J. exp. Biol. ***196****, 51–57 (1994)*
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GENE-PRODUCT DESIGNATIONS FOR AMINO ACID TRANSPORTERS

HALVOR N. CHRISTENSEN[1], LORRAINE M. ALBRITTON[4], DONALD K. KAKUDA[2,3] AND CAROL L. MACLEOD[4]

[1]*Pediatric Metabolism,* [2]*Graduate Program in Biomedical Sciences and* [3]*Cancer Center, Department of Medicine, Cancer Genetics Program, University of California, San Diego, La Jolla, CA 92093-0609-F, USA* and [4]*Department of Microbiology, University of Tennessee, Memphis, TN 38163, USA*

Summary

The molecular cloning of genes that encode amino acid transporters presents the scientific community with the opportunity to name their gene products using a scheme that could usefully recall the well-defined *transport system* most similar in properties to the newly identified cloned gene product. To avoid the problem of rising confusion, we propose to take advantage of established designation methods that indicate the types of amino acids transported and the co-substrate ion requirement of their transport. The economy obligated by the necessity to keep the number of symbols in a gene name to a minimum will rarely permit a listing of the full range of substrates, since amino acid transport systems have broad substrate specificities with co-substrate requirements that can differ in a substrate-specific manner. Hence, the use of established systems to codify groups of amino acid transport systems, which allow identification of the substrate range by using 1–3 letters, e.g. A, L or even ASC, could be integrated with a system used to indicate the ion-dependence of transport. The discoverers of transporters are mainly proceeding with commendable reserve and are inviting discussion, a desire which this essay urges be facilitated by more formal arrangements for further planning. These discoverers have also shown, along with an expressed desire for guidance, well-advised spontaneity in making reference to the substrate range, two trends that together suggest that a good set of designations can evolve that will be highly descriptive. We propose that this can be accomplished without a struggle to accommodate awkwardly to the requirements of the huge human genome data base cataloging system, nor to any single comprehensive systematic scheme. Instead, a combined scheme that takes into account the biological and biochemical characteristics, as well as the historical designations, of amino acid transport systems, is offered here for evaluation.

Introduction

The study of membrane transport is at a stage so lively that nearly every month a cDNA corresponding to yet another amino acid transporter is reported. We concentrate here on amino acid transporters because the problem for them appears to be especially challenging and important. The properties of the newly cloned transporters, usually

Key words: amino acids, transport systems, transporters, systematic nomenclature, sodium-dependence.

observed in the *Xenopus* oocyte, will often, but not always, correspond to a previously identified and characterized *transport system*. These systems are now generally well-described in a large supporting literature, one which serves by retrospect to define the properties of the protein product of the cloning. In occasional cases, new discriminations of transport activity will become possible, and further family relationships as to structure and function will become evident. This paper focuses on vertebrate systems, but the literature on which it is based shows close similarities over a wide range of species.

The central necessity in selecting designations is to ensure that the *name recalls the range of biological functions* carried out by each of these proteins. The challenge is to designate each transporter as a gene product in an abbreviated, unique way that will evoke its function and its experimental history, except when a protein may be encountered that apparently has no history. Such designations will provide a new precision in categorizing the functional molecules. The power of these achievements will depend on designations that assist in discriminating and recalling each gene product within a conventionally permissible number of symbols. It would be unrealistic to delay all naming until the discovery of a decisive feature that endows substrate-specificity to each transporter. Indications so far strongly suggest that if we do not take prompt collective action, we will find ourselves with highly heterogeneous sets of designations, often narrowly communicative and apt to be confusing.

How is the naming process developing?

A recent summary of glutamate transporters includes the designation EAAC1 for *e*xcitatory *a*mino *a*mino acid *c*arrier, along with three designations GLAST (for *gl*utamate and *a*spartate *t*ransporter) and GLT1 and GLTP (*gl*utamate *t*ransporters, both), which clearly indicate that reference is made to glutamate transport (see Kanai *et al.* 1993). All but one of these names conveys information that these transporters have similar structures and carry out similar transports of the dicarboxylic amino acids. The name EAAC1 does indeed recall a biological function, but it names a transporter that appears to have a much wider functional range. These authors write as follows ‘Based on the available information, it is plausible that EAAC1 and the acidic amino acid transport system X_{AG}^{-} represent the same transport system’ (Kanai *et al.* 1993), citing an earlier demonstration of the similarity of central nervous system (CNS) glutamate and aspartate transport to their hepatic transport by that system (Christensen and Makowske, 1983). Until transport is studied in parallel in non-neuronal and neuronal tissues, one cannot discern what traits may be unique to each. Therefore, recalling only the characteristic neuronal response seems narrow. This problem is particularly evident since EAAC1 mRNA is found in the liver, small intestine and heart, as well as in the brain (Kanai *et al.* 1993). Perhaps we could consider EAAC1 to be a provisional designation until its biological range is more precisely defined.

