An endogenous monocarboxylate transport in Xenopus laevis oocytes

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Tosco, M., M. N. Orsenigo, G. Gastaldi, and A. Faelli. An endogenous monocarboxylate transport in Xenopus laevis oocytes. Am J Physiol Regulatory Integrative Comp Physiol 278: R1190–R1195, 2000.—We investigated the existence of an endogenous system for lactate transport in Xenopus laevis oocytes. 36Cl-uptake studies excluded the involvement of a DIDS-sensitive anion antiporter as a possible pathway for lactate movement. L-[14C]lactate uptake was unaffected by superimposed pH gradients, stimulated by the presence of Na+, in the incubating solution, and severely reduced by the monocarboxylate transporter inhibitor p-chloromercuribenzenesulphonate (pCMBS). Transport exhibited a broad cation specificity and was cis inhibited by other monocarboxylates, mostly by pyruvate. These results suggest that lactate uptake is mediated mainly by a transporter and that the preferred anion is pyruvate. [14C]pyruvate uptake exhibited the same pattern of functional properties evidenced for L-lactate. Kinetic parameters were calculated for both monocarboxylates, and a higher affinity for pyruvate was revealed. Various inhibitors of monocarboxylate transporters reduced significantly pyruvate uptake. These studies demonstrate that Xenopus laevis oocytes possess a monocarboxylate transport system that shares some functional features with the members of the mammalian monocarboxylate cotransporters family, but, in the meanwhile, exhibits some particular properties, mainly concerning cation specificity.

Xenopus oocytes; lactate transport; pyruvate transport

XENOPUS OOCYTES ARE USED EXTENSIVELY FOR FUNCTIONAL EXPRESSION OF HETEROLOGOUS PROTEINS. THIS EXPERIMENTAL MODEL HAS PROVEN TO BE ESPECIALLY VALUABLE IN CLONING TRANSPORT SYSTEMS THAT MEDIATE UPTAKE OF IONS, SUGARS, AMINO ACIDS, AND OTHER NUTRIENTS (30). MOREOVER, XENOPUS OOCYTES HAVE BEEN SHOWN TO POSSESS A VARIETY OF ENDogenous TRANSPORT MECHANISMS FOR SEVERAL IMPORTANT SUBSTRATES (1, 5, 23, 31–34). Because the presence of endogenous transport systems could interfere with the analysis of heterologous functions, the endogenous characteristics should be carefully evaluated before starting an expression cloning project.

In studies designed to examine the possibility of using oocytes to express a heterologous transport system for lactate, we observed that oocytes have an endogenous mechanism for lactate uptake, as described in the present report. It is well known that these cells have very low pyruvate kinase activity and make little pyruvate and lactate through glycolysis (12). Nevertheless, oocytes do contain significant pyruvate and lactate levels; moreover, they develop better in media containing pyruvate or lactate as their carbon source (11). These observations could account for the presence of a lactate (or pyruvate) transport system in oocyte cell membranes that has not been investigated up to now.

Many mammalian cells are able to transport monocarboxylates across their plasma membrane. In general, three pathways for monocarboxylate transport have been described: 1) transport via a specific pH-dependent process mediated by a family of H+-monocarboxylate cotransporters (MCTs), 2) exchange with inorganic anions via anion exchange proteins, and 3) free diffusion of the undissociated acid (25). Aim of this work was to investigate the endogenous mechanism of lactate transport evidenced in Xenopus oocytes and, if a transporter is present, to search whether it shares any functional properties with the known isoforms encoded by MCT gene family.

