The Integrative Action of the Autonomic Nervous System

Almost all bodily functions are dependent on the functioning of the autonomic nervous system – from the cardiovascular system, the gastrointestinal tract, the evacuative and sexual organs, to the regulation of temperature, metabolism and tissue defense. Balanced functioning of this system is an important basis of our life and well-being. The Integrative Action of the Autonomic Nervous System: Neurobiology of Homeostasis gives a detailed description of the cellular and integrative organization of the autonomic nervous system, covering both peripheral and central aspects. It brings to light modern neurobiological concepts that allow understanding of why the healthy system runs so smoothly and why its deterioration has such disastrous consequences. This broad overview will appeal to advanced undergraduate and graduate students studying the neurobiology of the autonomic nervous system within the various biological and medical sciences and will give access to ideas propagated in psychosomatic disease and alternative medicines.

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The Integrative Action of the Autonomic Nervous System

Neurobiology of Homeostasis

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Supported by the German Research Foundation and the Max-Planck Society

CAMBRIDGE
UNIVERSITY PRESS

CAMBRIDGE UNIVERSITY PRESS
Cambridge, New York, Melbourne, Madrid, Cape Town, Singapore, São Paulo

Cambridge University Press
The Edinburgh Building, Cambridge CB2 2RU, UK

Published in the United States of America by Cambridge University Press, New York

www.cambridge.org
Information on this title: www.cambridge.org/9780521845182

First published 2006

Printed in the United Kingdom at the University Press, Cambridge

A catalog record for this publication is available from the British Library

ISBN-13 978-0-521-84518-2 hardback
ISBN-10 0-521-84518-1 hardback

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Foreword

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The autonomic nervous system carries the signals from the central nervous system to all organs and tissues of the body except skeletal muscle fibers. It is made up of preganglionic and postganglionic neurons linked together in functionally distinct pathways. The postganglionic terminals have specific relationships with their target tissue. As well as distributing centrally derived command signals, this system can also integrate reflex interactions between different parts of the peripheral nervous system, even without involving the spinal cord. All of these activities are specific for each organ system and attempts to generalize have often proved incorrect. The breadth and scope of involvement of this system in body function are obvious. The autonomic nervous system controls not only the quantity and quality of tissue perfusion in response to varying needs, and the maintenance of secretions for protection of the body's orifices and the lining of the gastrointestinal tract, but it also regulates the usually intermittent but complex functions of the abdominal viscera and pelvic organs, the mechanical aspects of the eye and the communication between the nervous system and the immune system. Many autonomic pathways are continuously active but they can also be recruited when the environmental and/or emotional situation demands it. This system is essential for homeostasis – hence the subtitle of this book.

Despite its enormous importance for the maintenance of normal physiology in all vertebrate species, and for the understanding of many clinical symptoms of disease, the autonomic nervous system has not, even transiently, been the center of attention in neuroscience research internationally over the past 40 years. Many seem to think that this system has been worked out and there is nothing new to investigate. The discovery of neuropeptides as putative transmitters was probably the only interlude that triggered widespread excitement. Others simply forget that the system exists except for emergencies.

Two views about the autonomic nervous system are often encountered:

1. that this system is similar to the endocrine system and its functions can all be explained by the pharmacological actions of the major neurotransmitters, noradrenaline and acetylcholine, possibly involving modulation by cotransmitters and neuropeptides, or
2. that the functions of this system are not important as life continues without them.

For anyone who thinks about it, at least the latter of these concepts is obviously not true. Life can be maintained in a cocoon in individuals

with autonomic failure but the ability to cope with external stressors severely compromises their quality of life. The extent to which the practical difficulties of daily life for people with spinal cord injury, which disrupts the links between the brain and the autonomic control of the body's organs, absorb personal energy and resources should not be underestimated by those who take their bodies for granted. Elderly people face similar problems as some of their autonomic pathways degenerate.

On the other hand, the former of the above two concepts dominates almost all current textbooks of physiology and neuroscience. It is true that some of the effects of autonomic nerve activity can be mimicked by the application of neurotransmitter substances locally or systemically. However, the mechanisms by which the same substances released from nerve terminals produce responses in the target tissue have proved to be quite different in most cases so far analyzed. This helps to explain the failure of many pharmaceutical interventions based on this simplistic idea as outlined above. What is important here is that the present volume collates the evidence against both these ideas and develops the factual and conceptual framework that describes how an organized system of functional nerve connections that operate with distinct behaviors is coordinated to regulate the workings of the organ systems of each individual.

