeostasis Revisited

Traditionally, physiologists and clinicians describe the normal activity of the heart as “regular sinus rhythm”. However, cardiac interbeat intervals fluctuate in a complex and apparently erratic manner in healthy subjects, even at rest. Analysis of heart rate variability has focused primarily on short-term oscillations associated with breathing (respiratory sinus arrhythmia, 0.15-0.40 Hz; and blood pressure control, approximately 0.1 Hz). The mechanism underlying such fluctuations is related primarily to competing neuroautonomic inputs. Parasympathetic (vagal) stimulation decreases the firing rate of pacemaker cells in the sinus node, while sympathetic stimulation has the opposite effect. The nonlinear interaction (competition) between these two branches of the involuntary nervous system is possibly the mechanism for much of the erratic heart rate variability recorded in healthy subjects, although non-autonomic factors may also play an important role. Further analysis of these complex

fluctuations seen under basal conditions indicates the presence of a hidden type of organization related to fractal scaling. The term “fractal” applies to a wide class of geometric objects and processes, which lack a characteristic scale of length or time, respectively. Fractal processes are characterized by having fluctuations over multiple orders of temporal magnitude. Furthermore, these fluctuations across different scales of time are statistically similar. This scaling property leads to the type of inverse power-law ($1/\beta$ -like) pattern observed when long-term heartbeat time series are subjected to spectral analysis. Such complicated heart rate fluctuations display the kind of long-range correlations typically exhibited by dynamic systems far from equilibrium, a property not accounted for by traditional models based on homeostasis. Additional analysis indicates that patients with a variety of life-threatening types of heart disease, including congestive heart failure, show a breakdown of this long - range correlation behaviour. Altered fractal properties of the heartbeat are also observed with physiological ageing.

More recent analyses indicate that the output of the physiological control system regulating the heartbeat is actually a member of a remarkable class of the most complex processes yet identified in nature, since they require a broad number of indices to characterize their scaling properties. This “multifractal” behaviour of the heartbeat cannot be explained by physical activity; rather, it appears to be an intrinsic feature of the neuroautonomic regulation of the heartbeat. Furthermore, this multifractality is related to nonlinear features of the healthy heartbeat that have yet to be fully characterized. From a physiological perspective, the detection of robust scaling in the heart rate dynamics is of interest for a number of reasons. First, these findings indicate that the healthy heartbeat is even more complicated than previously suspected, posing a challenge to ongoing efforts to develop realistic models of the control of heart rate and related processes under neuroautonomic regulation. Second, these findings raise the intriguing possibility that the control mechanisms regulating the heartbeat interact as part of a coupled cascade of feedback loops in a system operating far from equilibrium. The detection and quantification of these nonlinear and fractal properties of the heartbeat in health and disease offer new opportunities for clinical diagnosis and prognosis, by providing information that cannot be detected using standard measures based on mean and variance, or spectral analysis.

3.10 Relationship between sleep, sleep apnoea and Muscle Sympathetic Nerve Activity (MSNA)

Microneurographic measurements of sympathetic traffic during sleep are consistent with the paradigm that sympathetic nerve activity decreases progressively during the deepening stages of non-Rapid Eye Movement (REM) sleep. Arousal stimuli during non-REM sleep elicit

K complexes on the electroencephalogram, accompanied by bursts of sympathetic nerve activity and transient increases in blood pressure. This response of MSNA to arousal is strikingly different from the MSNA arousal relationship during wakefulness. During wakefulness arousal stimuli do not increase sympathetic activity. Thus, during normal sleep there may be a change in the neural processing of auditory and possibly other arousal stimuli. During REM sleep, MSNA increases to about twice the level seen during wakefulness and heart rate and blood pressure are similar to measurements when awake. There are marked fluctuations in all these measurements, with sympathetic nerve activity being especially increased during phasic REM, i.e. during episodes of rapid eye movements, which are also associated with intermittent surges in blood pressure and heart rate fluctuation.

The autonomic and haemodynamic changes during sleep may have important clinical implications. There is increasing evidence of a circadian rhythm in cardiovascular events, including sudden death. The mechanisms underlying this circadian rhythm are not known. The predominance of REM sleep in the early morning just prior to waking and the sympathetic and haemodynamic changes during REM, may be implicated in increased platelet aggregability, plaque rupture, and coronary vasospasm, thus possibly acting as a triggering mechanism for thrombotic events that may only become clinically manifest some time after waking.