METHODS

Xenopus oocytes. Portions of the ovaries of mature Xenopus laevis (Rettili di Schnaider, Varese, Italia) were removed under anesthesia (immersion in a 0.1% solution of ethylaminoazobenate under hypothermia), and small clumps of oocytes (stages 5 and 6 of maturation) were separated out with fine forceps in Ca2+-free ORII solution [(in mM): 82.5 NaCl, 2 KCl, 1 MgCl2, and 10 HEPES/Tris buffer, pH 7.5]. Oocytes were then defolliculated by gentle agitation for 60–90 min in ORII solution containing 1 mg/ml collagenase (type I D, Fluka). Oocytes of stages 5–6, after washing with ORII, were allowed to recover for 2 days at 18°C in modified Barth’s solution [(in mM): 88 NaCl, 1 KCl, 0.82 MgSO4, 0.41 CaCl2, 0.33 Ca(NO3)2, 2.4 NaHCO3, and 10 HEPES/Tris, pH 7.5] added with 3 mM Na pyruvate and 0.01 mg/l gentamicin with a daily change of medium and removal of damaged oocytes.

Isotope experiments. To measure uptake of either 36Cl (3.5 MBq/ml, Amersham), L-[14C(u)]lactate (6.46 GBq/mmol, NEN, Boston, MA), or [32P(u)]pyruvate (0.614 GBq/mmol, NEN), oocytes were incubated for 60–240 min in 120 µl solution 1 [(in mM): 100 NaCl, 2 KCl, 1 CaCl2, 1 MgCl2, and either 10 HEPES/Tris buffer, pH 7.5, or 10 MES/Tris buffer, pH 6.0] added with 1 mg/ml BSA and either trace amounts of 36Cl (final activity 0.14 MBq/ml), 0.5 mM L-lactate plus trace amounts of L-[14C]lactate (final activity 55 kBq/ml), or 0.5 mM pyruvate plus trace amounts of [32P]pyruvate (final activity
in the oocyte membrane, then transport of L-lactate
quent experiments. If a proton-lactate symport works
150-min incubation was selected once again for subse-
uptake was linear up to 240 min (not reported), a
experiments were performed. Because 0.5 mM L-lactate
for lactate movement.
DIDS (data not shown), thus excluding the presence of
some endogenous Cl

for the subsequent experiments, an incubation time of
150 min was selected. Oocytes of
Xenopus laevis exhibit
endogenous Cl
transport that is not inhibited by DIDS (data not shown), thus excluding the presence of
a DIDS-sensitive anion antiport as a possible pathway
for lactate movement.

To explore further the presence of a carrier-mediated
transport system for lactate, L-[14C]lactate uptake ex-
periments were performed. Because 0.5 mM L-lactate
uptake was linear up to 240 min (not reported), a
150-min incubation was selected once again for subse-
quent experiments. If a proton-lactate symport works
in the oocyte membrane, then transport of L-lactate
would be expected to be pH dependent. Fig. 1 shows the
effect of varying the incubation medium pH on the
uptake of 0.5 mM L-lactate. Decreasing buffer pH at 6.0
does not affect lactate uptake. In the same set of
experiments, we examined the effect of replacing Na
in the incubation medium with an equimolar concentra-
tion of tetramethylammonium (TMA

between TMA
and Na
conditions.

RESULTS

In mammalian cell membranes, lactate transport can
occur via the anion exchange system (25). Therefore,
initial experiments examined whether Xenopus oocytes
possess a Cl
––HCO
3
antiport mechanism. Incubating
oocytes with
Cl
showed linear uptake of the substrate
with time for at least 180 min (not reported). Therefore,
for the subsequent experiments, an incubation time of
150 min was selected. Oocytes of Xenopus laevis exhibit
some endogenous Cl
transport that is not inhibited by
DIDS (data not shown), thus excluding the presence of
a DIDS-sensitive anion antiport as a possible pathway
for lactate movement.

To investigate substrate specificity, we tested the
effect of various monocarboxylates (sodium salts) on
l-lactate transport by incubating the oocytes in a buffer
containing the different anions at a concentration of
5 mM (Fig. 3). The control condition was performed in

Fig. 1. Effect of an inwardly directed proton gradient on endogenous
l-lactate uptake in presence and in absence of Na
. Oocytes were
incubated in solution 1 added with 0.5 mM l-lactate and trace
amounts of l-[14C]lactate at pH 7.5 or 6.0. In tetramethylammonium
(TMA
) conditions, NaCl was isosmotically substituted by TMA-Cl in
incubating solution. Values are means ± SE. *Significant difference
between TMA
and Na
conditions.