The other three designations reviewed by Kanai *et al.* (1993), namely GLAST, GLT1 and GLTP, recall the molecules characteristically transported, a mode of functional description likely to survive. Involved in such ongoing efforts is a spontaneous recognition that a colloquial language for designating transporters is desirable for

ordinary discussions. In contrast, some of the names formed under the human genome project rules, which attempt to provide uniqueness for cataloging, seem obscure enough to hinder such discussions.

The need to address this general problem is clear from the numerous requests for guidance from researchers who recognize the risk of confusion as they puzzle over the choice of a designation. If our efforts should, in the meanwhile, help the larger data banks to cover our special needs, or even to allow the two nomenclatures to coalesce, so much the better.

What substrate properties serve as discriminators?

The features that can be useful in constructing an efficient plan for naming transporters have been identified from experience with transport systems (e.g. Bannai *et al.* 1984; Christensen, 1989). They arise from the *distinct structural features* that define the unexpectedly wide range of amino acid substrates. The discriminating features shown by transporters now being isolated are reassuringly similar to the structural features of those previously found to serve for the corresponding *transport systems*. The discriminatory features correspond to substrate fit at a recognition site, the relative placements of charged groups in space, and also of other groups that participate in bonding, such as hydrogen bonding, mutual bonding *via* a bridging ion such as Na^+, and apolar bonding. Additional features include the obstructing effects of side-chain groups, some of which have proved notably useful in discriminating transport by the familiar systems A and L (Oxender and Christensen, 1963; Christensen *et al.* 1969, see Table 1). The additional feature of the net charge on each amino acid, whether anionic, cationic or dipolar, serves as a major discriminator and will be discussed below. These features give discriminatory value to changes in Na^+ and H^+ concentration (see Table 2) and to the use of competing amino acid analogs that fit the same, or block another, transport recognition site.

Efficient discrimination relies on a description of the *structural range* of amino acid substrates served by a given transport system. Despite this focus on the substrates, much has also been learned about the structure of the mediating transporter even before the transporter was isolated. The availability of the transporters will allow ultimate description of the recognition sites inherent to their binding and release function. Furthermore, the knowledge already gained as to the specificity range of the binding and its response to co-substrates should facilitate that progress. Once a transporter is sequenced, we can add the information that certain amino acid residues are strategically positioned to explain that selectivity. Hence, the information accumulated during decades of transport study prepares us for the characterization of newly cloned transporters.

Names of systems extended to transporters

The names of amino acid transport systems have traditionally attempted to incorporate reference to the amino acids carried, even though their substrate

Table 1. *Extension of designations that recall transport systems*

System	Proposed designation	Substrates
Na^+-dependent		
A	AAT	Ala, Gly and many others
N	NAT	Gln, His, Asn
$B^{o,+}$	BAT	Ala, Lys, Arg, Gly
G	GAT	Gly (not for GABA)
y^+	yAT	Gln, homoser, citrulline†, others
Na^+-independent		
L	lAT (LAT)*	Leu, Ile, Val, Phe
$b^{o,+}$	bAT	Lys, Leu, Trp, Met
y^+	yAT	Arg, Lys

*For system L, the proposed designation uses a lower case l to signify the Na^+-independent property of this system.

The strategy which gives significance to the third letter from the right in identifying the amino acid transporter, by reference to the precedent transport system. An extra symbol may well be needed if a second transporter should prove also to correspond, for example, to system A. This was apparently done in forming SAAT. The use of two or three extra letters to recall the transport system has gained strength, as in ASCT and GLAST (Storek *et al*. 1992). Note that yAT appears twice through its service for Na^+-dependent transport of dipolar amino acid, a problem handled in a different way in Table 2.