Several studies have demonstrated consistently that patients with obstructive sleep apnoea have very high levels of sympathetic nerve traffic, even during wakefulness. These high levels of sympathetic activity are evident when patients are normoxic and in the absence of any breathing disturbance. High sympathetic activity is also independent of the presence of hypertension and is not explained by obesity. During sleep, oxygen desaturation and carbon dioxide retention both contribute to peripheral and central chemoreceptor activation with consequent increases in muscle sympathetic nerve activity. The resulting vasoconstriction elicits marked surges in blood pressure that are especially evident at the end of apnoea. Chemoreflex-mediated sympathetic activation and vasoconstriction during sleep in patients with sleep apnoea prevent any fall in blood pressure and sympathetic activity during sleep. Thus, the normal sleep stage related changes in sympathetic traffic, blood pressure and heart rate evident in young healthy subjects are markedly deranged in sleep apnoea. These patients, who have high sympathetic activity and often high blood pressure even during normoxic wakefulness, manifest further increases in sympathetic traffic and blood pressure during sleep. The autonomic and haemodynamic abnormalities described above may be implicated in increased cardiovascular morbidity and mortality in sleep apnoea patients. Abnormalities in cardiovascular variability may precede and perhaps predispose to cardiovascular dysfunction, particularly hypertension. Sleep

apnoea may also be an important factor contributing to increased cardiovascular risk in hypertensive non-dippers, namely those hypertensive patients whose blood pressures do not fall during sleep. It is also conceivable that since sleep apnoea and obesity frequently exist as co-morbidities, the high incidence of occult sleep apnoea in apparently asymptomatic obese people may contribute to the cardiovascular risk associated with morbid obesity.

3.11 Autonomic Correlation between Heart and Cerebrovascular System

Epidemiological, anatomic-functional and pathological findings indicate a reciprocal control between the heart and brain. Thus, emotions, anxiety or stress may influence heart activity through the mediation of the autonomic nervous system. Several systemic diseases, including atherosclerosis, may affect both the heart and brain in the same patients. Moreover, heart disease may secondarily cause cerebral damage by means of embolic or haemodynamic mechanisms. Heart embolism is indeed a frequent etiology of ischaemic stroke, in particular when the patient is younger than 45 years of age. On the other hand, the sudden reduction of cerebral perfusion due to heart failure or arrhythmias provokes faintness or syncope. Finally, there is increasing evidence that diseases affecting primarily the brain may secondarily modify heart function. The occurrence of electrocardiographic (ECG) abnormalities has been reported in association with cerebral or subarachnoid haemorrhage, ischaemic stroke and less frequently, brain tumours, infections and trauma.

The cardiovascular complications of stroke can be due to (1) preexisting diseases, which can be aggravated by stroke; (2) stroke-induced cardiac arrhythmias and ECG abnormalities; (3) neurogenic pulmonary edema; (4) hypertension and the potential problems associated with its aggressive therapy. With preexisting cardiovascular diseases, stroke may worsen the underlying condition due to either neurological deficits or secondary metabolic derangement. It is well accepted that the greatest risk of mortality following a transient ischaemic attack (TIA) or stroke is from cardiac sources. It is estimated that 33% of patients with TIAs or stroke have symptomatic coronary artery disease.

Patients with severe coronary artery disease subjected to an elevation in sympathetic nervous stimulation due to an intracerebral event could clearly suffer cardiac changes such as ischaemia or arrhythmias due to increased myocardial oxygen demand. The theory which has gained most wide support is that the discharge of catecholaminergic neurotransmitters into the systemic circulation in association with cerebral infarction, subarachnoid haemorrhage and increased intracranial pressure, plus increased vagal traffic to the heart, provokes both

hypertension and cardiac muscle damage. In addition to the increase in myocardial contractility and heart rate in general, there is evidence that local discharge of the sympathetic nerve fibres within the ventricular muscle itself leads to myofibrillar degeneration. The subendocardial changes seen on autopsy studies correlate with elevation of cardiac enzymes and are histopathologically distinct from ischaemic infarctions seen with coronary artery disease.