Fig. 3. Cis inhibition of l-lactate uptake by other monocarboxylates.
Oocytes were incubated in solution 1 added with trace amounts of
l-[14C]lactate and 5 mM NaCl or Na-l-lactate, Na-acetate, Na-propionate,
Na-butyrate, or Na-pyruvate. Values are means ± SE. With exception of
acetate, all monocarboxylates exert a statistically significant inhibition
of l-lactate uptake. ns, Not significant.
the presence of 5 mM NaCl added to the incubation medium. With respect to the control, acetate had no effect, butyrate, propionate, \( \text{d}-\text{lactate}, \) and \( \text{l}-\text{lactate} \) reduced the uptake by 41\%, 37\%, 26\%, and 50\%, respectively. However, the most remarkable cis inhibition was obtained in the presence of pyruvate, which reduced lactate uptake to a greater extent (75\%) than \( \text{l}-\text{lactate} \) itself. These results suggest that the transport system exhibits a broad substrate specificity for monocarboxylates and that the preferred anion among those tested is pyruvate.

Actually, cis-inhibition experiments provide evidence that the tested anions bind in a competitive manner to the \( \text{l}-\text{lactate} \) transport site, inhibiting its translocation, but this does not necessarily mean that they are transported as well. To get more insight on this point, we studied the uptake of pyruvate in the same experimental conditions set up for \( \text{l}-\text{lactate} \) and using the same incubation time, based on the finding that the time dependence of pyruvate transport was linear over 150 min (not reported). As shown in Fig. 4, the rate of pyruvate uptake is unaffected when the extracellular pH is lowered from 7.5 to 6.0, thus excluding a proton-dependent transport; once again the presence of Na\(^+\) exerts a stimulatory effect. By substituting Na\(^+\) with other monovalent cations (Fig. 5), the uptake decreases significantly, but a stronger reduction is evident in the presence of pCMBS. Cis inhibition by various monocarboxylates at an extracellular concentration of 5 mM is shown in Fig. 6. By comparing these results with the ones of Fig. 3, smaller percentages of inhibition are apparent; nevertheless these results support our previous data, confirming that the transport system functions primarily as a pyruvate carrier and accepts also \( \text{l}-\text{lactate} \) and butyrate.

To characterize this system, classical inhibitors of monocarboxylate transport in mammalian cells (13, 25) were tested, and results are reported in Table 1. All the tested substances exert an inhibitory action on pyruvate uptake; the most effective is \( \alpha \)-cyano-4-hydroxycinnamamide (\( \alpha \)-CnCN) followed by phloretin and 3-isobutyl-1-methylxanthine (IBMX).

![Fig. 4](image1.png)

**Fig. 4.** Effect of an inwardly directed proton gradient on endogenous pyruvate uptake in presence and in absence of Na\(^+\). Oocytes were incubated in solution 1 added with 0.5 mM pyruvate and trace amounts of \( { }^{14} \text{C} \)pyruvate at pH 7.5 or 6.0. In TMA\(^+\) conditions, NaCl was isosmotically substituted by TMA-Cl in incubating solution. Values are means ± SE. *Significant difference between TMA\(^+\) and Na\(^+\) conditions.

![Fig. 5](image2.png)

**Fig. 5.** Effect of monovalent cations on pyruvate uptake into oocytes. Oocytes were incubated either in solution 1 added with 0.5 mM pyruvate and trace amounts of \( { }^{14} \text{C} \)pyruvate or in same solution in which 100 mM NaCl was substituted by 100 mM TMA-Cl or KCl, CsCl, or LiCl. When added, pCMBS was 1 mM. Values are means ± SE. In presence of Na\(^+\), pyruvate uptake is significantly higher than all other uptake values.

