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RESEARCH ARTICLE

Lacosamide effects on placental carriers of essential compounds in comparison with valproate: Studies in perfused human placentas

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Abstract

Objective: Lacosamide is increasingly being prescribed to pregnant women, although its effects on the developing fetus have not been fully clarified yet. Previously, we have shown that several antiseizure medications, particularly valproate, can affect the expression of carriers of essential compounds in placental cells. Here, our aim was to assess the effect of short ex vivo exposure of human placentas to lacosamide on the expression of carriers of essential nutrients required by the human fetus.

Methods: Placentas were obtained from cesarean deliveries of women with no known epilepsy. Cotyledons were cannulated and perfused over 180 min in the presence of lacosamide at 2.5 μg/ml (10 μmol·L^{-1}, $n = 7$) or 10 μg/ml (40 μmol·L^{-1}, $n = 6$), representing low and high therapeutic concentrations, respectively, in the maternal perfusate. Valproate (83 μg/ml, 500 μmol·L^{-1}, $n = 6$) and the perfusion solution ($n = 6$) were used as the respective positive and negative controls. A customized gene panel array was used to analyze the expression of carrier genes in the perfused cotyledons.

Results: Following a 3-h perfusion, the mRNA expression of *SLC19A1* (encoding the reduced folate carrier 1) was downregulated in placentas treated with 10 μg/ml lacosamide (50%) as compared with the vehicle ($p < .05$). Across all groups, a significant difference was observed in the expression of *SLC19A3* (thiamine transporter 2; 52%, 20%, and 9% decrease by 10 μg/ml lacosamide, 83 μg/ml valproate, and 2.5 μg/ml lacosamide, respectively; $p < .05$).

Significance: Lacosamide at high therapeutic concentrations exerted pharmacological effects on the human placenta. Our findings, if manifested in vivo, suggest that lacosamide could potentially affect folate supply to the fetus and support therapeutic monitoring and careful adjustment of lacosamide plasma concentrations during pregnancy.

Michal Kovo and Sara Eyal contributed equally to the article.

KEYWORDS
antiepileptic drugs, antiseizure medications, folic acid, pregnancy, teratogenicity, valproic acid

1 | INTRODUCTION

Lacosamide, a synthetic derivative of the amino acid D-serine, was approved by the US Food and Drug Administration for use in epilepsy in 2008.[1] Over the past years, lacosamide has been increasingly prescribed as an add-on treatment for pregnant women, although its teratogenicity potential and its neurodevelopmental effects have not been clearly established.[2,3] Lacosamide shares with valproate the ability to induce histone hyperacetylation, which has been suggested as a mechanism of valproate teratogenicity.[4,5] However, the effects of valproate and lacosamide on histone acetylation are mediated by distinct mechanisms.[6–8]

In a series of in vitro, ex vivo, and in vivo studies, we have consistently demonstrated that the placenta is an important target of antiseizure medications (ASMs).[8–13] Specifically, several ASMs are capable of interfering with the expression of placental uptake carriers that mediate the transfer of essential compounds from maternal blood to fetal circulation and of efflux carriers that restrict the distribution of noxious compounds to the fetus. In our comparative studies, valproate, the most teratogenic ASM,[14] was also the drug that exerted the highest magnitude of effect on placental carrier expression.[8,11,13] Exposure of the human placentas to valproate resulted in significant downregulation of carriers of folate (57% decrease), glucose (48%), choline (36%), and thyroid hormones (44%).[10] Here, our goal was to assess lacosamide effects on key carriers in the human placenta, in comparison with those of valproate, which was included in the current study as a positive control. Lacosamide concentrations in this study reflected the suggested serum reference range of 2.5–10 μg/ml (10–40 μmol·L^{-1}), which was found to be well tolerated by the majority of adult patients.[15]

Key Points

- The effects of lacosamide on placental carriers of compounds essential for fetal development were studied in perfused human placentas
- Lacosamide altered the expression of carriers of folate and thiamine
- The effects of lacosamide on placental carrier expression were concentration-dependent
- Until clinical data are available, caution may be advised upon prescribing high therapeutic lacosamide doses to pregnant women

2 | MATERIALS AND METHODS

2.1 | Placental collection

The study was approved by the Edith Wolfson Medical Center Helsinki Committee (protocol 0040-10-WOMC), and written informed consent was obtained from participants prior to delivery. All procedures were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975 (as revised in 1983). We included healthy women who underwent elective cesarean delivery and gave their consent for participating in the study. Excluded women were those with multiple pregnancies (i.e., pregnancies with more than one fetus), known chronic diseases such as diabetes mellitus and chronic hypertension, or epilepsy. Placentas were obtained immediately after delivering the fetus and were transferred to the placental research laboratory within 10 min, in an isotonic sodium chloride solution.