Nevertheless, over the past 40 years, there have been remarkable strides in our understanding. Technical problems limit how the complexities of this system can be unraveled. There are enormous challenges involved in investigating a complex interconnected system made up of small neurons that are not always packaged together in precisely the same way between individuals. Even in the spinal cord, the neuroanatomical distribution and apparent imprecision have been daunting. To study this system requires patience and persistence in the development of manipulative and analytical skills. These attributes are relatively rare.

Fortunately, over this period, a small but steady stream of researchers has persisted in their endeavors to clarify how this functionally diverse system works. One of the most significant players has been Wilfrid Jänig. Wilfrid and his many students and collaborators at the Christian-Albrechts-Universität in Kiel have pursued a major and uniquely productive approach to understanding how sympathetic pathways work. This has been to apply the technique of extracellular recording from single identified axons dissected from peripheral nerves projecting to particular target tissues and therefore acting in known functional pathways. Over the 40 years, this work, originally in cats and latterly in rats, has revealed the principles underlying reflex behavior of sympathetic axons in the anaesthetized animal. The characteristic behavior of pre- and postganglionic neurons in over a dozen functional pathways has been defined. As the reader progresses through the book, it will become clear that many of these reflexes are also present in humans. The parallel technique of microneurography, pioneered by Hagbarth, has been

implemented over a similar period in the sympathetic pathways of conscious humans by Gunnar Wallin and his colleagues in Göteborg. While pathways to the viscera are currently too hard to study in humans because they are less accessible, the principles of their organization can be deduced from Wilfrid's data on pre- and post-ganglionic discharge patterns and from the analyses of ganglionic and neuroeffector transmission conducted by him and others.

Over the 40 years, Wilfrid's various interests have been broad but always focussed. They have taken him to many places to answer questions about the structure and function of sympathetic pathways. His earliest training in single unit recording was in sensory neurophysiology and this background has been the basis of his parallel studies of visceral afferent behavior and nociception. Early in his career, he was interested in integrative autonomic control at the higher levels of the nervous system and developed a passion to follow on the work of Philip Bard. After returning to Germany from New York in the 1970s, he conducted experiments on decorticate and decerebrate cats in which he created behaviors such as sham rage during which he planned to record and analyze the sympathetic outflow. These experiments did not progress because of limited resources, but instead he undertook a most detailed analysis of the distinctive behavior of skin and muscle sympathetic vasoconstrictor axons. These results provided evidence that strongly rejected popular ideas that a general level of "sympathetic tone" was the determinant of peripheral vascular resistance. It was clear that the reflex connectivity of the pathways involved in cutaneous and skeletal muscle blood flow are largely independent. This concept was more dramatically confirmed in recordings from humans where it is possible to demonstrate the strong emotional drive that modulates cutaneous vasoconstrictor activity (see Subchapter 4.1.2 in this book). Subsequently Wilfrid's laboratory has extended this type of analysis to over a dozen different pathways that they have studied in anesthetized animals.

I first met Wilfrid in 1979 when he came to give a seminar in Edinburgh where I was on sabbatical leave at the time. As my original background was in cardiovascular physiology, I had naturally read his work on vasoconstrictor discharge patterns and had lots of questions to ask him. Wilfrid invited me to visit Kiel on my way home (it was very cold and wet in November) and then he came to Melbourne to work with me to trace the peripheral sympathetic pathways quantitatively. In my laboratory at Monash University, I had established the retrograde tracing technique using horseradish peroxidase to identify the location of preganglionic neurons in the spinal cord as a prelude to recording intracellularly from them. He worked hard with me cutting and mounting thousands of sections and soon after I spent a similar period in Kiel helping his group establish the technique there. This quantitative work dovetailed well to explain how the axons that his group sampled in their recordings related to the entire population.

It has been my great privilege to continue to work with Wilfrid and his colleagues, particularly up to the early 1990s, undertaking studies for which he and I received the Max-Planck Forschungspreis for international collaboration in 1993. Since that time, and in various parts of Australia as I have moved between Universities, we have worked together and in parallel on aspects of the interactions between the sympathetic and sensory systems that may be involved in neuropathic pain after nerve injury. We have continued to communicate frequently and his younger colleagues, notably Ralf Baron, Ursula Wesselmann and Joachim Häbler, have spent time in Australia working in my laboratory. I hope and expect that these interactions will continue.