The basic transport parameters were determined for both lactate (Fig. 7) and pyruvate (Fig. 8). A \( K_m \) value of 6.74 ± 0.78 mM and a \( J_{\text{max}} \) of 681 ± 24 pmol⋅oocyte\(^{-1} \cdot \text{h} \) were calculated for \( \text{l}-\text{lactate} \), whereas kinetic parameters for pyruvate were \( K_m = 3.78 ± 0.51 \text{mM} \) and \( J_{\text{max}} = 391 ± 18 \text{pmol} \cdot \text{oocyte}^{-1} \cdot \text{h}^{-1} \) (\( r^2 = 0.992 \)). In both cases, when the data were transformed and plotted according to Eadie Hofstee, only one component was visible (Figs. 7, inset, and 8, inset).

**DISCUSSION**

Xenopus laevis oocytes have been extensively used to assess the functional properties of heterologous MCTs; in the course of these studies an endogenous lactate uptake was evidenced by some authors (3, 4, 22), even if smaller than the background transport found in mammalian cell lines (27). To date, however, the characterization of endogenous \( \text{l}-\text{lactate} \) transport systems has not been published.

Uptake of monocarboxylates could occur by nonionic diffusion of the undissociated acid or could be mediated...
by a transporter such as MCT or anion exchange protein (25). These three pathways can be distinguished by their properties: MCTs distinguish between the stereoisomers of lactate, transport monocarboxylates, but not dicarboxylates and are inhibited by pCMBS or α-CnCN (25). Anion exchange proteins catalyze the exchange of anions such as Cl\(^-\), HCO\(_3\^-\), monocarboxylates, and dicarboxylates; they do not distinguish between L- and D-lactate and are selectively inhibited by disulfonic stilbenes (SITS and DIDS) (10), whereas free diffusion of the undissociated acid would not be expected to be sensitive to inhibitors.

As a first step, we investigated the presence of an anion exchanger in the oocyte membrane. Previous works suggested that oocytes lack this antiport (14, 16, 18), but a great variability in the appearance of different transport systems in Xenopus oocytes has been reported (24, 32). The precise cause of the variability in expression of endogenous transport mechanisms is unknown but may have to do with subtle, as yet undetermined, environmental factors. However, a Cl\(^-\) transport is apparent that is not inhibitable by stilbene disulfonates. This finding confirms the absence of an anion exchange system, thus excluding this mechanism as a possible pathway for lactate influx. The small Cl\(^-\) influx evidenced could be ascribed to an Na\(^+\)-K\(^+\)-2Cl\(^-\) cotransport, described in Xenopus oocytes (32), as well as to Ca\(^{2+}\)-activated Cl\(^-\) channels (15).

Lactate movement was further studied by means of L\([\text{14C}]\)-lactate uptake. Uptake of 0.5 mM lactate exhibited the same order of magnitude as other data reported in the literature for background transport (3, 4) and was linear with time for at least 180 min (r = 0.998), as already observed for Cl\(^-\). No binding component was evident. The linearity with time for several hours is not surprising because of the large size of an oocyte, and similar findings were observed in the uptake of other substrates by Xenopus oocytes (23, 28, 34). It is well known that oocytes of stages 5–6 are characterized by a modest activity of many, perhaps all, transport systems; however, transport proceeds with more or less constant rates for many hours (14, 16, 18, 31). Shorter times of linearity have been reported (3, 4), but only after injection of cRNA coding for heterologous MCTs, that expressed much higher uptake rates of lactate.