2.2 | Perfusion of placental cotyledons

The perfusion experiments were performed at the placental laboratory at the Wolfson Medical Center under the supervision of M.K. using the method of Schneider et al.[16] as previously described by us[10,17] with few modifications. Briefly, the placental perfusion apparatus consisted of two independent perfusion circuits, representing the maternal and the fetal compartments, that individually maintained at stable temperature, pH, and flow rates during the dual-perfusion procedure (Figure 1A). An intact cotyledon, without visible tears on the maternal side, was selected from a peripheral zone of the placenta and was cannulated with the fetal artery and vein within 30 min after delivery. The cotyledon was then mounted in the perfusion chamber, and three blunt needles were introduced into the intervillous space of the lobe corresponding to the perfused isolated cotyledon (Figure 1B). An open circulation of 30 min was established using heparinized Krebs–Ringer solution (1000 ml, Teva) followed by further 30 min perfusion with tissue culture medium M199 (Sterile Earle's salt base with L-glutamate, Biological Industries) supplemented with 3 g/L bovine serum albumin, 1 g/L glucose, 10 IU/ml heparin, and 48 μg/ml gentamicin for both maternal and fetal circuits.

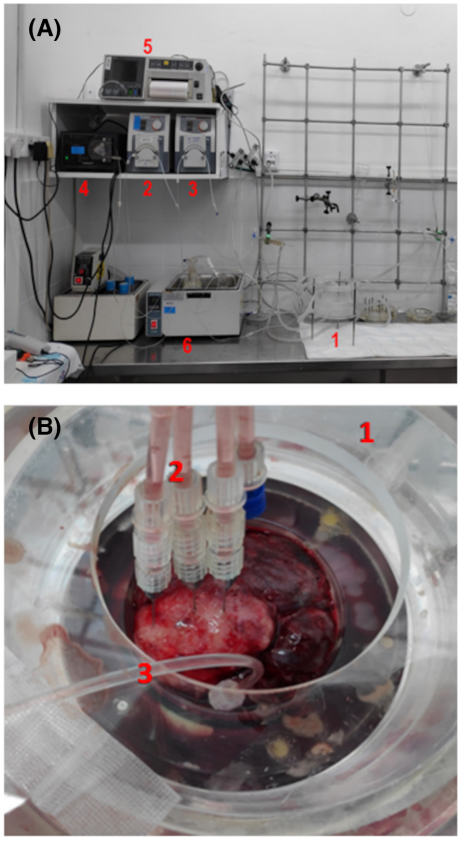

FIGURE 1 The human placental perfusion system, illustrating the methodology used for exposing placentas to the study drugs. (A) The perfusion apparatus. The apparatus consisted of independent maternal and fetal circuits. Shown are a perfusion chamber (1), the maternal perfusion pump (2), the fetal collecting pump (3), the maternal collecting pump (4), a continuous fetal monitor for tracking the stability of the fetal perfusion pressure (5), and a heating water bath (6). (B) A representative perfused cotyledon. The cotyledon was placed in a preheated perfusion chamber (1) with the maternal side facing upwards. The maternal perfusion pump (2) drove the flow of media toward the intervillous space of the cotyledon via three needles mimicking maternal arteries. Note the color differences between the cotyledon undergoing perfusion (to which the needles are connected; brighter) and the rest of the placental tissue. The maternal venous collecting pump (3) collected spillover from the placental tissue inside the chamber toward the maternal media in a closed circuit. The fetal circulation in the cotyledon was established through a branch of an umbilical artery and vein (not shown).

The perfusion experiment was performed in a close circuit after both maternal and fetal media were replaced. The following compounds were added to the maternal perfusate: sodium valproate, dissolved in double distilled water (83 μg/ml, 500 μmol·L^{-1}, Sigma-Aldrich, $n = 6$); lacosamide (2.5 μg/ml, 10 μmol·L^{-1}, $n = 7$; and 10 μg/ml, 40 μmol·L^{-1}, $n = 6$), prepared from Solution for Infusion (Aesica Pharmaceuticals). For the control group ($n = 6$), no vehicle was added to the perfusate, given that the exact composition of the lacosamide vehicle is unknown and that the proportion of the vehicle was negligible (1 ml in a total perfusate volume of 1 L). Samples from both maternal and fetal perfusates were collected at 90 and 180 min throughout the experiment.

