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The vesicular amine transporter family (SLC18): amine/proton antiporters required for vesicular accumulation and regulated exocytotic secretion of monoamines and acetylcholine

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Abstract The vesicular amine transporters (VATs) are expressed as integral proteins of the lipid bilayer membrane of secretory vesicles in neuronal and endocrine cells. Their function is to allow the transport of acetylcholine (by the vesicular acetylcholine transporter VAChT; SLC18A3) and biogenic amines (by the vesicular monoamine transporters VMAT1 and VMAT2; SLC18A1 and SLC18A2) into secretory vesicles, which then discharge them into the extracellular space by exocytosis. Transport of positively charged amines by members of the SLC18 family in all cases utilizes an electrochemical gradient across the vesicular membrane established by proton pumping into the vesicle via a vacuolar ATPase; the amine is accumulated in the vesicle at the expense of the proton gradient, at a ratio of one translocated amine per two translocated protons. The members of the SLC18 family have become important histochemical markers for chemical coding in neuroendocrine tissues and cells. The structural basis of their remarkable ability to transport positively charged amines against a very large concentration gradient, as well as potential disease association with impaired transporter function and expression, are under intense investigation.

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Discovery of the vesicular amine transporters (VATs)

That specific protein transporters must be responsible for the vesicular uptake of acetylcholine and biogenic amines required for neurotransmission was first appreciated when specific inhibitors for amine uptake into storage vesicles were found that also depleted the corresponding amines from neuroendocrine tissues, and interfered with cholinergic and monoaminergic neurotransmission (see [7, 29, 30, 44] and references therein). Rodent VMAT1 (SLC18A1) and VMAT2 (SLC18A2) were identified structurally by cloning cDNAs encoding proteins that conferred the ability to sequester the neurotoxin 1-methyl-4-phenylpyridinium (MPP+) [24] or biogenic amines [11], on non-amine accumulating recipient cells. The human VMATs, hVMAT1/SLC18A1 and hVMAT2/SLC18A2 were cloned from human cDNA libraries using the rat homologs as probes, and their transport properties verified functionally in heterologous-cell amine uptake assays [10, 15]. hVAChT/SLC18A3 was cloned from a human cDNA library [13] following homology cloning of rodent VAChT/slc18a3 [13] using a *Caenorhabditis elegans* putative vesicular acetylcholine transporter (unc-17) cDNA as probe [1], coupled with functional demonstration of proton- and ATP-dependent, and vesamicol-sensitive, acetylcholine transport in CV-1 fibroblasts expressing the heterologous VAChT cDNA. The structure, function, and role in neuronal and endocrine cell function of the VATs/SLC18 s have been recently and comprehensively reviewed [5, 7, 12, 29, 33, 42, 44]. Recently, VMAT expression in non-neuroendo-

Table 1 SLC18—the vesicular monoamine/acetylcholine transporter (VMAT/VAChT) family (*5HT* 5-OH-tryptamine, *SIF cell* small, intensely fluorescent cell, *GI* gastrointestinal,*EC* enterochromaffin, *ECL* enterochromaffin-like,*ChAT*choline acetyltransferase)

Human gene name	Protein name	Aliases	Predominant substrates	Transport type/ coupling ions*	Tissue distribution and cellular/ subcellular expression	Link to disease	Human gene locus	Sequence accession ID	Splice variants and their specific features
SLC18A1	VMAT1	CGAT, VAT1	5HT, dopamine, adrenaline, noradrenaline, histamine	E/H^+	Adrenal gland (medulla), sympathetic ganglia (SIF-cells), carotid body, skin (Merkel cells), GI tract (EC cells), Subcellular: large dense-core vesicles		8p21.3	NM, _003053	
SLC18A2	VMAT2	SVAT. SVMT, VAT2 (MAT)	5HT, dopamine, adrenaline, noradrenaline, histamine	E/H^+	Brain (neurons), adrenal gland (medulla), sympathetic ganglia (neurons, SIF cells), carotid body, small and large intestine (neurons), stomach (neurons and ECL-cells), endocrine pancreas, basophils, mast cells, dendritic cells and platelets, Subcellular: large dense-core vesicles, small, dense-core vesicles, tuberovesicular structures and small synaptic (dopaminergic) vesicles	Cardio-vascular, drug addiction [42]	10q24.-3-q25.1	NM, _003054	
SLC18A3	VAChT		Acetylcholine	E/H^+	Brain (neurons), peripheral nervous system (neurons), intestine (neurons), Subcellular: small synaptic vesicles	Myas-thenic syn-dromes (ChAT only) [9]	10q11.2	NM, _003055	R-type, (minor variant), V-type, (major variant)

* *E* Exchanger

crine amine-storing tissues has been documented, and the potential contribution of altered VAT structure and expression to human neuropsychiatric and movement disorders examined (Table 1).