Experimental data suggest a role for the brain in the genesis of some arrhythmias. This intrinsic brain-heart relationship is an area of great interest because it will have relevance to the pathophysiology and could lead to prevention of sudden cardiac death. Thus, the site of the brain infarct appears to be an important factor in the genesis of arrhythmias secondary to stroke.

3.12 Action of Calcium Channel Blockers on the Autonomic System

Calcium antagonists lower blood pressure mainly through vasodilation and reduction of peripheral resistance and like other vasodilators can be expected to activate the sympathetic nervous system. Recent studies suggested that the use of calcium antagonists leads to an increased morbidity and mortality in patients with hypertension and coronary artery disease. It has been hypothesized that these unexpected findings with short-acting (SA) calcium antagonists could be due, at least in part, to a reflex increase in sympathetic activity. Regardless of whether or not it participates in the pathogenesis of pressure elevation, sympathetic activity has been identified as a powerful nonhaemodynamic risk factor for a variety of cardiovascular and metabolic disorders. The activity of the sympathetic nervous system can be indirectly assessed by plasma levels of norepinephrine (NE).

To evaluate the effects of calcium antagonists on sympathetic activity in hypertensive patients, a MEDLINE search for English language articles published between 1975 and May 1996 using the terms calcium antagonists, sympathetic nervous system, and catecholamines was conducted. Clinical studies only reporting the effects of calcium antagonists on blood pressure, heart rate and plasma norepinephrine (NE) levels in patients with hypertension were included. Data were combined and analyzed according to class of calcium antagonist (dihydropyridine vs. non-dihydropyridine), their duration of action (short acting [SA] vs long-acting [LA]), and treatment duration. Sixty-three studies involving 1252 patients were identified. Acutely after single dosing, SA calcium antagonists decreased mean arterial pressure by 13.7 plus or minus 1.1% and increased heart rate by 13.7 plus or minus 1.4% and NE levels by 28.6 plus or minus 2.5%. Change in NE levels correlated with change in heart rate ($r=0.59$, $p<0.01$) and inversely with change in arterial pressure ($r=0.46$, $p<0.05$) in patients taking dihydropyridine calcium

antagonists acutely. With sustained therapy, both classes of SA calcium antagonists increased NE levels. Whereas NE levels remained slightly elevated and heart rate unchanged with LA dihydropyridine calcium antagonists, both heart rate and NE levels decreased with LA non-dihydropyridine calcium antagonists.

Can the present findings shed some light on the controversy surrounding the calcium antagonists as a class? Solid experimental and clinical reports attest to the fact that stimulation of the sympathetic nervous system can be detrimental for the cardiovascular system. Thus, an excessive sympathetic drive has been associated with a whole host of disorders ranging from hypertension, insulin resistance/glucose intolerance, dyslipoproteinaemia and arteriosclerosis to myocardial ischaemia, arrhythmias and sudden cardiac death. The administration of a SA calcium antagonist can cause a precipitous fall in arterial pressure associated with a reflex increase in sympathetic stimulation, heart rate, cardiac output, and left ventricular stroke work. In patients with compromised coronary reserve, this sequence of events may lead to myocardial ischaemia, angina, acute myocardial infarction, and even death.

However, even a more sustained, low-grade catecholamine bombardment of the cardiovascular system could be detrimental, as was documented in experimental and clinical models in congestive heart failure and left ventricular hypertrophy. Thus, the persisting sympathetic stimulation as is observed with SA calcium antagonists could override or at least mitigate the beneficial effects of the decrease in arterial pressure. Of note, in recent data purporting to show an adverse outcome with calcium antagonists, only SA agents were used.

In contrast, blood pressure falls more smoothly and blood pressure variability and sympathetic activation are less pronounced with the LA calcium antagonists than with the SA agents. Alderman et al recently documented a 5- to 8-fold lower risk ratio (for morbidity and mortality) in patients treated with a LA calcium antagonist when compared to those treated with SA drug. LA non-dihydropyridine calcium antagonists have the additional advantage of even decreasing sympathetic activity and heart rate, whereas these remain slightly elevated with some of the LA dihydropyridine molecules. Clearly, calcium antagonists are a heterogeneous group of drugs. Their effect on sympathetic activity offers a possible explanation for the difference in outcome that was recently observed between SA and LA compounds.