At the end of the 180-min perfusion experiment, a bolus of 2.5 mg prostaglandin E2 (PGE_2; dinoprostone, Pfizer) was added to the fetal arterial side, and the fetal vasculature response was recorded. The cotyledon was weighed, and 200–300-mg tissue samples were collected for evaluation of carrier expression. All tissue samples were stored at −80°C until analysis. In addition, 1.5-ml perfusate samples were collected at the end of the experiment from the fetal and the maternal reservoirs for transplacental transfer analysis. Samples were stored until analysis at −80°C.

2.3 | Total RNA extraction

Small tissue pieces of up to 30 mg each (coefficient of variation < 10%) were cut out of each placental tissue sample with a sterile ice-cold blade. Samples were then washed two times with cold phosphate-buffered saline to remove remnants of blood and perfusate. Total mRNA was isolated using the RNeasy mini kit (Qiagen). The small pieces were placed into 2-ml Eppendorf tubes containing mixed-sized stainless-steel beads and homogenized according to the instructions of the kit's manufacturer using the Bullet Blender Homogenizer (Next Advance). RNA integrity and purity were verified by ND-1000 spectrophotometer (NanoDrop Technologies) based on ratios of absorption at 260/280 nm and 260/230 nm. Mean and range values were 2.09 (2.08–2.10) and 2.08 (2.01–2.17), respectively.

2.4 | Gene expression assays

Expression across a predefined gene array was conduct using the nCounter gene expression assay (NanoString Technologies), which captures and counts individual mRNA transcripts.[18] Briefly, for each gene of interest, a probe library is made with a capture probe, which contains a sequence complementary to a particular target mRNA plus a short common sequence coupled to an affinity tag, and a reporter probe, coupled to a color-coded tag. Unique pairs of capture and reporter probes detect transcripts for each gene of interest.[18] The analysis was conducted by the same external provider as in our previous perfusion study,[8] using mRNA samples with no treatment group identifiers. Raw gene expression data were normalized by the geometric mean of spikes in positive control probes and by the geometric mean of three housekeeping genes: hypoxanthine phosphoribosyl transferase 1, TATA-box binding protein, and β-actin. Samples with normalized count < 50 were considered below the limit of detection and were

excluded from the analysis. Changes in the levels of target gene expression from the treatment groups were further normalized to those of the control group. A hierarchically clustered heatmap of normalized digital counts was used to identify regions and targets with similar profiles.

Quantitative real-time polymerase chain reaction was used to validate the nCounter gene expression data for selected carriers as previously described.[8]

2.5 | Transplacental transfer analysis

Lacosamide serum concentrations in fetal and maternal perfusates were determined using the commercial Rufinamide, Felbamate and Lacosamide in Serum/Plasma–HPLC kit (Chromsystems Instruments & Chemicals) that includes the columns and reagents (e.g., the mobile phase). The analysis was conducted using a high-performance liquid chromatography (HPLC) LaChrom instrument (Merck-Hitachi) with photodiode array ultraviolet detection (Varian ProStar, SpectraLab Scientific). The lower limit of quantification of lacosamide was 1 μg/ml. All samples were tested using the same kit.

2.6 | Statistical analysis

The Kruskal–Wallis test, followed by Dunn posttest, was used to assert the statistical significance ($p < .05$) of the differences between experimental groups (InStat, GraphPad Software). Data are presented as median and interquartile range.

3 | RESULTS

3.1 | Pregnancy and placenta characteristics did not differ between treatment groups

Table 1 presents the clinical features of the pregnancies and placental cotyledons. All patients were treated with prophylactic antibiotics (cefazolin) 15 min before starting the cesarean section, as a routine departmental protocol. Vital signs were monitored in all women prior to delivery. All women in the study were Middle Eastern (Jewish and Arab).

Viability parameters of the studied placentas are presented in Table 2. The pH levels and fetal artery pressure levels of maternal and fetal perfusate were stable during the entire duration of the perfusion experiment, with no significant differences between the study groups ($p > .05$). Following PGE_2 administration to the fetal arterial line, similar increases in pressure was observed in all studied groups. The beta subunit of human chorionic gonadotropin was not detected in any of the fetal perfusates.