Wilfrid's early studies of sympathetic activity were made when Robert Schmidt was in Kiel and were conducted in parallel with studies of somatosensory, particularly nociceptive, afferents. This anteceded his interest in visceral afferent function to which he applied the same technical expertise to unravel the behavior of these neurons, particularly in pelvic organ reflexes. His interests in nerve injury were pursued in part with Marshall Devor in Jerusalem. This involved extended studies of the ectopic activity of sensory neurons after peripheral nerve lesions and the role of sympathetic activity in triggering this. His laboratory has also conducted a wide range of studies on the effects of various nerve lesions on the properties of sympathetic and afferent axons. As Wilfrid appreciated that the problem of neuropathic pain was probably related to inflammation, he sought out Jon Levine in San Francisco where he was exposed to a very strong research community involved in pain and inflammation research. He has a prodigious output from Jon's laboratory deciphering the components of the neuroimmune interactions using rigorous and systematic approaches to identify the pathways and sites at which the hypothalamo–pituitary–adrenal axis (HPA) intervenes in inflammation and in nociception, in some cases with sympathetic involvement. More recently, Wilfrid and Ralf Baron have worked with the clinical community worldwide on clarifying the misnamed concept of "reflex sympathetic dystrophy" and developing the newer definitions of various "complex regional pain syndromes" to help to clarify the diagnosis of the mechanisms underlying chronic neuropathic pain.

When visiting my laboratories at Monash and the Baker Institute in Melbourne, and subsequently at the Universities of New South Wales and Queensland, and more recently at the Prince of Wales Medical Research Institute in Sydney, Wilfrid has been able to visit many neuroscientists around Australia where research on the neurobiology of the autonomic nervous system and on central cardiovascular control is prolific by world standards. He has seized upon these opportunities to learn what the community of Australian autonomic researchers is doing and has established strong relationships with the leaders of many active laboratories including those of David Hirst, Ian Gibbins and Judy Morris, John Furness, Marcello Costa,

Christopher Bell, Janet Keast, Sue Luff, James Brock, Roger Dampney, Robin McAllen, Bill Blessing, Paul Korner, Dick Bandler, Paul Pilowsky, and Dirk van Helden. This extensive Australian involvement in autonomic neuroscience arose in part from the students who trained with Geoff Burnstock and Mollie Holman in Melbourne in the 1960s and 1970s and who have taken their skills across the country and have been training the next generations since that time. Despite the divergence of their specific interests, this community continues to be one of the largest internationally working in the autonomic nervous system. Wilfrid's exposure to the cellular, pharmacological and neuroanatomical aspects of ganglionic and junctional transmission in the peripheral pathways gave him a very wide view of autonomic effector systems, which he has so cleverly incorporated into this book.

Throughout these years, Wilfrid has been a prodigious author of textbook chapters and review articles. Although many of the former have been written in German, he has also developed and expounded his ideas about neural control of vasoconstriction, pain and the sympathetic nervous system, the consequences of nerve injury, the involvement of the HPA axis in inflammation and nociception, and on clinical aspects of these topics. This book arises from this lifetime of synthetic writing and from his reflection on the wider issues of this area of science. It also is the product of his frustration, which I share, with the limited availability of publications that summarize the scientific background and present the current status of our understanding of how the autonomic nervous system works. As in his experiments, he has dissected the system into the major functional pathways in which reflex behavior and cellular mechanisms have been well investigated. He reviews and synthesizes the available information on the spinal cord and brain stem components of autonomic reflexes and then resynthesizes these output systems into a complex package that includes the control of autonomic discharge patterns from the midbrain and higher centers. He has extracted the key information yielded by both classical and modern technical approaches used to study these components of the nervous system. He has incorporated the conceptual background behind each area of research. Finally, he discusses how the old "unifying" concepts of Cannon and Hess misrepresented the diversity of autonomic outflow patterns that the brain recruits during the various behaviors that function to conserve the body in a range of environmental circumstances. This philosophical base needs to replace the widely held views mentioned earlier if we are to progress our understanding of this important set of control systems. The present *tour de force* has involved discussion and input from many of Wilfrid's collaborators and colleagues around the world whose contributions have ensured that the final product really contains the most up-to-date summary of our current knowledge of autonomic function.