3.13 Correlation between Autonomic Function, Gastrointestinal Function and the Heart

During the last two decades, advances in stereotaxic and microinjection procedures, single unit electrical recording of autonomic nerve activity, sensitive neuroanatomic tracing techniques and the characterization of many neuropeptides and their receptors as well as the development of selective receptors antagonists have given new impetus to exploring how the central nervous system (CNS) regulates visceral function through autonomic nervous system pathways. More has been learned about brain sites of actions and biochemical codings involved in autonomic regulation of gastrointestinal and cardiovascular functions. Thyrotropin-releasing hormone (TRH) and corticotropin-releasing hormone (CRF) are key neuropeptides which have physiological relevance to the modulation of autonomic outflow during stress and the impact on alterations of gastrointestinal function under these conditions.

TRH has an excitatory effect on preganglionic vagal motor neurons (DMN) resulting in the stimulation of gastric vagal efferent discharges. The use of antisense strategy against the TRH receptor located in the dorsal vagal complex and TRH antibody into the dorsal vagal complex showed that medullary TRH is a physiological stimulant of vagal outflow to the stomach and is involved in gastric secretory and motor responses to sham feeding, cold exposure and 2-deoxyD-glucose. TRH microinjected into the DMN at the level of the area postrema activated postganglionic cholinergic enteric neurons in the stomach and duodenum regulating epithelial, parietal, enterochromaffin, enterochromaffin-like, endothelial and smooth muscle cells as shown by the vagal atropine-dependent increase in gastric acid, pepsin, mucus, nitric oxide (NO), serotonin, calcitonin-gene related peptide (CGRP), prostaglandins and histamine release, the increase in mucosal blood flow, the stimulation of gastric, duodenal and colonic contractility and transit, and the modulation of resistance of the gastric mucosa to injury. Low levels of vagal stimulation of central TRH results in a cytoprotective effect against ethanol-induced gastric lesions through increase in gastric mucosal blood flow and prostaglandin and NO - dependent mechanisms. Medullary TRH has been shown to be involved in the vagally mediated adaptive gastric cytoprotection whereby gastric exposure to a mild irritant protects the mucosa against the formation of lesions induced by a strong irritant. Under conditions of vagal stimulation induced by central injection of TRH at maximal gastric acid secretory dose, the formation of haemorrhagic lesions is observed in 24 - h fasted rats, and medullary TRH which is activated by cold exposure is involved in cold-resistant stress induced gastric lesions. The central action of TRH to stimulate gastric function through vagal pathways is modulated by a number of brain peptides/neurotransmitters which act by either potentiating (serotonin, PS4, peptide YY) or

inhibiting TRH actions (CRF, bombesin, interleukin-1, CGRP, substanceP). Medullary TRH also potently influences the cardiovascular system through activation of the sympathetic nervous system leading to hypertensive response. TRH receptor antisense has been shown to reduce the blood pressure in spontaneous hypertensive rats.

4. CONCLUSIONS AND RECOMMENDATIONS

4.1 Discussion

The Autonomic Nervous System

Studies of the autonomic nervous system date back to the antiquity. Systematic study of ANS function has led to the discovery of fundamental principles in our understanding of modern physiology, pharmacology, neuroendocrinology and molecular medicine.

Structural and Chemical Organization of the Autonomic Neuroeffector System

What has been called the autonomic nervous system should actually be viewed as independently regulated effectors that maintain homeostasis. Stress should be viewed as a condition leading to stressor-specific compensatory changes rather than a non-specific response of the body to any demand.

Neuropeptides and Autonomic Nervous Function

There is immense diversity in brain neuropeptide action, brought about by: (1) many independent genes and associated alternate splicing; many instances of co-localization in one cell; (2) differential processing of precursors; (3) Multiple receptor subtypes; (4) differential release. Many peptides act both centrally and peripherally (via the endocrine system) to produce a coordinated response to a physiological or psychological perturbation. Research on the peptide arginine vasopressin has provided evidence for its involvement in suppression of fever (antipyresis) and elevation of blood pressure. Vasopressin function in the brain is influenced by gender, reproductive state and recent experience. Pharmacological intervention into central control at the ANS is possible but difficult due to accessibility problems; promising avenues include the use of peptide mimetics and antisense molecules. Another potential target could be processing and degrading enzymes.