3.2 | Lacosamide alters the mRNA levels of placental carriers

Relative mRNA expression in the 25 placentas that were included in the study is presented as a heatmap (Figure 2A). The cluster analysis showed unique patterns of gene expression and coregulation by lacosamide and valproate. For instance, *SLC6A4* (encoding the serotonin transporter) was clustered together with *SLC19A3* (the thiamine transporter 2, *THTR2*), *SLC13A3* (the sodium-dependent dicarboxylate transporter), *SLC19A1* (the reduced folate carrier 1, *RFC1*), and *SLC43A2* (the L-type amino acid transporter 4, *LAT4*; boxed cluster), with similar lacosamide effects on their expression within each placenta (Figure 2B,C). Expression of *RFC1* was downregulated at high therapeutic lacosamide concentrations by 52% as compared with control placentas ($p < .05$). Across all groups, a significant difference was observed in the expression of *SLC19A3* (52%, 20%, and 9% decrease by 10 μg/ml lacosamide, 83 μg/ml valproate, and 2.5 μg/ml lacosamide, respectively; $p < .05$). These findings, along with comparisons with the other studied genes, are presented numerically in Table 3.

3.3 | Lacosamide crosses the placental barrier

Lacosamide, at both its low and high therapeutic concentrations, crossed the placental barrier from the maternal to fetal side following 3-h perfusion (Figure 3).

TABLE 1 Clinical characteristics of the studied groups

Treatment group	Control, $n = 6$	2.5 μg/ml lacosamide, $n = 7$	10 μg/ml lacosamide, $n = 6$	83 μg/ml valproate, $n = 6$
Maternal age, years	32.4 (31.1–39.4)	34.0 (29.2–38.2)	34.3 (31.6–34.8)	35.3 (33.1–36.7)
Gestational age, weeks	38.6 (38.2–39.1)	38.9 (38.3–39.8)	38.4 (37.8–39.1)	38.6 (38.4–38.7)
Birth weight, g	3324 (2966–3679)	3514 (3217–3686)	3104 (2527–3458)	3169 (2970–3645)
Cotyledon weight, g	25.9 (24.0–29.4)	23.5 (18.3–26.4)	26.9 (24.7–40.2)	25.7 (14.5–41.0)

Note: Data are presented as median and interquartile range. Sequential variables did not differ between the groups ($p > .05$, Kruskal–Wallis analysis).

TABLE 2 Viability parameters of the studied placentas

Parameter	Control, $n = 6$	2.5 μg/ml lacosamide, $n = 7$	10 μg/ml lacosamide, $n = 6$	83 μg/ml valproate, $n = 6$
pH level				
Maternal reservoir	7.39 (7.38–7.40)	7.39 (7.38–7.40)	7.39 (7.38–7.40)	7.39 (7.38–7.41)
Fetal reservoir	7.40 (7.38–7.41)	7.40 (7.39–7.41)	7.39 (7.38–7.40)	7.39 (7.38–7.40)
Pressure				
Experimental, mmHg	32 (22–50)	40 (32–51)	37 (25–46)	33 (27–44)
PGE_2 effect, % change[a]	76 (70–96)	64 (43–86)	75 (55–89)	84 (71–96)

Note: Data are presented as median and interquartile range.

Abbreviation: PGE_2, prostaglandin E_2.

[a]PGE_2 effect is the change in pressure induced by injection of 2.5 mg PGE_2 at the end of the perfusion experiment.

