CATECHOLAMINES IN NON-NEURAL CELLS OF THE CNS: A POSSIBILITY

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CATECHOLAMINES have many functions in biological systems; they transmit messages between cells over long distances as hormones and over short distances as transmitter substances for neurons in the sympathetic nervous system and in certain areas of the central nervous system. However, in the brain, cells other than neurons may contain catecholamines. Such cells are most likely neurosecretory, and the catecholamine compounds contained in these cells may function other than as a neurotransmitter. The non-neural nature of some catecholamine-containing cells in the brain may contribute to the problems encountered in determining the physiological role of these compounds and to the controversy regarding dopamine's role in gonadotrophin secretion (SCHNEIDER and MCCANN, 1970; FUXE and HÖKFELT, 1970).

I will focus here on the dopamine-containing cells of the arcuate nucleus-median eminence area and their role in the regulation of anterior pituitary secretion. Firstly, the small dopamine cells of the arcuate nucleus (AN) are at best atypical neurons in that they do not form synapses (AJIKA and HÖKFELT, 1973). That is, using either the standard gluteraldehyde-OsO_4 procedure or the ethanolic-phosphotungstic acid stain, no synaptic profiles were observed in median eminence either between axon and axon, or between axon and dendrite. Rather, the efferent cell processes of AN appear to terminate adjacent to perivascular spaces (STOECKART *et al.*, 1972). The situation in the AN can be contrasted with the substantia nigra-corpus striatum dopamine-containing neurons which do form morphological synapses (AJIKA and HÖKFELT, 1973).

Secondly, there is the extreme resistance of AN dopamine to the depleting effect of 6-hydroxy-dopamine (6-OHDA), (CUELLO, SHOEMAKER and GANONG, 1973). In experiments involving chronic third ventricle cannulation in rats, high doses of 6-OHDA delivered directly into the third ventricle reduced hypothalamic norepinephrine levels to less than 10 per cent of normal. The dopamine levels, however, were unaffected (Table 1). Dopamine levels in the brain are usually more resistant to the depleting action of 6-OHDA (URETSKY and IVERSEN, 1970; LYTLE *et al.*, 1972) but even at doses of 6-OHDA (with Pargyline and DMI pretreatment) that will deplete caudate dopamine, hypothalamic dopamine is not affected (Table 2). Clearly, the two dopamine-containing systems differ from each other in rather important characteristics.

The notion that some catecholamine-containing cells in the central nervous system may be neurosecretory rather than true neurons is not a new one (BERN and KNOWLES, 1966; KNOWLES, 1967). Many hormone producing cells in a variety of peripheral tissues contain large amounts of catecholamines. The frequent association between polypeptide hormone production and the ability to take up and form catecholamines and 5-HT by decarboxylation has led PEARSE (1968) to term these cells members of the APUD series (an acronym for Amine and Precursor Uptake and Decarboxylation). Interestingly,

TABLE 1. HYPOTHALAMIC CATECHOLAMINES 15 DAYS AFTER INJECTING 6-OHDA INTO THIRD VENTRICLE

Treatment	Norepinephrine (μg/g)	Dopamine (μg/g)	Corticosterone (μg/100 ml)
Control (NaBr)	1·13 ± 0·09	0·41 ± 0·03	5·5 ± 0·8
6-OHDA (200 μg ×2)	0·19 ± 0·03	0·42 ± 0·03	8·3 ± 1·5
Significance	$P < 0·001$	N.S.	N.S.

Animals were stereotaxically implanted with a stainless steel cannula in the midline of the brain directly into the 3rd ventricle several days prior to drug administration. Each rat received 2 injections (10 μl) 48 hr apart of either 200 μg of 6-OHDA (the hydrobromide salt dissolved in distilled water) or NaBr equiosmolar to the drug. Animals were decapitated and bled 15 days after the second injection in a resting condition, 3 hours after light onset. (CUELLO, SHOEMAKER and GANONG, 1973).

TABLE 2. COMPARISON OF DOPAMINE DEPLETION IN HYPOTHALAMUS AND 'CORPUS STRIATUM' USING 6-OHDA (PARGYLINE & DMI)

Treatment	Hypothalamus (μg/g)	Corpus striatum (μg/g)	LH (ng/ml)
Control (NaBr ×2)	0·60 ± 0·03	1·48 ± 0·08	47·8 ± 5
6-OHDA (200 μg; Pargyline, DMI, pretreat ×2)	0·60 ± 0·02 N.S.	1·10 ± 0·23 $P < 0·05$	61·0 ± 11 N.S.

Adult male albino rats were twice injected intracisternally 24 hr apart with either NaBr (10 μl) or 6-OHDA (200 μg). The animals receiving 6-OHDA were given pargyline (50 mg/kg) i.p. and Desmethylimipramine (DMI) (25 mg/kg) i.p. 30 min previously. Ether anesthesia was administered before intracisternal injection; Penicillin-streptomycin (i.m.) after. All animals were sacrificed 2 weeks post-injection at 3 hr after light-onset: blood samples were taken at that time for radio-immunoassay of LH using the N.I.H. standard.

these peripheral amine-containing endocrine cells appear to be derived embryonically from the neural crest. Although these cells have the enzymatic capacity to decarboxylate amines, there is no evidence that the amines are synthesised in the cells, nor is the specific function of such amines known.

OWMAN (1973) has hypothesised that amine ares normal constituents of all polypeptide-hormone producing endocrine cells, and that the intracellular amines function in the formation, storage and/or release of the hormone.

What is needed is an intensive morphological investigation of these catecholamine-containing cells to provide us with information regarding their secretory capability and the precise nature and termination of their processes. A combination of electron microscopy, autoradiography, and fluorescence histology (see BLOOM, 1972; BLOOM and CRAYTON, 1972) could be utilised to yield considerable information. One study using a combination of techniques has been published on the periventricular cell group in the toad hypothalamus (MCKENNA and ROSENBLUTH, 1971). These workers find the catecholamine-containing cells do not form synapses, and are more analogous to peripheral chromaffin cells than to CNS neurons.

Another type of study that could enhance our understanding of catecholamine function in neuroendocrine regulation is turnover studies using radioactive tracers. The use of catecholamine synthesis inhibitors would not be recommended for these studies because the amines may not be synthesised in the AN cells. Although there are certain limitations associated with turnover studies (see discussion by WURTMAN, 1971), these methods could correlate the turnover rate of amines and/or releasing factors with different endocrine states, even if, as RODRIGUEZ (1972) has suggested, amines and hypothalamic releasing factors are contained in the same cell.

The initial descriptions of the catecholamine-containing cells of the hypothalamus (CARLSSON, FALCK and HILLARP, 1962; FUXE, 1964) carefully pointed out that no direct evidence identified such cells as neurons. By design and interpretation, however, virtually all studies of the role played by the dopamine cells of the hypothalamus in pituitary control assume the cells are neurons. A plethora of experiments has been done using synthesis inhibitors, electrical stimulation, receptor blockers, depleting and repleting agents, agonists and antagonists, alone or in combinations, to determine the function of the dopamine 'neurons' in gonadotrophin secretion. The possibility that dopamine may reside in brain cells that do not function as neurons, that it may not be synthesised in these cells, and that it may function in the binding and release of polypeptide hormones is testable. It is a hypothesis which must be explored before further conceptual progress in catecholamine-neuroendocrine regulatory function can occur.

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