Autonomic Nervous System and its Neuroendocrine Regulation

The ANS is regulated by neuropeptides and hormones. The interactions between the ANS and various endocrine systems are the object of active investigation. The adipocyte hormone leptin is a pulsatile signal of nutritional status which modulates key functions of the nervous system. Leptin is required for the optimal functioning of the ANS. The ob/ob mouse has decreased sympathetic tone. Adult patients with leptin gene mutation also have sympathetic dysfunction, manifested by postural hypertension, impaired response to cold pressor test and the absence of a response to median nerve and auditory stimulation in sympathetic skin response tests. Future studies should dissect at the molecular level the mechanisms underlying the interactions among nutritional status, endocrine regulation, and ANS function.

The Endocrine Heart and the Clinical Impact of the Natriuretic Peptides

Urodilatin (URO) is a member of the natriuretic peptide family and was isolated from human urine at the Lower Saxony Institute for Peptide Research. In the last years physiological and pharmacological studies revealed the following main effects of URO: natriuresis, diuresis, vasodilation, and bronchodilation. Based upon these effects this peptide was developed for clinical applications in the treatment of acute renal failure, congestive heart failure, and bronchial asthma. URO is the first peptide that was isolated and developed for clinical applications.

Stress and the Cardiac Response

Although a variety of invasive and direct techniques are available to assess various aspects of the integrated actions of the autonomic nervous system, direct continuous measurements that would allow assessment in real life conditions are lacking. Indirect approaches however are available that can explore some important aspects of autonomic control. Multiparametric measures can better quantify the complex adjustments of the autonomic nervous system to various physiopathological stimuli particularly focusing on cardiovascular control. This function of control mechanisms, especially sympathetic predominance, are associated with greater cardiovascular risk. Experimental and clinical studies have been used to assess the details of sympathetic and parasympathetic responses to various stressors.

Neural and Peptidergic Control of Water Balance

Atrial and natriuretic peptide (ANP) and oxytocin (OT) are natriuretic hormones that

play a fundamental role in the regulation of extracellular fluid volume. These peptides are localized in neurons in the hypothalamic and brainstem areas. Both peptides ANP and OT induce natriuresis through cGMP signalling. The CNS seems to modulate ANP secretion from the heart through the activation of oxytocinergic neurons in the PVN and SON which project to the neural lobe. The OT modulates ANP secretion by action on its OT receptors in the atria. Analyzing the interaction of the autonomic nervous system with the natriuretic peptides should be a major focus of future research in that area.

Autonomic Nervous System and Adrenocortical Function: What Can be Learned from Transgenic Models and Knockout Mice?

The autonomic nervous system and the HPA axis are closely associated at the level of the adrenal gland. Animal models of overexpression and depletion of catecholamines as well as of altered function of components of the HPA axis provide further evidence that this interdependence of the two systems is of functional and physiological relevance to the dysregulation in this relationship and may be involved in the pathophysiology of adrenal disease. The detailed analysis of the physiology and pathophysiology of these intraadrenal regulatory mechanisms may further extend our knowledge of the pathology of adrenal diseases and related disorders and may eventually reach clinical relevance in the development of more specific and more efficient therapeutic strategies for such diseases.

Nonlinear Dynamics and Autonomic Control of the Heartbeat: Homeostasis Revisited

Detection and quantification of non-linear and fractal properties of the heartbeat in health and disease offer new opportunities for clinical diagnosis and prognosis by providing information that cannot be detected using conventional measures. Therefore, this technique should find a more widespread application in clinical medicine.

Relationship between Sleep, Sleep Apnoea and Muscle Sympathetic Nerve Activity

Microneurographic measurements of sympathetic traffic during sleep are consistent with the paradigm that sympathetic nerve activity decreases progressively during the deepening stages of non-REM sleep. During REM sleep, MSNA increases to about twice the level seen during wakefulness and heart rate and blood pressure are similar to measurements when awake. Patients with obstructive sleep apnoea have very high levels of sympathetic nerve traffic, even during wakefulness. During sleep, oxygen desaturation and carbon dioxide retention both

contribute to peripheral and central chemoreceptor activation with consequent increases in muscle sympathetic nerve activity. The resulting vasoconstriction elicits marked surges in blood pressure that are especially evident at the end of apnoea. Chemoreflex - mediated sympathetic activation and vasoconstriction during sleep in patients with sleep apnoea prevent any fall in blood pressure and sympathetic activity during sleep. Thus, the normal sleep stage related changes in sympathetic traffic, blood pressure and heart rate evident in young healthy subjects is markedly deranged in sleep apnoea. The autonomic and haemodynamic abnormalities described above may be implicated in increased cardiovascular morbidity and mortality in sleep apnoea patients.

