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# MOLECULAR AND CELLULAR INTERACTIONS UNDERLYING HIGHER BRAIN FUNCTIONS

Proceedings of the 9th Meeting of the International Neurobiology Society, held at the Abbaye Royale de Fontevraud (France), on September 1-4, 1981

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## Preface

This volume constitutes the proceedings of the 9th Meeting of the International Neurobiology Society on "Molecular and Cellular Interactions Underlying Higher Brain Functions", held at the Abbaye Royale de Fontevraud (France) from September 1 to 4, 1981.

The organizing committee consisted of Drs. Jean-Pierre Changeux, Jacques Glowinski, Michel Imbert (all France) and Floyd Bloom (San Diego, CA, U.S.A.). About 110 participants from 13 countries attended the meeting.

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## SECTION I

# **Molecular Mechanisms of Information Transfer**



# **Chemical Communication in the CNS: Neurotransmitters and Their Function**

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## **INTRODUCTION**

In considering current work on neurotransmitters at least four major categories of information merit our attention. First, there is the process of transmitter discovery, and the likelihood that future application of molecular genetics methods may accelerate and broaden the search for those neurotransmitters which await discovery (see Bloom, 1981; Baxter this volume). Second, there are the cellular strategies by which already discovered transmitters are localized, and their mechanisms of cell-cell communication expressed. From these sorts of studies the spatial and functional domains over which specific transmitters operate can be characterized and contrasted (see Bloom, 1979; Siggins and Bloom, 1981). Third, are parallel molecular level studies which for some transmitters permit biochemical assessment of functions other than direct electrophysiological regulation of target cells and which may represent other facets of a set of holistic actions. Finally, a fourth body of work attempts to relate cellular and molecular actions of transmitters to regulation of behaviors. In this essay I will briefly comment on the metabolic properties of the presumed cortical transmitter vasoactive intestinal polypeptide (VIP), and on the mechanisms possibly underlying the behavioral effects of arginine-vasopressin (AVP) a hypothalamic peptide presumed to operate as a neurotransmitter as well as in a more classical endocrine hormone role.

## **METABOLIC ACTIONS OF PRESUMPTIVE TRANSMITTERS: VIP**

VIP is a 28 amino acid polypeptide first isolated from porcine intestine by Said and Mutt (1970). It shares structural homologies with other gastrointestinal peptides such as glucagon, secretin and gastric inhibitory peptide. Biological effects range from systemic vasodilatation, increased cardiac output and hyperglycemia, to smooth muscle relaxation, regulation of secretory processes in the gastrointestinal tract and stimulation of glycogenolysis in liver slices (see Said, 1980). VIP-immunoreactive material occurs in highest concentration in cerebral cortex; here neurons with VIP-like immunoreactivity release the peptide in vitro. Furthermore, brain membranes specifically bind radiolabeled VIP (Taylor and Pert, 1979) and a VIP-stimulated adenylate cyclase has been identified in various areas of the central

nervous system (Quik et al., 1978; Deschodt-Lanckman et al., 1977). We have employed the method of Quach et al. (1978) to determine whether cortical actions of VIP include evidence of metabolic control functions such as glycogenolysis (Magistretti et al., 1981).

#### *Effects of VIP on [ $^3\text{H}$ ]glycogen levels*

On incubations in vitro, mouse brain slices incorporate glucose; the [ $^3\text{H}$ ]glycogen content increases linearly during 30 min of incubation. VIP  $10^{-7}$  M, added after 30 min of incubation, induces a rapid fall in the [ $^3\text{H}$ ]glycogen content. This glycogenolytic action of VIP was concentration-dependent. The Eadie-Hofstee plot of the dose-response curve yields an  $\text{EC}_{50}$  of 26 nM and a maximal glycogenolytic effect of 77% of basal levels (correlation coefficient of regression line: 0.992).

