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Current Aspects of Synaptic Transmission in the Nervous System

Arnold S. V. Burgen, University of Cambridge

Sir Arnold Burgen wurde am Dies academicus 1983 von der Universität Zürich, auf Vorschlag der Medizinischen Fakultät, zum Ehrendoktor ernannt.

Sir Arnold Burgen, als Pharmakologe an der Londoner Universität ausgebildet, wurde 1949 Professor für Physiologie an der McGill Universität in Montreal, 1962 Pharmakologie-Professor in Cambridge und 1971 Direktor des National Institute for Medical Research in Mill-Hill, London. Seit 1982 arbeitet Sir Arnold Burgen wieder in Cambridge und ist Master des Darwin College. 1972–1975 war Sir Arnold Präsident der International Union of Pharmacology, und seit 1980 Vice President, seit 1981 Foreign Secretary der Royal Society. Er ist Inhaber von zwei Ehrendoktoraten, nämlich der University of Leeds und der McGill University, Montreal. Er wurde für seine Forschungen auf dem Gebiet der Pharmakonrezeptoren, insbesondere der muskarinisch-cholinergen Rezeptoren, geehrt. Diese Rezeptoren scheinen von grosser Bedeutung für die Hirntätigkeit, insbesondere für psychische Funktionen wie Gedächtnisbildung, Erkennen, Lernvorgänge usw., zu sein. Ihre spezifische Markierung ergibt zum ersten Mal die Möglichkeit, direkt quantitativ das organische Substrat von psychischen Leistungen zu erkennen. Sir Arnold Burgen betätigte sich auch auf anderen Gebieten der Molekularen Pharmakologie, wo er mit den neuesten Methoden der Physikochemie direkte Einwirkungen von Pharmaka auf das biologische Substrat, d.h. auf Enzyme, Proteine usw., erfasste.

Die Laudatio zur Verleihung des Titels lautet: In Anerkennung seiner ausserordentlichen Leistungen auf dem Gebiet der Molekularen Pharmakologie, insbesondere bei der Erkennung von hochspezifischen Rezeptoren im Gehirn, welche eine grosse Bedeutung für die psychischen Funktionen haben. *Peter G. W[illegible]*

When the proposal that synaptic transmission in the nervous system might be chemical in nature began to be discussed in earnest, it was realised that logically the excitatory and inhibitory properties of synapses could be accounted for with the involvement of only a single transmitter, but with two kinds of receptor, excitatory and inhibitory.

However, the fact that the only plausible transmitter known, acetylcholine, had a most uneven distribution in the central nervous system and was virtually absent from the posterior spinal roots, led to the suggestion that there must be a second "sensory" transmitter. This accorded with the existing model system, the autonomic nervous system for which such a binary character had long been accepted.

Events have proved this prediction to be grossly in error. There has not appeared a second transmitter but rather an abundance of further transmitters. Among small molecules we must count noradrenaline, dopamine, serotonin, glycine, glutamate and histamine but then a growing number of peptides – vasopressin, oxytocin, angiotensin, enkephalins, endorphins, substance P, somatostatin, cholecystokinin (CCK), vasointestinal peptide (VIP), and so on. The number is continually growing and it would be no surprise if the total number were to exceed one hundred. It has not been possible to identify one single sensory transmitter in posterior root fibres, indeed in the minority of these fibres in which identification has been possible, more than three transmitters have been found.

On the other hand, the evaluation of the receptors for transmitters by binding and functional studies has revealed another set of complexities. It is probable that these receptors are rarely, if ever, singular, but are divided into more or less well defined subtypes which differ in chemical sensitivities and their distribution within the nervous system. Examples are the α_1, α_2, β_1, β_2 subtypes of the adrenergic receptors and the K, μ and δ subtypes of the opiate receptor. It is further

plain that several types of receptor can coexist on a single neurone, so that it can be responsive to more than one transmitter.

To complicate the matter still further, histochemical studies have revealed that the presence of more than one transmitter in a single neurone is not uncommon, indeed several examples of three transmitters in a single cell are known and it is likely that as sensitive immunochemical techniques come into wider use, this number will grow. Does the existence of multiple transmitters mean that they will be released with nerve activity and produce postsynaptic effects? The best evidence for this has come from the autonomic nervous system. It has been known for a long time that in the cat the stimulation of the chorda tympani nerve produces both secretion of saliva from the submaxillary gland and also a large increase in the blood flow through the gland; these effects can be simulated by intra-arterial acetylcholine. The muscarinic antagonist atropine abolishes both the effects of acetylcholine, but while it blocks the secretory effects of chorda stimulation it has no effect on the vasodilator effect. The solution to this enigma was found recently by Lundberg. The chorda neurones contain two transmitters, acetylcholine and VIP – both of which are capable of stimulating secretion and causing vasodilatation. It is evident that whereas the dominant secretory effect is mediated by acetylcholine the dominant vasodilator effect is mediated by VIP. The phenomenon of corelease can therefore lead to an asymmetry in the action of agonists and antagonists which is of considerable importance. Agonists will always be effective whereas antagonists will only be effective as synaptic blocking agents if they are acting against the dominant agent in a corelease situation. In the periphery it is generally the case that acetylcholine and noradrenaline are dominant over the peptides – otherwise autonomic pharmacology would not have developed in the way it has. We do not know what is the rule in the central nervous system. It is possible that the disappointing effects of some transmitter antagonists in central nervous behaviour may be attributable to corelease. What is the function of corelease? Could it be a safety mechanism that guards against the block of vital pathways by ingested poisons or a way of providing both abrupt and sustained synaptic action?

These newer findings of chemical diversity in the nervous system provide new tools for the morphologist but they also pose tremendous questions that will need to be answered before we feel we are beginning to understand the organisation of the nervous system. They also suggest reasons why neuropharmacology has not so far lived up to expectations but also gives hope for the future.

Prof. Dr. Sir Arnold S. V. Burgen, University of Cambridge, England