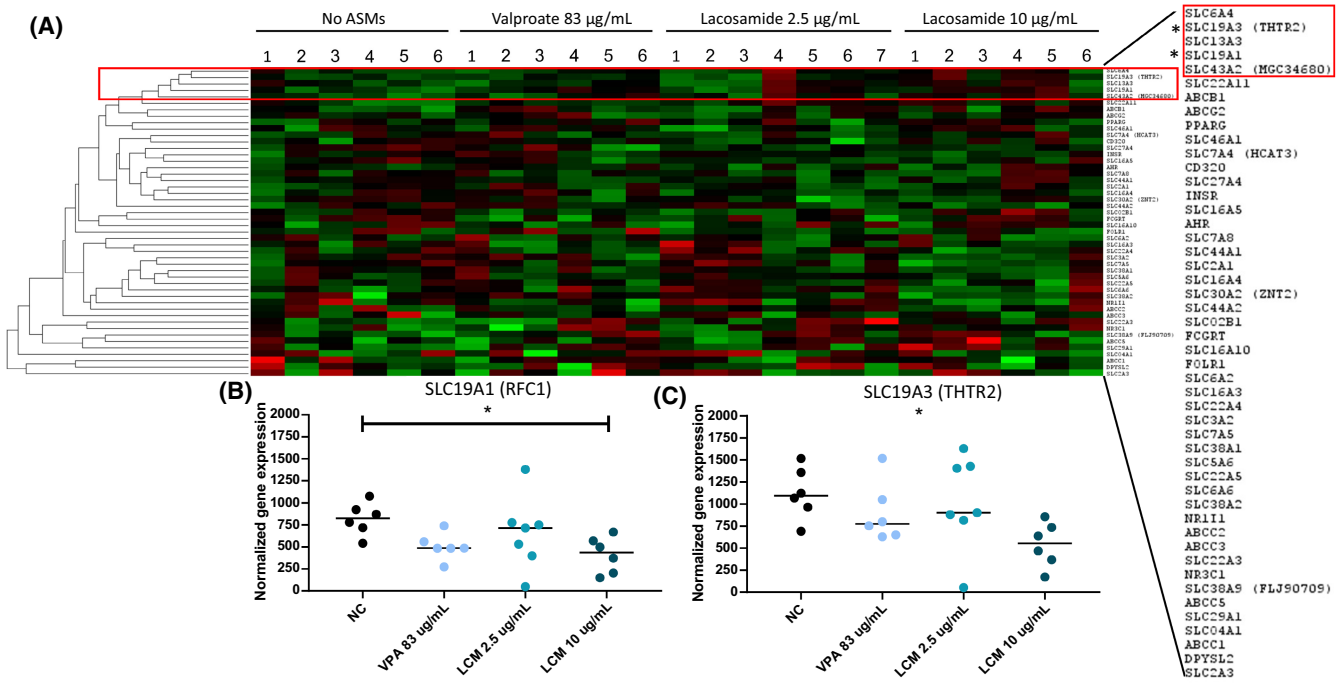

FIGURE 2 Effect of lacosamide on the expression of placental carriers and related targets (mRNA level), in comparison with valproate and with the negative control (no active compounds). (A) Hierarchically clustered heatmap of placental carrier mRNA expression, grouped by treatment. The heatmap was generated with data from all the studied placentas. Green and red represent lower and higher expression levels, respectively. The rectangle highlights an example of genes with associated expression patterns. The right part of the figure is an enlargement of the gene order. (B, C) Expression of selected genes. ASM, antiseizure medication; LCM, lacosamide; NC, negative control (no ASM supplementation to the perfusate); VPA, valproate. Asterisks denote genes significantly affected by the pharmacological treatments.

4 | DISCUSSION

Our findings demonstrate that lacosamide at high therapeutic concentrations can modulate key transport mechanisms at the human placenta. Lacosamide was not included in our initial studies because we prioritized comparisons across ASMs with established teratogenicity profiles. However, given the increasing use of lacosamide in pregnant women, the absence of clear teratogenicity data, and induction of histone acetylation by lacosamide, we aimed at assessing the effects of this ASM on the human placenta and comparing them with those of valproate.

Overall, the scope of lacosamide effects on placental carriers was narrower than that previously reported for valproate.[10] Fewer carriers were affected, in line with our previous findings in a placental cell line,[8,11,13] although this observation requires validation in a larger population. The effects of valproate were overall of lower magnitude in the current cohort compared with our previous study, but the trends were very similar, and the differences are attributable to the large between-subject and within-placenta variability in structure, blood flow, and gene expression.[10,19,20] In addition, the smaller group size in the current study was associated with lower power to detect