Functional characteristics and structural information

VATs accumulate singly positively-charged amines into the relatively proton-impermeable acidic secretory vesicles at the expense of proton antiport through the transporter protein (protons are first accumulated in secretory vesicles via a vacuolar ATPase not physically associated with the transporter) with a two proton:one amine stoichiometry, and to a final substrate concentration of up to 500 mM, exceeding that found in the cytosol by 100-fold (ACh) to 10,000-fold (biogenic amines)[29].

The VATs (SLC18 s) are members of a larger solute carrier family, the TEXANs (toxin extruding antiporters). This class of transporter is found in many microorganisms and confers resistance to antibiotics and antiseptics in bacteria and yeast [17, 31]. NorA, a quinolone resistance protein from *Staphylococcus aureus*, and Bmr, a multiple drug resistance protein from *Bacillus subtilis*, are the closest relatives of the mammalian proteins, with the highest degree of homology detected in the six N-terminal putative transmembrane domains (i.e. 28% identity between VMAT1/SCL181A and Bmr) [36, 37]. Recently, a family of small, multi-drug resistance proteins that also function as TEXANs has been characterized and employed by Schuldiner and colleagues as a model system for VAT transport function, in which the role of transmembrane domain-resident negatively charged amino acids in substrate transport can be examined in detail [18, 28].

As far as is known, all metazoans that have acetylcholine- and biogenic amine-containing secretory vesicles have VATs that are structurally well-conserved [33]. Mammalian VMAT1s generally show greater than 80% overall sequence identity, as do mammalian VMAT2s, while hVMAT1 (SLC18A1) has only 60% sequence identity with hVMAT2 (SLC18A2), and hVMAT1 and hVMAT2 have about 40% sequence identity with hVAChT (SLC18A3). The hVATs are 12-transmembrane domain (TMD) proteins based on Kyte-Doolittle hydropathy analysis of their primary sequences [10, 13, 15], and 10-transmembrane domain proteins based on MAXHOM alignment using the "profile-fed neural network systems from Heidelberg" (PHD) program (http://dodo.cpmc.columbia.edu/predictprotein/) [8, 34, 35]. The 10-TMD model for VAT differs principally from the 12-TMD model in failing to assign TMDs II and IV to the membrane, and placing these residues instead in the vesicle lumen (TMD II containing the LFASKA motif) or

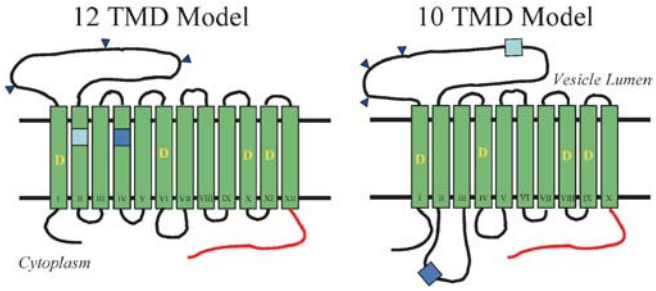

Fig. 1 Putative topologies of human vesicular amine transporters (VATs). In the 12-transmembrane domain (*TMD*) model the LFASKA motif (*light-blue box*) and the LQGxGS motif (*dark-blue box*) reside within TMDs II and IV, respectively. In the 10-TMD model, TMDs II and IV do not assign to the membrane, placing these motifs in the vesicle lumen and the cytoplasm, respectively. *Blue triangles* mark potential glycosylation sites. *D* indicates aspartate residues potentially critical for substrate recognition, substrate transport and antagonist binding. The cytoplasmic C-terminus (*red*) is important for trafficking to the correct vesicle type, for recycling, and for phosphorylation. The loop sizes do not reflect their natural sizes

in the cytoplasm (TMD IV containing the conserved LQGxGS motif). Physical evidence to distinguish between these two models is lacking. The brief physical description of the VATs below assumes that they have 12 TMDs, following the current literature.