Autonomic Correlation between Heart and Cerebrovascular System

Autonomic correlation between the heart and cerebrovascular system, epidemiological, anatomical, functional, and pathological findings indicate reciprocal control between the heart and the brain. Events that start in the brain can affect cardiac arrhythmias; likewise heart disease can result in cerebral damage due to emboli or changes in haemodynamic function. Additionally, systemic diseases such as atherosclerosis can affect both the heart and the brain. Arrhythmia can cause stroke, which in turn can cause arrhythmia. Future work in this field should elucidate the pathways and mechanisms for the reciprocal relation between brain and heart. This work is of relevance to cardiovascular diseases that are the major cause of death in industrialized countries.

Action of Calcium Channel Blockers on the Autonomic System

SA calcium antagonists stimulate sympathetic activity when given acutely and over the long term, irrespective of their molecular structure. Sympathetic activation is less pronounced with LA dihydropyridine calcium antagonists and falls with LA non-dihydropyridine calcium antagonists. These data offer a possible pathophysiological explanation for the paradoxical increase in morbidity and mortality observed in some studies using SA calcium antagonists.

Correlation between Autonomic Function, Gastrointestinal Function and the Heart

During the last two decades a growing body of evidence has shown that specific neuropeptides have marked effects on visceral function via centrally mediated changes in autonomic outflow to the gastrointestinal tract. The medullary TRH plays a physiological role in stimulating vagal outflow to the gut, while central CRH decreases gastric vagal activity.

4.2 Conclusions and Recommendations

- In contrast with the view that the ANS is solely composed of two antagonist components, the ANS should now be conceptualized as consisting of multiple components that may be independently regulated. In response to different challenges to homeostasis, the body has available a variety of effector systems including the ANS to maintain homeostasis. Accordingly, future research in this field should include multiple - dependent measurements assessed simultaneously to elucidate patterns of neuroendocrine responses.
- In view of the relevance of normal and abnormal ANS function to general health, non - invasive measures can be of great value. For example, cardiovascular risk stratification could be enhanced by adding measures of ANS dysfunction. Future work should be focused on validation of autonomic measurements as a predictor of clinical outcome.
- Future studies should examine the effect of interactions between various components of the autonomic nervous system and peptidergic systems on the regulation of body fluid dynamics. Such interactions should be examined in the brain and periphery using the tools of classical physiology as well as antisense and transgenic methods.
- In view of the striking physiological actions of CRF and TRH on visceral function mediated through the ANS, it is recommended that further research should be directed at unravelling the biochemical coding and sites of action of transmitters involved in the central regulation of ANS during stress and pathophysiological conditions.
- Recent strategies in peptide research led to the isolation of peptides currently developed in preclinical as well as clinical conditions. Therefore, screening for, isolation, and development of peptides may represent a powerful attractive tool in the field of drug development.
- Further research needs to be conducted to ascertain the impact of environmental and nutritional factors on autonomic function and its neuroendocrine regulation.
- Further research is recommended on the interaction of endocrine function and the autonomic nervous system and its impact on endocrine disease, stress and public health.
- It is considered particularly important to promote studies on the interface between autonomic nervous system function and the regulation of sleep. It has been estimated that

40 million people in the United States have sleep disorders. This leads one to assume that sleep disorders are a public health problem of high prevalence worldwide. The regulation of sleep by the ANS is therefore an area of investigation of high medical relevance.

- International efforts should be encouraged to collect, archive, and disseminate large - scale annotated databases of continuous physiological recordings including electrocardiograms and other related signals from subjects with various cardiovascular and neuroautonomic syndromes, and from appropriate control subjects. Efforts should be made to encourage basic investigation and teaching of nonlinear dynamics as part of the approach to exploring and understanding complex neuroautonomic regulation in health and disease.
- In the treatment of patients with cardiovascular diseases attention should be paid to the effect of drugs on autonomic regulation.

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