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Review

Serotonin innervation of basal ganglia in monkeys and humans

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ABSTRACT

This review paper summarizes our previous contributions to the study of serotonin (5-hydroxytryptamine; 5-HT) innervation of basal ganglia in human and nonhuman primates under normal conditions. We have visualized the 5-HT neuronal system in squirrel monkey (*Saimiri sciureus*) and human postmortem materials with antibodies directed against either 5-HT, 5-HT transporter (SERT) or 5-HT synthesizing enzyme tryptophan hydroxylase (TPH). Confocal microscopy was used to compare the distribution of 5-HT and dopamine (DA; tyrosine hydroxylase-immunolabeled) axons in human, while the ultrastructural features of 5-HT axon terminals in monkey subthalamic nucleus were characterized at electron microscopic level. In monkeys and humans, midbrain raphe neurons emit axons that traverse the brainstem via the transtegmental system, ascend within the medial forebrain bundle and reach their targets by coursing along the major output pathways of the basal ganglia. These 5-HT axons arborize in virtually all basal ganglia components with the substantia nigra receiving the densest innervation and the striatum the most heterogeneous one. Although the striatum – the major basal ganglia input structure – appears to be a common termination site for many of 5-HT ascending axons, our results reveal that the widely distributed 5-HT neuronal system can also act directly upon neurons located within the two major output structures of the basal ganglia, namely the internal pallidum and the substantia nigra pars reticulata in monkeys and humans. This system also has a direct access to neurons of the DA nigrostriatal pathway, a finding that underlines the importance of the 5-HT/DA interactions in the physiopathology of basal ganglia.

Contents

Abbreviations: A, anterior; ac, anterior commissure; al, ansa lenticularis; Aq, cerebral aqueduct; CD, caudate nucleus; CeM, central medial thalamic nucleus; cp, cerebral peduncle; cr, capsule of red nucleus; D, dorsal; DA, dopamine; db, dendritic branch; DRN, dorsal raphe nucleus; fx, fornix; GP, globus pallidus; GPe, external segment of GP; GPi, internal segment of GP; ic, internal capsule; IC, inferior colliculus; ICa, island of Cajella; L, lateral; LD, lateral dorsal thalamic nucleus; lf, lenticular fasciculus (field H2); LV, lateral ventricle; mfb, medial forebrain bundle; mlf, medial longitudinal fasciculus; MRN, median raphe nucleus; mt, mammillo-thalamic tract; mtg, mammillo-tegmental tract; NA, nucleus accumbens; NST, nucleus of the stria terminalis; opt, optic tract; P, paraventricular thalamic nucleus; PUT, putamen; Rt, reticular thalamic nucleus; S, septum; SC, superior colliculus; SERT, serotonin transporter; SI, substantia innominata; SN, substantia nigra; SNc, pars compacta of SN; SNr, pars reticulata of SN; STN, subthalamic nucleus; STR, striatum; Th, thalamus; TH, tyrosine hydroxylase; TPH, tryptophan hydroxylase; VA, ventral anterior thalamic nucleus; VLP, ventolateral posterior thalamic nucleus; VTA, ventral tegmental area; xscp, decussation of the superior cerebellar peduncle; ZI, zona incerta; 5-HIAA, 5-hydoxyindolacetic acid; 5-HT, 5-hydroxytryptamine (serotonin); III, oculomotor nerve root fibers.

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1. Serotonin and basal ganglia

Serotonin (5-hydroxytryptamine, 5-HT) is a multifaceted transmitter produced and released by a widely distributed neuronal system that reaches virtually all major forebrain structures (Jones, 2005; Monti and Jantos, 2008; Steriade, 2004). Endowed with a markedly collateralized axon, the 5-HT neurons have their cell body mainly confined to the raphe nuclei, which were originally divided into nine entities (groups B1–B9 of Dahlstroem and Fuxe, 1964). This elongated cell column is commonly divided into a small caudal group comprising the medullary raphe nuclei and projecting to the spinal cord and a large rostral group scattered along the pons and midbrain and containing the dorsal (DRN, B6 and B7) and median (MRN, B8) raphe nuclei, which together supply about 85% of the 5-HT forebrain innervation (Hornung, 2003; Monti and Jantos, 2008; Parent, 1996).

The basal ganglia, which play a crucial role in the control of motor behavior (Parent and Hazrati, 1995), are among the various forebrain structures that receive a particularly dense 5-HT innervation from the midbrain raphe nuclei (Di Matteo et al., 2008). The complex distributional pattern of 5-HT axons within the various components of the basal ganglia has been unraveled by several mapping studies undertaken principally in rats (Harding et al., 2004; Moore et al., 1978; Mori et al., 1985a,b, 1987; Parent et al., 1981, 2010; Steinbusch, 1981). Detailed information about the 5-HT innervation of the basal ganglia has also been gathered in monkeys (Azmitia and Gannon, 1986; Lavoie and Parent, 1990; Mori et al., 1985a,b, 1987; Parent et al., 2010; Schofield and Everitt, 1981), but relatively little information is currently available on the 5-HT innervation of the human basal ganglia. Except for the pioneering histofluorescence investigations of embryonic brain tissue that provided the very first images of the monoamine-containing neuronal systems in the human brain (Olson et al., 1973), the more recent morphological investigations of the 5-HT neuronal system in humans have focused primarily on the raphe nuclei (Baker et al., 1991a,b; Hornung, 2003). Useful information on the 5-HT content of human basal ganglia in both health and disease conditions has nevertheless emerged from postmortem biochemical studies (Hornykiewicz, 1998; Kish et al., 2008; Lloyd et al., 1974; Walsh et al., 1982).

