Biochemical Pharmacology, Vol. 25, pp. 1817–1818. Pergamon Press, 1976. Printed in Great Britain.

COMMENTARY
THE PEPTIDERGIC NEURON: A WORKING HYPOTHESIS

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The term "peptidergic neuron" has been used for those hypothalamic neurons which originate in the supraoptic and paraventricular nuclei, and synthesize oxytocin and the antidiuretic hormone [1]. It has also been pointed out that these nerve fibres, belonging functionally and morphologically to a neurosecretory system, form "peptidergic synapses" on the surfaces of epithelial cells.

A few years later, it was postulated that "there exist peptidergic neurons which are, in addition to cholinergic and aminergic neurons, widely distributed in brain tissues" [2]. This hypothesis was based on findings about oxytocin and the antidiuretic hormone, the hypothalamic peptides influencing the adenohypophysis, substance P and peptides possibly related to it, and the information-transferring polypeptides. Within the past six years considerable progress has been made with regard to relevant peptides and thus a reconsideration of the basis for the conception is in order.

(1) As comprehensively reviewed [3], the hypothalamic peptides which stimulate or inhibit the anterior-pituitary-hormone release are widely distributed in the brain and have pharmacological in addition to endocrine potency. This review further summarizes many findings indicating neurophysiological functions of these peptides, but connects the term "peptidergic neuron" only to peptides of hypothalamic origin.

(2) The long-known pharmacologically active principle of extracts from nervous and intestinal tissue, substance P [4, 5] has been identified as the undecapeptide H-Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH_2 and synthesized [6, 7]. The very uneven distribution of this peptide in the brain with concentrations highest in substantia nigra and hypothalamus [2], has been confirmed with the radioimmunoassay technique [8, 9, 10, 40]. Most of the substance P present in the brain is located in nerve ending particles [8, 9], it is released from cerebral cortex in the cat [11]. Much higher amounts of substance P exist in the dorsal, rather than in the ventral, root [12, 13, 40]. Its presence in the plexuses of Auerbach and Meissner has been verified [14]. This peptide powerfully depolarizes spinal motoneurons in the frog [13] and, when applied by microiontophoresis, central neurons of the cat [15–17]. Furthermore, it stimulates the paravascular sensory nerve endings of the rabbit's ear [18] and, in the nanomolar range, sensitizes the nerves of the guinea pig vas deferens to transmural stimulation more than acetylcholine, val^5-angiotensin-II-asp^1-β-amide, and bradykinin [19]. Substance P enhances the adenylate cyclase activity in different areas of the human brain but not in liver tissue [9]. In the whole animal, crude and pure preparations of this peptide exert a tranquillizing rather than stimulatory effect [20]. Thus, substance P has been proposed as a transmitter of primary sensory neurons [12, 13] or as a modulator of neuronal activity [2, 17].

(3) The brain tissue synthesizes training-induced peptides which have sequences thought to be specific for the behavioural situation during the training period [21, 22]. For two out of nine postulated peptides the chemical structure is known: the dark-avoidance peptide, scotophobin, is the pentadecapeptide Ser-Asp-Asn-Asn-Gln-Gln-Gly-Lys-Ser-Ala-Gln-Gln-Gly-Gly-Tyr-NH_3 and the noise-habituation peptide, ameletin, possibly has the structure Glu-Glu-Gly-Tyr-Ser-Lys [23]. These two peptides, when injected, induce two different types of behaviour in untrained animals. Thus, the function of brain structures regulating the behaviour, or involved in the process of learning, is susceptible to peptides. This is stressed by numerous findings on the influence of pituitary hormones on the acquisition and retention of learned behaviour [24].

(4) The tridecapeptide Glu-Leu-Tyr-Glu-Asn-Lys-Pro-Arg-Arg-Pro-Tyr-Ile-Leu-COOH, Neurotensin (bovine), has recently been detected in extracts from hypothalamus [25]. This peptide causes hypotension, contraction of smooth muscles (relaxation of the duodenum), an increase in vascular permeability and hyperglycemia. In contrast with substance P, neurotensin is completely inactive on the transmurally-stimulated guinea pig vas deferens [19].

(5) A complete renin–angiotensin system, independent of that of the periphery, has been discovered in the brain [26, 27]. In dog brain, angiotensin could not be detected in the cerebellum but in the total brain, basal nuclei and brain stem, with hypothalamus containing the highest concentrations [26]. In the human brain, the angiotensin-forming enzyme content of cerebellar cortex was notably higher than that of hypothalamus or frontal cortex [28]. This is fascinating with regard to the pharmacological effects of angiotensin in the central nervous system [29].

(6) The long-known dipeptide carnosine (β-alanyl-L-histidine), because of both its specific localization and behaviour in biochemical and physiological experiments, is envisaged as a putative neurotransmitter in the primary olfactory pathway [41].

(7) There are even more pharmacologically active substances of peptidic nature in brain tissue. From human and bovine cortex, but not from globus pallidus and substantia nigra, a principle called Fc can be extracted which behaves like an acidic and trypsin-resistant peptide. In contrast with substance P and kinins, Fc exerts very weak circulatory effects but stimulates the isolated gut indirectly by releasing acetylcholine from the intramural plexuses. The structure

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of Fc awaits elucidation. There are perhaps different Fc-peptides present in the tissue of hypothalamus, amygdaloid nucleus, and red nucleus [30]. It is not clear whether the pharmacologically active phosphopeptide called "nerveside" [31] is identical with Fc. Like Fc, it is acidic, occurs preferentially in cortical tissue and stimulates isolated guts by releasing acetylcholine. The finding in human and vertebrate cortical grey tissue of a peptide reacting with antigastrin antibodies [32] is a new indication for the existence of a pharmacologically active brain peptide with acidic nature. Interestingly, neither gastrin nor an impure preparation of Fc sensitize the nerves of the guinea pig vas deferens to transmural stimulation [19].

A peptide with antistrychnine potency can be extracted from brain and spinal cord [33]. Yields were highest from the cortex, but gut-contracting activity was missing. Finally, sleep-promoting factors of possible peptide nature have been detected in dialysates from blood leaving the brain circulation of sleeping animals 134] and in the effluent from perfusion of the mesencephalic reticular formation of a sleep-deprived cat [35].

Finally, in brain tissue, there exist bradykinin-like polypeptides together with enzymes for their liberation and catabolism [36]. The kinin concentrations were highest in hypothalamus and decreased to 4 per cent of the normal level during fever caused by bacterial pyrogens [37]. The classical kinin, bradykinin, is capable of influencing neurological processes since it is a potent pain-producing compound [18] and, when injected intracerebroventricularly, causes somatic and behavioural changes [38].

Taken together, these results form a broad basis for the working hypothesis that there exist peptidergic neurons, i.e., neurons which synthesize at least one specific peptide. The peptides could act as transmitter substances or modulators of neuronal activity [39], or even have targets outside the brain as the releasing factors of the hypothalamus, or oxytocin and the antidiuretic hormone. All peptides mentioned besides those with known neuroendocrine functions, are candidates for neurological functions and none of them can be neglected. Future research in this field must consider that: (1) peptides present in extracts from nervous tissue could be associated with a distinct type of the neuron proper, with glial cells, or with vascular tissues; (2) peptides are more complex molecules than acetylcholine or catecholamines, and (3) time courses of peptide action may be slower than those of conventional transmitter effect [17]. Research on neuropeptides should concern especially the interactions with neurological functions, and the systems of peptide synthesis and degradation in nervous tissue.

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