

available at www.sciencedirect.comwww.elsevier.com/locate/brainres**BRAIN
RESEARCH****Research Report**

Tissue distribution of Ret, GFRalpha-1, GFRalpha-2 and GFRalpha-3 receptors in the human brainstem at fetal, neonatal and adult age

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ABSTRACT

Occurrence and localization of receptor components of the glial cell line-derived neurotrophic factor (GDNF) family ligands, the Ret receptor tyrosine kinase and the GDNF family receptor (GFR) alpha-1 to -3, were examined by immunohistochemistry in the normal human brainstem at fetal, neonatal, and adult age. Immunoreactive elements were detectable at all examined ages with uneven distribution and consistent pattern for each receptor. As a rule, the GFRalpha-1 and GFRalpha-2 antisera produced the most abundant and diffuse tissue labelling. Immunoreactive perikarya were observed within sensory and motor nuclei of cranial nerves, dorsal column nuclei, olivary nuclear complex, reticular formation, pontine nuclei, locus caeruleus, raphe nuclei, substantia nigra, and quadrigeminal plate. Nerve fibers occurred within gracile and cuneate fasciculi, trigeminal spinal tract and nucleus, facial, trigeminal, vestibular and oculomotor nerves, solitary tract, medial longitudinal fasciculus, medial lemniscus, and inferior and superior cerebellar peduncles. Occasionally, glial cells were stained. Age changes were appreciable in the distribution pattern of each receptor. On the whole, in the grey matter, labelled perikarya were more frequently observed in pre- and perinatal than in adult specimens; on the other hand, in discrete regions, nerve fibers and terminals were abundant and showed a plexiform arrangement only in adult tissue; finally, distinct fiber systems in the white matter were immunolabelled only at pre- and perinatal ages. The results obtained suggest the involvement of Ret and GFRalpha receptors signalling in processes subserving both the organization of discrete brainstem neuronal systems during development and their functional activity and maintenance in adult life.

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1. Introduction

The receptor complex for the trophins of the glial cell line-derived neurotrophic factor (GDNF) family comprises a common signalling component, the transmembrane receptor tyrosine kinase Ret (Baloh et al., 2000; Airaksinen and Saarma, 2002), and an extrinsic protein belonging to a family of gly-

cosyl phosphatidylinositol (GPI)-linked receptors, called GDNF family receptor alpha (GFRalpha), which behaves as the ligand binding element. Four distinct specific GFRalpha receptors, GFRalpha-1 to GFRalpha-4, have been identified, which mediate the influence of the GDNF family trophins on the development, differentiation, and maintenance of mature phenotype of distinct and partially overlapping central and

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peripheral neuronal populations (see [Airaksinen and Saarma, 2002](#)). Each of the GDNF family members interacts preferentially with one of the GFRalphas. Thus, GDNF, the earliest discovered factor of the family, binds preferentially to GFRalpha-1, neurturin (NTN) to GFRalpha-2, artemin (ART) to GFRalpha-3, and persephin (PSP) to GFRalpha-4 ([Jing et al., 1996, 1997; Baloh et al., 1997, 1998; Klein et al., 1997; Enokido et al., 1998](#)). The GFRalpha–ligand complex leads either to recruitment of Ret and subsequent intracellular signalling, or to Ret-independent signalling (see [Airaksinen and Saarma, 2002](#)). Though usually bound to the plasma membrane, GFRalpha molecules can be produced in soluble form after alternative splicing and cleavage processes ([Airaksinen and Saarma, 2002; Hase et al., 2005](#)).

Ret and GFRalpha receptors have been widely studied by Northern blot analysis and in situ hybridization histochemistry in the rat and mouse brain and their expression has been found consistent with areas of the brain where neurons responsive to the GDNF family ligands are located ([Treanor et al., 1996;](#)

[Trupp et al., 1995, 1997; Nosrat et al., 1997; Suvanto et al., 1997; Sanicola et al., 1997; Widenfalk et al., 1997; Glazner et al., 1998; Golden et al., 1998; Worby et al., 1998; Yu et al., 1998; Masure et al., 1998, 1999; Naveilhan et al., 1998; Burazin and Gundlach, 1999](#)). Though transcripts for Ret and one at least of the GFRalpha receptors are usually co-expressed, mismatch of the two components has been described in some brain regions ([Trupp et al., 1997; Worby et al., 1998; Glazner et al., 1998; Masure et al., 1998; Golden et al., 1998; Burazin and Gundlach, 1999](#)).