†Baydoun *et al.* (1994).

specificities are often broad. In fact, the expected specificity range for most amino acid transporters is so broad that listing all of the substrates for each in its designation is not possible even if the one-letter code for amino acids is used. It would, furthermore, be unrealistic to delay all designations until a sequence generating a receptor site that crucially determines transport specificity is known for each case. Only occasionally will the recall obtained by listing even a very few amino acid substrates justify the space consumed. An even more economical evocation of the substrate range for a transporter could be obtained by incorporating into the designation (Table 1) one of the letters already familiar that names a given transport system or a family of systems, e.g. transport systems A, N and L, as defined in the introduction. Table 1 shows why selected letters should be reserved from competing uses. This added clue may be inserted as the third letter from the right. The insertion of the whole three-letter designation for system ASC, as now proposed from the laboratory of Amara for the transporter ASCT1, is good (Arriza *et al.* 1993), especially if, with practice, we are reminded that aspartate and its analogs become substrates too on lowering the pH. That confirmation (Kilberg *et al.* 1994) probably accounts for its similarity to various glutamate transporters.

Direct use of the discriminators in naming

As we have said, the designations of well-established transport systems convey information on whether their amino acid substrates carry or do not carry a net charge. A

Table 2. *Extension of the XYZ scheme for amino acid transport systems*

Transport system	Suggested name for cloned transporter	Types of amino acids included under that designation		
		X (x)	Y (y)	Z (z)
y^+	yZ (yZAT)	None	Cationic	Gln, homoser and others
$B^{o,+}$	YZ	None	Cationic	Many zwitterionic
$b^{o,+}$	yz	None?	Cationic	Many and Leu
ASC	XZ	Below pH 5.5		Above pH 5.5
		Asp and its four-carbon analogs	Scarcely	Three- to five-carbon with or without polar side chain, proline
X^-_{AG}	X (XAG)	Asp and Glu	None	None
x^-_C	x (xC or xSS)	Cystine, Glu	None	None

Extension of the XYZ scheme for transport systems (Bannai *et al.* 1984) to suggest a plan by which several transporters might be designated, especially those with affinities both for amino acids with and without a net charge. For the two important glutamate-transporting systems listed last, X^-_{AG} and x^-_C, the abbreviations X and x probably do not carry sufficient specificity, but might be supplemented as suggested in parentheses. Note that the designations alone provide information as to the substrates transported. Capitalization indicates when the transport is Na^+-dependent. For system ASC, lowering the pH changes the substrate recognition from Z to X, from three to four carbons in length, and whether the side chain is polar or not (Makowske and Christensen, 1982).

second major discriminator denotes those systems that are dependent on, or independent of, an ion such as sodium for cotransport (Bannai *et al.* 1984). Special problems arise for cases where a mediator transports two dissimilar groups of amino acids, depending on their net charge. For example, transport systems, including system ASC, show the characteristic transport of both zwitterionic and anionic amino acids. To exploit the important discriminators for such cases, provisional advantages can be seen in the XYZ scheme (familiar to students of amino acid transport systems; see Bannai *et al.* 1984). This scheme uses X to stand for anionic, Y for cationic and Z for zwitterionic amino acids.

Two of these letters, *capitalized* or *lower case* according to the sodium-dependence of the transport, then entered into the transporter designation (Table 2). For example, instead of the name y^+ for that transport system, the designation yZ (where Z refers to zwitterionic, perhaps leading to yZAT) might be incorporated into the code for a transporter that carries zwitterionic ('neutral') as well as cationic amino acids (Kakuda *et al.* 1993). Some readers will recall that the letter y gained its relevance to cationic amino acids when we found that the earlier designation system Ly^+ restricted attention to its lysine substrate. Deleting the L left y^+, and these dispositions of Y and Z left X for the anionic amino acids. We hope this perhaps surprising scheme will not be dismissed without careful attention to the real problem we face in designating transporters in relation to the molecules they carry and their ion requirements.

Discussion

Everyone we have consulted has agreed that further discussion is needed to help coordinate designations, ultimately leading to one that is uniquely descriptive for each transporter. This goal does not necessarily force all designations into a single comprehensive system. A further reason for encouraging discussion now is to prevent petty over-concerns about the naming process from retarding the astonishing momentum of transporter discovery. Nevertheless, a gratifying and impressive reserve has been shown by various discoverers in making provisional their designation until the functional range of a new transporter is more fully uncovered. Thought might be given to urging a broad agency, such as the Journal for Experimental Biology or the International Union for Pure and Applied Chemistry, to designate several persons to serve as a 'working nomenclature commission', ideally representing the full range of persons concerned with amino acid transport, presumably including biologists in general and, specifically perhaps, biochemists, general physiologists, neurophysiologists, microbiologists, pharmacologists, etc., before the accumulation of narrowly evocative designations may overwhelm us.

C.M. was supported by the American Cancer Society Grant IM653 and is a Clayton Foundation Investigator. D.K. was supported by USPHS Training Grant GM07752-15 and ACS IM653.

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