The N- and C-termini of the VATs are cytoplasmic, based on the observed cytoplasmic localization of the C-terminus, and the assumption that VATs have an even number of TMDs. All hVATs (SLC18As) exhibit greatest sequence identity within the putative transmembrane domains, and least within the putative glycosylated loop between TMDs I and II. All VATs contain the LFASKA motif in the putative TMD II, and the LQGxGS motif in putative TMD IV. Although the functions of these two motifs are undefined, they provide convenient "bookmarks" for discussion of the 10-TMD and 12-TMD models for VAT structure (Fig. 1). The conservation of these two sequences may, itself, lend indirect support to the 12-TMD model, since membrane-resident sequences tend to be more highly conserved across species and VAT isoforms than non-membrane-resident sequences. A second element in support of the 12-TMD model is a proposed "salt bridge" between charged residues in putative TMD II and XI in the 12-TMD model [27]: interactions between K139 and D427 would be more likely if both were membrane-resident. A cysteine bridge between luminal loops 1/2 and 7/8 (in the 12 TMD model), postulated by Ruoho and colleagues, could exist in either the 12- or the 10-TMD model for the VATs [41]. Finally, more primitive TEXANs investigated by Schuldiner and colleagues appear to function as trimers of 4-TMD protein monomers (see above): conservation of this overall structure-function logic in mammalian VATs would suggest that the 12-TMD arrangement is the correct one. Despite the preponderance of evidence in favor of the 12-TMD model, additional direct experimental evidence is required for final structural assignments (see Fig. 1).

All VATs contain aspartate (D) residues in TMDs I, VI, X, and XI. The VMAT aspartate residues in TMDs I, X, and XI are thought to be critical for substrate recognition [26] and transport [27, 39]. The aspartates in TMD X and XI of VAChT appear to be equally important for acetylcholine recognition and transport, while those in TMD IV (conserved among all known metazoan VAChTs) and TMD X are critical for vesamicol binding [20]. The cytoplasmic C-terminus of all VATs contains sequences required for (potentially phosphorylation-dependent) trafficking to the correct vesicle type (small synaptic vesicles for VAChT and large dense-core vesicles for VMATs), for recycling via endocytosis, and for phosphorylation that may control other aspects of transporter function (see [22] for review and references).

Pharmacology and imaging

Pharmacologically and clinically important drugs that interact with the VATs include vesamicol (VAChT/SLC18A3) [30], tetrabenazine (VMAT2/SLC18A2) and reserpine (VMAT2 and VMAT1/SLC18A1) [19, 23]. These drugs block amine uptake by VAChT and VMATs, respectively, and have pharmacological effects consistent with abrogation of amine storage and neurotransmission. Importantly, labeled vesamicol and tetrabenazine analogs exist that have been used successfully in brain imaging of vesicular transporter protein density in diseases such as Parkinson's, schizophrenia, and Alzheimer's disease (see [5] for review and references). The human isoforms of VMAT1 (SLC18A1) and VMAT2 (SLC18A2) transport catecholamines and serotonin, and are inhibited by reserpine, equally well, but hVMAT2 transports histamine, and is blocked by tetrabenazine, much better than hVMAT1, and rodent VMAT isoforms (slc18a1 and slc18a2) also exhibit these differences [14, 15, 25].

Expression patterns

VAChT is co-expressed invariably with the biosynthetic enzyme for generating acetylcholine, choline acetyltransferase (ChAT), in neurons, and from the same gene locus as ChAT [6]. In humans, ChAT, but not VAChT (SLC18A3), however, is found in the placenta [3]. VAChT is a unique marker for cholinergic synapses and neuroeffector junctions, usually far easier to visualize than ChAT (Fig. 2E,F). In rodents, VMAT1 is expressed predominantly in neuroendocrine cells, and VMAT2 in neurons (Fig. 2A–D) [32, 45]. In humans, VMAT1 and VMAT2 are expressed at equivalent levels in neuroendocrine cells [e.g. adrenal medulla, small, intensely fluorescent (SIF) cells]. VMAT2 is the only VMAT isoform expressed in human and rodent neurons, plate-