#### *Effects of other substances on [ $^3\text{H}$ ]glycogen levels*

Norepinephrine (NE) also displays glycogenolytic action as shown by Quach et al. (1978) and confirmed by us (Magistretti et al., 1981). An Eadie-Hofstee plot of the dose-response curve gives an  $\text{EC}_{50}$  of 500 nM and a maximal glycogenolytic effect of 70.5% of basal levels (correlation coefficient of regression line: 0.972). Secretin at a  $5 \times 10^{-7}$  M concentration also decreased the [ $^3\text{H}$ ]glycogen content of the slices to 40.6% of basal levels (Table I). Glucagon had no glycogenolytic effect. Other putative cortical neurotransmitters, such as  $\gamma$ -aminobutyric acid (GABA), glutamic acid, aspartic acid and somatostatin did not decrease the [ $^3\text{H}$ ]glycogen levels in the slices (Table I). Carbamylcholine, a cholinergic agonist, was similarly inactive (Table I). Preliminary results indicate that somatostatin does not antagonize the glycogenolytic effect induced by VIP.

#### *Interactions between VIP and NE*

The decrease in [ $^3\text{H}$ ]glycogen levels induced by  $10^{-6}$  M NE was effectively blocked ( $P < 0.01$ ) by D, L-propranolol,  $10^{-5}$  M, a  $\beta$ -adrenergic antagonist (Table I).

TABLE I

*P* = statistical significance assessed by one way analysis of variance, followed by paired comparisons with a Newman-Keul test. Tests here based on quadruplicate results from one series; similar results obtained in 2-4 replicate series. (Data from Magistretti et al., 1981.)

Drug tested (M)	% Glycogenolysis	P
VIP ( $5 \times 10^{-7}$ M)	66.5	<0.01
NE ( $10^{-6}$ M)	60.9	<0.01
NE + VIP	64.4	<0.01
NE + propranolol ( $10^{-5}$ M)	12.9	n.s.
VIP + propranolol	64.4	<0.01
Propranolol ( $10^{-5}$ M)	-1.2	n.s.
Secretin ( $5 \times 10^{-7}$ M)	40.6	<0.01
No effects at $10^{-5}$ M		
GABA, Glu, Asp, carbamylcholine		
Somatostatin, glucagon		

In contrast to this result, D,L-propranolol did not antagonize the glycogenolytic action of VIP,  $10^{-7}$  M. The  $\beta$ -adrenergic blocker did not affect the [ $^3$ H]glycogen levels when tested alone.

No significant difference in the glycogenolytic effect of  $10^{-7}$  M VIP was apparent between mice in which an 85% depletion in cortical NE was induced by intracisternal 6-hydroxydopamine (6-OHDA) injection and control mice. Finally, VIP and NE tested together at supramaximal concentrations showed no additive effects (Table I).

Thus, among the various putative neurotransmitters tested, only VIP and NE had an effect on [ $^3$ H]glycogen levels: they induced a concentration-dependent hydrolysis of the newly synthesized [ $^3$ H]polysaccharide. The  $EC_{50}$  for this effect was 26 nM for VIP and 500 nM for NE. The maximal [ $^3$ H]glycogen hydrolysis induced by both neurotransmitters was 75–80% of basal levels. A common feature which distinguishes NE and VIP from other cortical neurotransmitters is their ability to stimulate the membrane-bound enzyme adenylate cyclase. This action suggests a possible molecular mechanism responsible for the glycogenolytic action of the two substances. Quach et al. (1978) have demonstrated that the effect of NE on [ $^3$ H]glycogen levels was potentiated by the phosphodiesterase inhibitor isobutylmethylxanthine (IBMX) and mimicked by dibutyryl-cyclic-AMP. In our studies, the effect of VIP also was potentiated by IBMX (see Magistretti et al., 1981), suggesting that the glycogenolytic action of the peptide was mediated by cyclic AMP. Glycogen hydrolysis induced by the two cortical neurotransmitters, will result in an increased glucose availability for the generation of phosphate-bound energy in those cellular elements receiving terminals from VIP and NE neurons. This similar action of the two neurotransmitters at the cellular level is particularly interesting, given the neuronal organization of the cortical noradrenergic and VIP systems. Recently we have obtained a detailed immunohistochemical characterization of the cortical VIP neurons; our observations indicate that individual VIP neurons extend across the entire vertical thickness of the cerebral cortex, but arborize in a narrow radial column with minimal branching in the horizontal plane. This orthogonal pattern of spatial organization, confers upon the VIP neuron the capacity to regulate energy metabolism locally, within individual columnar modules. This anatomical profile for VIP contrasts with the mainly tangential organization of the coeruleo-cortical noradrenergic projection, which thus has spatial capacity to exert similar metabolic actions more globally, throughout a vast expanse of cortex. More detailed electrophysiological observations are needed to determine whether NE and VIP share other functional effects on target cell activity (see Bloom, 1979). However, VIP and NE do display similar glycogenolytic actions in peripheral tissues. This shared action may indicate that certain substances, with specific hormonal roles in several cell systems, may also exert the same homeostatic functions at the cellular level within the central nervous system, where their effects are constrained by the spatio-temporal function precision inherent to neural transmission.