Since their discovery, the GDNF family ligands have received particular attention because of their therapeutic potential in numerous neuropathological conditions, such as neurodegenerative diseases ([Tseng et al., 1998; Rosenblad et al., 1999, 2000; Perez-Navarro et al., 2000; Tomac et al., 2002; Holm et al., 2002; Marco et al., 2002; Dowd et al., 2005; Oiwa et al., 2006](#)), motor neuron diseases ([Wang et al., 2002; Manabe et al., 2003; Ekesteren, 2004; Watabe et al., 2005; Barati et al., 2006](#)), brain injury ([Kitagawa et al., 1999; Tsai et al., 2000; Arvidsson et al., 2001; Sarabi et al., 2001, 2003a; Miyazaki et al.,](#)

Table 1 – Medulla oblongata

	Ret		GFRalpha-1				GFRalpha-2				GFRalpha-3			
	Cells		Fibers		Cells		Fibers		Cells		Fibers		Cells	
	n	a	n	a	n	a	n	a	n	a	n	a	n	a
Arcuate nucleus			(+)		(+)		(+)				(+)			
Area postrema	+		+				(+)				(+)			
Central reticular nucleus, dorsal part	+		(+)		(+)				+					
Central reticular nucleus, ventral part	+		(+)		(+)	(+)								
Commissural nucleus			(+)		(+)	++	+						(+)	
Cuneate fasciculus			+				+	(+)			++	(+)		
Cuneate nucleus	+	(+)	+	+	+	+	+	(+)	(+)		+	(+)		+
Dorsal accessory olivary nucleus	(+)		(+)		+				(+)				(+)	(+)
Dorsal motor nucleus of the vagus nerve	(+)				(+)	+			++				(+)	
External cuneate nucleus	+		(+)	(+)	+	+			(+)	+			(+)	+
Gigantocellular reticular nucleus	+				+				++					
Gracile fasciculus			+				+	(+)			++	(+)		
Gracile nucleus					+	+			(+)	(+)			(+)	
Hypoglossal nerve			+				+				+			
Hypoglossal nucleus	+	+	(+)		++	+			(+)	(+)	(+)		(+)	(+)
Inferior cerebellar peduncle			(+)				(+)	(+)			(+)			(+)
Inferior vestibular nucleus	(+)				(+)	(+)			(+)				+	
Lateral paragigantocellular reticular nucleus									+					
Lateral reticular nucleus	(+)	(+)	+	(+)		++			+		(+)	(+)		
Medial accessory olivary nucleus	(+)	(+)	(+)		+	+			+	(+)			(+)	(+)
Medial lemniscus			(+)				+				(+)			
Medial longitudinal fasciculus			(+)				+				(+)			(+)
Medial vestibular nucleus					(+)	+			(+)					
Nucleus ambiguus	+		(+)			+			+					
Nucleus of the solitary tract						+								
Nucleus raphe magnus						+								
Nucleus raphe obscurus						+								
Parvocellular reticular nucleus						+								
Principal olivary nucleus	(+)	(+)	(+)	(+)	+	+	(+)	(+)	+	(+)			(+)	(+)
Solitary tract			(+)	(+)			+	+			+			
Spinal nucleus of the trigeminal nerve, caudal part	+	(+)	(+)	+	(+)	(+)		(+)	(+)		+		(+)	(+)
Spinal nucleus of the trigeminal nerve, interpolar part	+	(+)	(+)		(+)	(+)	(+)	(+)					(+)	
Spinal tract of the trigeminal nerve				+			(+)	(+)			(+)	(+)		(+)
Ventral grey column	+	+			+	+		(+)	+	(+)			+	(+)
Vestibular nerve							(+)				(+)			

Distribution of neuronal cells and fibers immunoreactive to Ret, GFRalpha-1, GFRalpha-2, and GFRalpha-3 at pre- and perinatal (n), and adult age (a). Empty boxes mean no staining; (+): sparse; ++: moderate; +++: abundant.

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