To identify the driving forces for transport, lactate uptake was measured both in the presence of Na\(^+\) and in a medium in which Na\(^+\) was replaced with TMA\(^+\), either at pH 7.5 or at pH 6.0 (Fig. 1). It is known that a disequilibrium distribution of H\(^+\) ions is present across the cell membrane of Xenopus oocytes (5); from energetic considerations, an equilibrium internal pH (pH\(_{\text{in}}\)) value near 6.25 has been calculated, whereas the observed pH\(_{\text{in}}\) steady-state value is ~7.45. Na\(^+\)/H\(^+\) exchanger was indicated as the principal H\(^+\) extrusion mechanism, and a proton conductance, if present, seems to be of negligible importance (5). It has been reported that when external pH is shifted to acidic values, oocytes reach a steady-state pH, that remains constant for ~21 h (6); when pH\(_{\text{H}}\) is set at 6.0, pH\(_{\text{H}}\) equilibrates at ~7.29 (37). The above considerations indicate that the preset experimental condition is useful for our investigation. Moreover, to confirm that the imposed pH gradient between external medium and cells keeps constant, we measured external pH after 150 min of incubation, without obtaining any

### Table 1: Effect of different inhibitors on pyruvate uptake

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>pmol/Oocyte</th>
<th>n</th>
<th>% Inhibition</th>
</tr>
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<tbody>
<tr>
<td>None</td>
<td>158 ± 13</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>IBMX</td>
<td>48 ± 5</td>
<td>23</td>
<td>69</td>
</tr>
<tr>
<td>NaSCN</td>
<td>118 ± 11</td>
<td>21</td>
<td>25</td>
</tr>
<tr>
<td>DIDS</td>
<td>120 ± 6</td>
<td>30</td>
<td>24</td>
</tr>
<tr>
<td>α-CnCN</td>
<td>27 ± 2</td>
<td>22</td>
<td>83</td>
</tr>
<tr>
<td>Phloretin</td>
<td>43 ± 6</td>
<td>22</td>
<td>73</td>
</tr>
<tr>
<td>Quercetin</td>
<td>120 ± 9</td>
<td>20</td>
<td>24</td>
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</tbody>
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Values are means ± SE for Xenopus oocytes [number (n)]. The oocytes were incubated in solution 1 added with 0.5 mM pyruvate, trace amounts of [\text{14C}]pyruvate and 3 mM 3-isobutyl-1-methylxanthine (IBMX) or sodium thiocyanate (NaSCN), α- cyano-4-hydroxycinnamate (CnCN), quercetin, 2 mM phloretin, or 0.1 mM DIDS. Results are all statistically different from the absence of inhibitor.

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L-Lactate uptake was unaffected by alteration of the pH, indicating no role of transmembrane pH gradients. On the contrary, the presence of Na+ increased lactate uptake, with respect to its substitution with TMA+, K+, Rb+, Cs+, and Li+ (Figs. 1 and 2). Experiments involving cation substitution in the outer solution and lasting 2 h or more have been frequently reported in the literature (14, 16, 31), and the uptake of some compounds was unaltered by these ion substitutions after 120–210 min of incubation (1, 23). Therefore, the reduced lactate uptake should not reflect long-term metabolic or toxic effects, but rather a direct effect of the cation substitution on transport; moreover, lactate uptake was significantly reduced by pCMBS in the presence of both Na+ and K+ (Fig. 2). It has been reported that in Xenopus oocytes, the ratio between Na+ and K+ permeabilities is about 0.1; actually the membrane potential is mainly imposed by a K+ current (7). Moreover, the kinetic studies reported in Fig. 7 give no evidence for a lactate anion diffusion. These observations allow us to exclude an involvement of electric effects on Na+ stimulatory action. This point is strengthened by the inhibition exerted, both in the presence of Na+ and K+, by pCMBS, which is a well-known inhibitor of monocarboxylate transport, suggesting that lactate uptake is mediated mainly by a transporter. These results indicate that the transport system in oocyte is pH independent and cation stimulated, with the maximal stimulation exerted by Na+. Thus an interesting difference arises between mammalian cells and Xenopus oocytes with regard to lactate uptake. In fact, in mammalian cell lactate is transported by monocarboxylate-H+ or -Na+ cotransporters (25), and in the latter case, the stimulation is strictly specific for Na+ over other cations (2, 17, 20). Nonionic diffusion of the undissociated acid, however, might be responsible for the small amount of lactate uptake insensitive to pCMBS (Fig. 2), because lactic acid (pKₐ 3.9) is highly lipid soluble and equilibrates readily across the membranes. Nevertheless, the possibility of incomplete inhibition by pCMBS cannot be ruled out.