Despite, or because of, this diversity of inputs, this book provides Wilfrid Jänig's unique overview of the autonomic nervous system.

Without his driving fascination with how the whole autonomic system works in the body, this book would never have been written. No-one else currently has the conceptual breadth and capacity to integrate so many aspects to compose this amalgam. He has collected all the available data from the past and the present and fitted them together with what is known of the central control and spinal integration that determine the activity patterns in each outflow pathway. He has taken the knowledge from Langley's time, through Cannon, Hess and Bard, Burnstock and Holman, to the recent application of cellular biology and molecular genetics to collate a truly comprehensive compendium. I am delighted that he has committed himself to drawing together so many diverse aspects of autonomic function in one place and to give us a truly integrated overview of what is known at the beginning of the twenty-first century. He has made very clear what he feels are the major questions that remain to be answered. I know that Wilfrid will contribute to many of those answers.

Preface

In the late 1960s, while I was working in Robert F. Schmidt's laboratory in the Department of Physiology of the University of Heidelberg, conducting experiments on cutaneous primary afferent neurons and presynaptic inhibition in the spinal cord, Robert introduced me to the sympathetic nervous system. We worked on somato-sympathetic reflexes and other spinal reflexes, some of the work being conducted with Akio Sato. At this time, I tried to understand *The Wisdom of the Body* by Walter Bradford Cannon (Cannon 1939) and *Vegetatives Nervensystem* by Walter Rudolf Hess (Hess 1948). However, from 1971 to 1974, I continued with my experimental work on the somatosensory system and concentrated with Alden Spencer on the cuneate nucleus and thalamus in the Department of Neurobiology and Behavior of the Public Health Institute of the City of New York (directed by Eric Kandel).

While working in New York I came into contact with Chandler McCuskey Brooks (Downstate Medical Center, State University of New York). He invited me to attend the Centennial Symposium "The Life and Influence of Walter Bradford Cannon, 1871–1945: The Development of Physiology in this Century" (Brooks *et al.* 1975). Chandler encouraged me to concentrate scientifically on the autonomic nervous system; he remained very supportive until his death seventeen years later. This influence and particularly the books of Cannon and Hess led to my decision to leave the somatosensory field and redirect my research, after my return to Germany, to investigations of the sympathetic nervous system. The books by Cannon and Hess, and the published papers on which they are based, aroused from the beginning my opposition on the one hand and my secret admiration for the authors on the other. This ambiguity in my scientific attitude towards Cannon and Hess has always been in the background of the scientific activities in my laboratory, of my teaching and of my writing on the autonomic nervous system.

I am particularly grateful to two persons who have kept me going on the scientific path amidst trials and tribulations to unravel some of the mysteries of the autonomic nervous system. Robert Schmidt has made me invest time in writing textbook chapters since 1971. Elspeth McLachlan has always been extremely supportive and virtually carried me through some periods of doubt and despondency throughout the 25 years we have worked experimentally together. She introduced me to the Australian Autonomic Neuroscience and is responsible for this book being in some ways an Australian book (see below). Finally, the many young students in my laboratory, some now professors, influenced me by their enthusiasm despite my being entirely uncompromising, which was sometimes hard for them to digest.

The German Research Foundation has fully supported my research over more than 30 years. Without this continuous funding, for research that was often methodologically, and as regards content, not in the mainstream, I never would have been able to continue my research on the autonomic nervous system for so many years. So I am deeply grateful to the many anonymous referees of the German Research Foundation for their fair judgment.

Finally, and most important, on a very personal level, the research over these decades, and still continuing, could never have happened without the never-ending tolerance and support of my wife Ute and our sons Nils and Volker. My family life has sustained my research more than anything else.

I want this book to be a forum for ongoing discussion. I strongly encourage young scientists to invest their time in research on the autonomic nervous system. While writing the book I was in continuous discourse with many scientists in Australia, Europe and the United States addressing various scientific aspects of the book. These scientists have made a major contribution.