The present review paper summarizes the results of our recent immunohistochemical study of the organization of the 5-HT innervation of human basal ganglia undertaken with antibodies raised against the 5-HT transporter (SERT) and tryptophan hydroxylase (TPH), the rate-limiting enzyme in 5-HT synthesis (Wallman et al., 2011). These antibodies were applied to human postmortem material obtained from healthy adult individuals. The data that stemmed from this study are here compared to the results of our previous investigations of the 5-HT innervation of the basal ganglia in the squirrel monkey (*Saimiri sciureus*) (Lavoie and Parent, 1990; Parent et al., 2010). Hopefully, this comparative review will lead to a more global understanding of the role of 5-HT at basal ganglia level in primates and a better appreciation of the complex neurochemical changes that occur within these nuclei in neurodegenerative diseases.

2. Methodological approaches

The observations reported here are based on the analysis of human postmortem material obtained from individuals with no clinical or pathological evidence of neurological or psychiatric disorders, and from the brains of young adult squirrel monkeys (*S. sciureus*). The postmortem human brains were fixed by immersion in 4% in cold paraformaldehyde, whereas the brains of squirrel monkeys were dissected out after the animals had been sacrificed by transcardial paraformaldehyde perfusion under deep barbiturate narcosis. The brains were cut at 50 μm along the coronal or sagittal plane with a freezing microtome or a vibratome. The sections were then immunostained with antibodies against SERT, TPH or 5-HT itself (for details, see Wallman et al., 2011). In addition, some basal ganglia sections were immunostained with an antibody raised against the enzyme tyrosine hydroxylase (TH), a marker of dopamine (DA) neuronal profiles, to compare the distribution of ascending 5-HT and DA pathways. Furthermore, ultrathin sections through the monkey subthalamic nucleus (STN) were prepared to examine the ultrastructural features of the 5-HT neuronal profiles within this basal ganglia component (for details, see Parent et al., 2010).

The immunostained sections of human and monkey brains were observed and photographed under both bright and darkfield illuminations, as well as with a confocal fluorescence microscope, and the location of the 5-HT axons and terminals in the various components of the basal ganglia of each species were precisely mapped at four corresponding rostrocaudal levels. In humans, the location of the 5-HT cell bodies in DRN and MRN and the initial trajectory of their ascending axons were further studied by analyzing serial parasagittal sections immunostained for either SERT or TPH. Immunofluorescence sections were observed with a confocal laser-scanning microscope LSM 5 PASCAL, whereas the ultrathin SERT-immunostained sections of the monkey STN were examined with a Phillips CM100 electron microscope. Quantitative and stereological procedures were used to determine the number, size and ultrastructural features of 5-HT axon varicosities in the monkey STN.

3. Topographical organization of serotonin ascending projections

In both humans and monkeys, the origin and initial trajectory of the ascending 5-HT fibers are particularly well outlined on brainstem sections cut along the sagittal plane. A multitude of thick and nonvaricose SERT or 5-HT-immunopositive (+) fibers (Fig. 1A) arise from the neurons of the DRN (Fig. 1B) and, less abundantly, from those of the MRN at various levels along the upper brainstem. These fibers form several small and intertwined fascicles, which appear in the sagittal plane as a remarkably complex reticulum covering much of the central core of the midbrain tegmentum (Fig. 1A). The bulk of these fibers arches rostroventrally and, as they penetrate the decussation of the superior cerebellar peduncles, they break out into a multitude of small and compact fascicles (Fig. 1C). More rostrally, these fibers collect themselves dorsomedially to the substantia nigra (SN) in the form of a rather diffuse bundle that passes partly through the ventral tegmental area and ascends within the lateral hypothalamic area along the medial forebrain bundle (Figs. 1A, 2A, 3A and 4A). The bundle of SERT+ fibers tapers as it ascends within the lateral hypothalamic area because several immunoreactive fascicles detach themselves from it at different caudorostral levels. These fascicles sweep laterally to innervate various components of the basal ganglia, such as the STN, globus pallidus (GP) and putamen. Many SERT+ or 5-HT+ axons are closely intermingled within the internal medullary lamina, which divides the GP into an internal (GPi) and an external (GPe) segment, as well as in the external medullary lamina, which separates the GPe from the putamen (Figs. 2D, 3A, 3B, 4A and 4B). Other immunoreactive fibers ascend within the internal capsule, as well as in the external capsule, which separates the putamen from the claustrum, en route to the cerebral cortex (Fig. 3B–C).

In squirrel monkeys, the comparison of adjacent sections immunostained for 5-HT and TH has revealed that, in the lateral hypothalamic area, the 5-HT+ axons are overall more diffusely