The substrate specificity has been extensively explored using competition experiments, and, as indicated in Fig. 3, other monocarboxylates are transported into Xenopus laevis oocytes coupled with Na+. Despite differences in animals and experimental protocols, there is remarkable agreement with data reported in the literature regarding monocarboxylate transporter selectivity: a wide range of monocarboxylates inhibit lactate transport (17, 25, 29). Moreover, the stereospecific transport of L-lactate over D-lactate is in good agreement with that of other monocarboxylate transporters (8, 9, 25).

Data of Figs. 3–6 give evidence that pyruvate is the favorite substrate of the oocyte transport system, which translocates this anion with a pattern of functional properties overlapping the one evidenced for lactate. The smaller cis-inhibitory effect of D-lactate and propionate on pyruvate uptake with respect to L-lactate uptake (Figs. 3 and 6) could be in agreement with a preferential binding of the transporter to pyruvate. This hypothesis was confirmed by the kinetic studies reported in Figs. 7 and 8. Uptake of both L-lactate and pyruvate was saturable and fitted to simple Michaelis-Menten kinetics. As expected, Xenopus laevis oocyte transporter handles pyruvate with a slightly higher affinity for pyruvate compared with L-lactate.

The data presented in this paper propose that both lactate and pyruvate are transported across the plasma membrane of Xenopus laevis via a cation-activated monocarboxylate transporter. This transport system could play a special physiological role, introducing into the oocyte pyruvate and lactate that could act both as oxidizable fuel and/or as a carbon source in the glycolytic direction. Clear evidence has emerged that non-ionic diffusion might account for an insignificant fraction of monocarboxyate uptake: uptake is stimulated by cations, mainly by Na+, is a saturable function of both lactate and pyruvate concentration, is cis inhibited by other monocarboxylates, and inhibited to a similar extent by pCMBS and other well-known inhibitors of monocarboxylate transporters, such as α-CN, phloretin, and IBMX. Furthermore, kinetic studies yielded evidence that the diffusion component of both lactate and pyruvate transport is barely detectable and not statistically different from zero.

The presence of an MCT family with several members has recently been confirmed by the cloning and sequencing of eight mammalian isoforms (21). Among the MCT isoforms, there are diversities in kinetics, substrate, and inhibitor characteristics. These differences have led some authors (19, 27, 35) to propose that the properties of MCT isoforms are related to the metabolic requirement of the tissue in which they are expressed and may partially reflect the ability of MCT to interact specifically with other membrane proteins (25). It remains to be resolved whether, in Xenopus laevis oocytes, the monocarboxylate handling could be mediated by one of the several, recently cloned but not quite functionally characterized, MCT isoforms (27). The results presented here provide evidence that Xenopus oocyte membranes possess a monocarboxylate transport system that shares some features with the members of the MCT family described in mammalian cells. Uptake of L-lactate and pyruvate by Xenopus oocytes was found to be sensitive to the presence of known inhibitors of mammalian MCTs (see Table 1); the systems are closely related also with respect to substrate specificity and kinetic parameters. The major difference between mammalian cells and Xenopus oocytes is the cation dependency; as a matter of fact, whereas MCTs are strictly H+ or Na+ dependent, the oocyte transporter appears to be activated by Na+ and not by proton gradients, but, unexpectedly, it exhibits a broad cation specificity.

Perspectives

Because of similar functional properties as mammalian systems, Xenopus laevis oocyte transporter may be presumed to have some degree of sequence identity to
mammalian MCTs. However, studies are currently under way to perform the molecular characterization of the oocyte monocarboxylate transporter, because the difference between the endogenous uptake system and the ones of mammalian cells with respect to cation specificity seems indeed to provide evidence for a distinct transport mechanism in oocytes.

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