- I would particularly like to thank those who undertook to read and comment on chapters or subchapters of the book. *AUSTRALIA*: Richard Bandler (Sydney), Bill Blessing (Adelaide), James Brock (Sydney), Roger Dampney (Sydney), John Furness (Melbourne), Ian Gibbins (Adelaide), Elspeth McLachlan (Sydney), Judy Morris (Adelaide), Paul Pilowsky (Sydney), Terry Smith (Reno, Nevada, USA), Dirk van Helden (Newcastle). *EUROPE*: Niels Birbaumer (Tübingen, Germany), John Coote (Birmingham, England), Sue Deuchars (Leeds, England), Peter Holzer (Graz, Austria), Winfried Neuhuber (Erlangen, Germany), Julian Paton (Bristol, England), Hans-Georg Schaible (Jena, Germany), Gunnar Wallin (Göteborg, Sweden). *NORTH AMERICA*: Gerlinda Hermann (Baton Rouge, Louisiana), Arthur Loewy (St. Louis, Missouri), Orville Smith (Seattle, Washington), Larry Schramm (Baltimore), Alberto Travagli (Baton Rouge, Louisiana).
- I am thankful to those who never hesitated to think about and answer my questions. *AUSTRALIA*: Andrew Allen (Melbourne), David Hirst (Melbourne), Ida Llewellyn-Smith (Adelaide), Susan Luff (Melbourne), Vaughn Macefield (Sydney), Robin McAllen (Melbourne). *EUROPE*: Jean-François Bernard (Paris, France), Uwe Ernsberger (Heidelberg, Germany), Björn Folkow (Göteborg, Sweden), Rupert Hölzl (Mannheim, Germany), Andrew Todd (Glasgow, Scotland). *NORTH AMERICA*: Susan Barman (East Lansing, Michigan), Bud Craig (Phoenix, Arizona), Lori Birder (Pittsburgh), Chet de Groat (Pittsburgh), Patrice Guyenet (Charlottesville, Virginia), John Horn (Pittsburgh), Kevan McKenna (Chicago), Shaun Morrison (Beaverton, Oregon), Michael Panneton (St. Louis, Missouri), Terry Powley (West Lafayette, Indiana), Clifford Saper

(Boston), Ann Schreihofer (Augusta, Maine), Ruth Stornetta (Charlottesville, Virginia), Holly Strausbaugh (San Francisco).

Eike Tallone (Kiel) has my very special thanks. She is responsible for the graphical work in almost all figures of this book. Without her, the figures would not be of such high quality.

Abbreviations

The main abbreviations used are listed below. Special abbreviations related to anatomical structures in the lower brain stem or hypothalamus are listed in the legends of the figures and tables, particularly Figures 10.2, 11.13, 11.14 and Tables 8.2 and 8.3.

ACC	anterior cingulate cortex
ACh	acetylcholine
AgAgCl	silver-silver chloride
AP	area postrema
ATP	adenosine triphosphate
BAT	brown adipose tissue
BDNF	brain-derived neurotrophic factor
BNST	bed nucleus of the stria terminalis
BP	blood pressure
c, C	cervical (segment)
CA	central autonomic nucleus
Ca^{2+}	calcium
cAMP	cyclic adenosine monophosphate
CCK	cholecystokinin
CGRP	calcitonin gene-related peptide
ChAT	choline acetyltransferase
CL	centrolateral nucleus (thalamus)
CM	circular musculature (gastrointestinal tract)
CN	cuneiform nucleus
CNS	central nervous system
CPA	caudal pressure area
CRG	central respiratory generator
CRH	corticotropin-releasing hormone
CRPS	complex regional pain syndrome
CSN	carotid sinus nerve
CST	cervical sympathetic trunk
CTb	cholera toxin subunit B
CVC	cutaneous vasoconstrictor (neuron)
CVD	cutaneous vasodilator (neuron)
CVLM	caudal ventrolateral medulla
cVRG	caudal ventral respiratory group
DC	dorsal column (spinal cord)
DCN	dorsal commissural nucleus (spinal cord)
DH	dorsal horn (spinal cord, trigeminal)
DMNX	dorsal motor nucleus of the vagus
DR	dorsal root
DRG	dorsal root ganglion
DVC	dorsal vagal complex
DYN	dynorphin
DβH	dopamine-β-hydroxylase