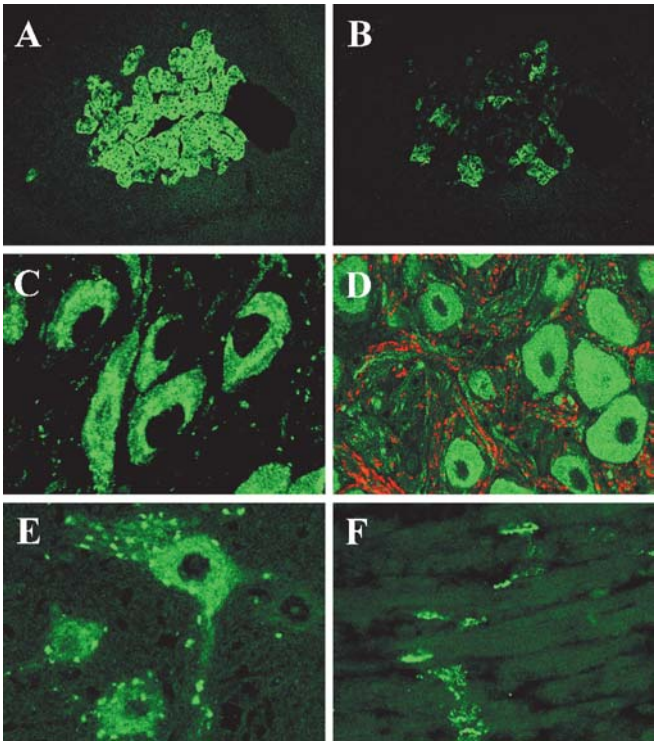

Fig. 2A–F Confocal images of VAT expression. **A** Vesicular monoamine transporter-1 (VMAT1)/slc18a1 immunoreactivity (IR) in chromaffin cells in mouse adrenal medulla. **B** VMAT2/slc18a2-IR in mouse adrenal medulla, on an adjacent section. Note restriction of VMAT2 to a subset of cells. Primate adrenal medullary cells express both VMAT1 and VMAT2 to similar extents [15]. **C** VMAT2/SLC18A2-IR in neurons in substantia nigra of rhesus monkey. Note subcellular granular staining. **D** VMAT2/slc18a2-IR (*green*) in sympathetic neurons in rat superior cervical ganglion. Vesicular acetylcholine transporter (VAChT)/slc18a3-IR (*red*) is present in preganglionic fibers, similarly to human/non-human primate peripheral nervous system. **E** VAChT/SLC18A3-IR in neurons of human facial motor nucleus. Note cholinergic synapses on cell bodies and proximal dendrites. **F** VAChT/SLC18A3-IR in human motor endplates

lets, basophils, mast cells, and dendritic cells*[1] [8, 15, 46]. Whether a neuron is func- tionally noradrenergic, serotonergic, dopaminergic, or histaminergic depends on the co-expression of biosynthetic enzymes and plasma membrane transporters for each biogenic amine, and the expression of VMAT2 in all catecholamine-, serotonin- or histamine-synthesizing neurons. There are some interesting exceptions. VMAT2 is expressed transiently during development, along with the plasma membrane 5-HT transporter (5-HTT, also known as the NaCl-dependent serotonin transporter, SERT), in rodent thalamocortical neurons that do not appear to express biosynthetic enzymes for biogenic amines [21, 38]. Neurons of the primate nucleus tractus solitarius and olfactory cortex express tyrosine hydroxylase (TH), but lack VMAT2 (see [44] and references therein). The functional significance of neurons expressing various aminergic traits without VMAT expression is unclear. Ugrumov and colleagues have noted that some hypothalamic neurons possess TH, lack aromatic L-amino acid decarboxylase (AADC) and can synthesize DOPA, while others lack TH, possess AADC, and can synthesize dopamine from exogenously supplied DOPA. They have suggested that these two individually deficient monoaminergic trait-expressing neuronal populations might complement each other in *trans*, the TH+/AADC– neurons synthesizing DOPA and secreting it to be taken up and synthesized into dopamine by the TH–/AADC+ neurons [2].

[1] **Note added in proof*: VMAT2 is expressed in human pancreatic endocrine cells containing insulin but absent from islet cells expressing glucagon, somatostatin or pancreatic polypeptide [Anlauf M, Eissele R, Schäfer MK-H, Eiden LE, Arnold R, Pauser U, Klöppel G, Weihe E (2003) Expression of the two isoforms of the vesicular monoamine transporter (VMAT1 and VMAT2) in the endocrine pancreas and pancreatic endocrine tumors. J Histochem Cytochem (In press)].

Transgenic/knockout studies

Homozygous knock-out of VAChT leads to failure of cholinergic neurotransmission in *C. elegans*, and homozygous knock-out of VMAT (there is only one isoform in worms) leads to an egg-laying- and locomotion-defective phenotype similar to treatment with reserpine [1, 4]. Homozygous knock-out of VMAT2 in mice is lethal, but partially rescuable with amphetamine, which can release biogenic amines from nerve terminals via a non-exocytotic mechanism [16]. Heterozygous knock-out of VMAT2 in mice shows a clear gene dosage effect, with a halving of dopamine, norepinephrine, and serotonin content in brain [16, 40, 43].

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