## VASOPRESSIN AND BEHAVIORAL REGULATION IN THE RAT

Substantial evidence exists to support the hypothesis that neurohypophyseal hormones, in addition to integrating fluid volume, blood pressure, and temperature, may also be involved in adaptive behavior, perhaps even "memory". In early work,



TABLE II

*Effects of arginine-vasopressin and a peptide antagonist of arginine-vasopressin and a peptide antagonist on the rate of extinction of active avoidance responding*

(Results from Koob et al., 1981.)

<i>Experimental condition</i>	<i>Mean number avoidance responses (<math>\pm</math>S.E.M.)</i>
First extinction trial	7.98 $\pm$ 0.15 (27)
Second extinction trial (2 h)	
Saline + saline	5.65 $\pm$ 0.65
Saline + 6 $\mu$ g AVP	6.25 $\pm$ 0.75
dPTyr-(Me)AVP + AVP	5.65 $\pm$ 0.65
Third extinction trial (4 h)	
Saline + saline	2.80 $\pm$ 0.7
Saline + 6 $\mu$ g AVP	6.05 $\pm$ 0.5*
dPTyr-(Me)AVP + AVP	2.65 $\pm$ 0.4
Fourth extinction trial (6 h)	
Saline + saline	1.75 $\pm$ 0.7
Saline + 6 $\mu$ g AVP	6.20 $\pm$ 0.7*
dPTyr-(Me)AVP + AVP	1.55 $\pm$ 0.7

\* Results significantly different from control (saline) or AVP + dPTyr-(Me)AVP injected rats.

hypophysectomized rats were found deficient in a number of behavioral situations, especially the acquisition and extinction of aversively motivated tasks (see De Wied, 1980 for review). These deficiencies were reversible by administration of a crude pituitary extract, Pitressin, and in later work by arginine-vasopressin (AVP) in microgram amounts injected subcutaneously. Furthermore, lysine-vasopressin delayed extinction in an active avoidance task in intact animals and improved retention of a passive avoidance task. In more recent work, intraventricular injection of nanogram quantities of AVP significantly delayed extinction of the active avoidance response (De Wied, 1976), while anti-vasopressin serum inhibited the retention in the passive avoidance test (Van Wimersma Greidanus et al., 1975).

We have sought to reproduce and extend some of the findings of De Wied and his colleagues regarding the effects of vasopressin on learned behavior. More specifically, we sought to examine the effects of both subcutaneous and intraventricular injection of vasopressin and a new vasopressin antagonist on the extinction of an active avoidance response (see Table II). Our methods and detailed results are reported elsewhere (Le Moal et al., 1981; Koob et al., 1981).

#### BEHAVIORAL EFFECTS OF ARGININE VASOPRESSIN AND THE VASOPRESSIN ANTAGONIST PEPTIDE dPTyr-(Me)AVP

Injection of 1  $\mu$ g AVP subcutaneously after the first 10 extinction trials significantly prolonged the extinction of the avoidance response. Similar effects were