ECG	electrocardiogram
EJC	excitatory junction current
EJP	excitatory junction potential
ENK	enkephalin
EPSP	excitatory postsynaptic potential
EUS	external urethral sphincter
FB	Fast Blue
FG	Fluoro-gold
FRA	flexor reflex afferent
GABA	γ-aminobutyric acid
GAL	galanin
GALT	gut-associated lymphoid tissue
GIT	gastrointestinal tract
GLP-1	glucagon-like peptide 1
GnRH	gonadotropin-releasing hormone
GR	grey ramus
GSR	galvanic skin response
HGN	hypogastric nerve
HR	heart rate
5-HT	5-hydroxytryptamine (serotonin)
HRP	horse radish peroxidase
HVPG	hypothalamic visceral pattern generator
IC	intercalate spinal nucleus
ICC	interstitial cell of Cajal
IGLE	intraganglionic laminar ending (enteric nervous system)
IJP	inhibitory junction potential
IL	interleukin
ILF	funicular part of the intermediolateral nucleus
ILP	principal part of the intermediolateral nucleus
IMA	intramuscular array (enteric nervous system)
IMG	inferior mesenteric ganglion
IML	intermediolateral nucleus (spinal cord)
INA	integrated nerve activity
INSP	inspiratory
IPANs	intrinsic primary afferent neurons (enteric nervous system)
IP_3	inositol 1,4,5-triphosphate
IPSP	inhibitory postsynaptic potential
IRH	inhibitory releasing hormone
IVLM	intermediate ventrolateral medulla
l,L	lumbar (segment)
LAH	long afterhyperpolarizing
LH	lateral hypothalamus
LHRH	luteinizing hormone-releasing hormone
LM	longitudinal musculature (enteric nervous system)
lPMC	lateral pontine micturition center
LRN	lateral reticular nucleus
LSN	lumbar splanchnic nerve
LST	lumbar sympathetic trunk

LTF	lateral tegmental field
MC	mast cell
MCC	middle cingulate cortex
MDvc	ventral portion of the medial dorsal nucleus (thalamus)
MMC	migrating myoelectric complex (enteric nervous system)
mPMC	medial pontine micturition center
MP	myenteric plexus (enteric nervous system)
MR	motility-regulating (neuron)
mRNA	messenger ribonucleic acid
MVC	muscle vasoconstrictor (neuron)
MVD	muscle vasodilator (neuron)
NA	nucleus ambiguus
NAd	noradrenaline
NANC	non-adrenergic non-cholinergic
NGF	nerve growth factor
NK1	neurokinin 1
NMDA	N-methyl-D-aspartate (acid)
NO	nitric oxide
NOS	nitric oxide synthase
NTS	nucleus tractus solitarii
NPY	neuropeptide Y
OVLT	organum vasculosum laminae terminalis
PAF	platelet-activating factor
PAG	periaqueductal grey
PBC	parabrachial complex
Pf	parafascicular nucleus (thalamus)
PGE	prostaglandin E
PHA-L	phaseolus vulgaris leuco-agglutinin
PHR	phrenic nerve
PKA	protein kinase A
PMC	pontine micturition center
PMNL	polymorphonuclear leukocyte
PO	posterior nucleus (thalamus)
PRV	pseudorabies virus
PSDC	postsynaptic dorsal column
PVH	paraventricular nucleus of the hypothalamus
REM	rapid eye movement
RH	releasing hormone
RVC	renal vasoconstrictor (neuron)
RVLM	rostral ventrolateral medulla
rVRG	rostral ventral respirator group
s,S	sacral (segment)
SCG	superior cervical ganglion
sEJP	spontaneous excitatory junction potential
SG	stellate ganglion
SM	sudomotor (neuron)
SMC	smooth muscle cell
SMP	submucosal plexus (enteric nervous system)

SOM	somatostatin
SP	substance P
SPN	sacral parasympathetic nucleus
STT	spinothalamic tract (neuron)
t,T	thoracic (segment)
TH	tyrosine hydroxylase
TrkA	tyrosine kinase A (receptor)
TNF	tumor necrosis factor
TRH	thyrotropin-releasing hormone
VH	ventral horn (spinal cord)
VIP	vasoactive intestinal peptide
VLM	ventrolateral medulla
VMM	ventromedial medulla
VMb	basal part of the ventromedial nucleus (thalamus)
VMpo	posterior part of the ventromedial nucleus (thalamus, primate)
VPI	ventral posterior inferior nucleus
VPL	ventral posterior lateral nucleus (thalamus)
VPM	ventral posterior medial nucleus (thalamus)
VPpc	ventral posterior parvicellular nucleus of the thalamus (rat)
VR	ventral root
VRG	ventral respiratory group
VVC	visceral vasoconstrictor (neuron)
WHBS	working-heart-brain-stem preparation
WR	white ramus
X	vagus nerve/nucleus