Evidence for a Degeneration of Indoleamine Containing Nerve Terminals in Rat Brain, Induced by 5,6-Dihydroxytryptamine

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Summary. 5,6-dihydroxytryptamine (5,6-DHT) has been found to induce a substantial degree of "chemical degeneration" of indoleamine containing nerve terminals in the rat brain following a single intraventricular injection of 75 μg 5,6-DHT per animal. The disintegration of varicose terminal portions of serotonin containing neurons is reflected
1. by a loss of yellow fluorescent varicosities in certain defined parts of the rat CNS, despite a mild inhibition of the serotonin catabolizing enzyme monoamine oxidase with nialamide in the pretreated animals,
2. by a significant drop of the chemically measurable 5-hydroxytryptamine content in nearly all parts of the rat brain and spinal cord,
3. by the appearance of highly, orange or brownish fluorescent axons provided with numerous unusually large, distorted and intensely fluorescent swellings ("droplets"), resembling proximal stumps of mechanically severed indoleamine containing axons,
4. a temporary increase in the amount of indoleamine fluorophores stored in some neuronal pericarya, and
5. the electron microscopical demonstration of degenerating synaptic swellings of unmyelinated axons at all sites investigated.

The selectivity of the effect of 5,6-DHT on indoleamine neurons is indicated by the absence of similar signs of injury in catecholamine containing neurons of the rat CNS.

Keywords: Indoleamine containing nerve terminals — Chemically induced degeneration — 5,6-dihydroxytryptamine — Rat brain.

Introduction

The discovery that 6-hydroxydopamine is capable of causing a "chemical sympathectomy" of peripheral noradrenergic (Tranzer and Thoenen, 1967; Haeusler, Haefely, and Thoenen, 1969; Jonsson and Sachs, 1970; Furness, Campell, Gillard, Malmfors, Cobb, and Burnstock, 1970; Baumgarten, Holstein, and Owman, 1970; Thoenen, 1971) and a degeneration of terminal varicose portions of central noradrenaline- and dopamine-containing neurons (Uretsky and Iversen, 1970; Breese and Traylor, 1970; Bell, Iversen, and Uretsky, 1970; Iversen and Uretsky, 1970) has greatly stimulated and facilitated neuroanatomical and neurophysiological studies on the distribution and function of CNS catecholamine neurons in laboratory animals (Ungerstedt, 1971).

Due to several circumstances knowledge on the occurrence, distribution, synaptic relationship and function of 5-hydroxytryptamine (5-HT) and possibly

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hitherto unidentified (non-serotonin) indoleamine containing neurons (see Björklund, Falck, and Stenevi, 1970)—which in mammals are said to occur only in the central but not in the peripheral nervous system—is poor and fragmentary, compared to the wealth of information on catecholamine neurons. One main reason for this discrepancy rests on the fact that the Falck-Hillarp method—which enables a visualization of a great number of biogenic and non-biogenic monoamines, their precursors and metabolites (for review see Corrodi and Jonsson, 1967)—is not as sensitive for 5-HT as it is for catecholamines.

Thus, the fluorescence yield of 5-HT is only about 50% that of noradrenaline or dopamine, and the exposure of the 5-HT fluorophore to blue excitation light (at about 365 nm) causes a rapid photodecomposition of the beta-carboline formed from 5-HT by formaldehyde condensation. The rapid fading of the 5-HT fluorophore renders the documentation of 5-HT containing structures in nervous tissue difficult or even impossible, a fact, which explains why there have appeared so few publications on the distribution of 5-HT neurons in the mammalian and non-mammalian brain (Dahlström and Fuxe, 1964, 1965; Braak and Baumgarten, 1967; Fuxe and Ungerstedt, 1968; Baumgarten and Braak, 1968; Fuxe, Hökfelt, and Ungerstedt, 1968; Braak, Baumgarten, and Falck, 1968; Baumgarten, 1972).

On the other hand, the average diameter of varicose preterminal and terminal swellings of 5-HT containing neurons in the mammalian brain ranges in the order of about 0.05–0.5 μm, thus being in part below the resolution power of the light microscope. In this respect, 5-HT neurons show morphological characteristics similar to dopamine neurons where any distinct visualization of the tiny densely packed axonal varicosities, e.g. in the striatum of mammals, is hardly possible in specimens from untreated animals (Fuxe, Hökfelt, and Ungerstedt, 1968).

One methodological approach to overcome the difficulties outlined above and to provide a means of mapping 5-HT neurons in the mammalian brain is to interrupt the 5-HT pathways by electrolytic or surgical lesions (Anden, Dahlström, Fuxe, Larsson, Olson, and Ungerstedt, 1966; Stenevi, 1971). Any such approach is hampered by the simultaneous damage of neurons of any transmitter type and of non-neuronal tissue elements in the brain which are difficult to avoid. The development of a neurochemical which enables a chemical destruction of indoleamine neurons would help to prevent the complications of surgically or electrolytically induced brain damage and would provide the experimental basis for refined neuroanatomical studies on 5-HT and related indoleamine containing neuron systems.

A short communication on the degeneration inducing effect of 5,6-dihydroxytryptamine (5,6-DHT) on CNS indoleamine neurons has been published separately (Baumgarten and Lachenmayer, 1972). The aim of the present paper is to give a more detailed account on the action of 5,6-DHT on central monoamine containing neurons in the rat brain.

Material and Methods

Adult (200–250 g) male albino rats (Wistar strain) were used for the present study. For fluorescence and electron microscopy as well as for chemical investigations the animals were pretreated with a single intraventricular injection of 75 μg 5,6-DHT (free base), applied as the creatininsulfate-H₂O-complex (Schlossberger and Kuch, 1960) and the animals were killed.