TABLE 3 Transcript levels in the perfused placentas

	2.5 μg/ml lacosamide	10 μg/ml lacosamide	83 μg/ml valproate	p_{total}
Placentas, *n*	7	6	6	
Gene symbol (protein)				
ABCB1 (P-gp)	80 (51–103)	51 (36–72)	59 (44–95)	>.05
ABCG2 (BCRP)	109 (71–140)	80 (68–91)	106 (86–152)	>.05
AHR	80 (47–97)	66 (43–88)	64 (42–87)	>.05
CD320 (TCN2R)	115 (64–144)	73 (61–99)	74 (65–83)	>.05
DPYSL2	104 (91–115)	106 (90–126)	106 (91–121)	>.05
FCGRT	134 (109–177)	96 (83–106)	145 (122–182)	>.05
FOLR1	116 (104–147)	100 (84–151)	80 (61–131)	>.05
INSR	82 (53–97)	90 (66–115)	82 (64–95)	>.05
NR1I1 (VDR)	75 (68–104)	173 (148–197)	174 (151–192)	>.05
NR3C1 (GR)	88 (63–105)	75 (64–86)	89 (75–110)	>.05
PPARG	92 (64–105)	81 (59–98)	83 (67–97)	>.05
SLC2A1 (GLUT1)	86 (64–92)	62 (40–81)	70 (57–109)	>.05
SLC2A3 (GLUT3)	104 (91–113)	89 (76–99)	112 (93–141)	>.05
SLC3A2 (LAT 4F2hc subunit)	85 (62–129)	99 (58–138)	91 (72–139)	>.05
SLC5A6 (SMVT)	79 (48–93)	91 (71–101)	91 (67–98)	>.05
SLC6A2 (NET)	98 (84–125)	108 (103–126)	97 (68–106)	>.05
SLC6A4 (SERT)	108 (86–120)[a]	69 (33–84)	101 (74–117)	>.05
SLC6A6 (TAUT)	59 (46–68)	92 (64–106)	87 (53–114)	>.05
SLC7A4 (HCAT3)	92 (58–102)	59 (47–65)	70 (39–88)	>.05
SLC7A5 (LAT1)	73 (54–96)	109 (91–112)	86 (65–96)	>.05
SLC7A8 (LAT2)	94 (64–108)	81 (34–94)	81 (43–94)	>.05
SLC13A3 (NADC3)	116 (102–146)[a]	68 (31–77)	112 (104–121)	>.05
SLC16A10 (MCT10)	98 (78–121)	73 (53–114)	113 (99–164)	>.05
SLC16A3 (MCT4)	88 (60–96)	87 (76–104)	110 (98–123)	>.05
SLC16A4 (MCT5)	87 (49–113)	71 (35–112)	70 (57–108)	>.05
SLC16A5 (MCT6)	104 (80–129)	88 (67–119)	102 (89–117)	>.05
SLC19A1 (RFC1)	93 (74–128)[a]	50 (28–62)	62 (50–69)	.030[b]
SLC19A3 (THTR2)	91 (80–107)	48 (25–56)	80 (71–100)	.041[b]
SLC22A11 (OAT4)	72 (42–94)	62 (43–70)	86 (77–101)	>.05
SLC22A3 (OCT3)	56 (23–87)	53 (32–68)	91 (45–127)	>.05
SLC22A5 (OCTN2)	84 (70–90)	101 (84–113)	97 (81–112)	>.05
SLC27A4 (FATP4)	114 (75–141)	106 (70–166)	115 (99–124)	>.05
SLC29A1 (ENT1)	91 (54–114)	68 (59–76)	92 (82–128)	>.05
SLC30A2 (ZNT2)	124 (91–135)	91 (54–102)	100 (89–107)	>.05
SLC38A1 (SNAT1)	89 (64–101)	103 (60–126)	97 (67–129)	>.05
SLC38A2 (SNAT2)	75 (61–83)	93 (69–113)	68 (47–96)	>.05
SLC38A9 (URLC11)	88 (68–101)	72 (60–82)	75 (58–89)	>.05
SLC43A2 (LAT4)	75 (50–91)	56 (47–60)	75 (69–83)	>.05
SLC44A1 (CTL1)	101 (82–120)	79 (55–94)	102 (72–118)	>.05
SLC44A2 (CTL2)	91 (63–119)	99 (74–113)	84 (62–99)	>.05

TABLE 3 (Continued)

	2.5 μg/ml lacosamide	10 μg/ml lacosamide	83 μg/ml valproate	p_{total}
SLC46A1 (PCFT)	126 (89–140)	82 (68–93)	92 (74–99)	>.05
SLCO2B1 (OATP2B1)	127 (116–136)	75 (68–87)[a]	117 (101–138)	>.05
SLCO4A1 (OATP4A1)	66 (39–102)	112 (87–169)	161 (131–191)	>.05

Note: Values are presented as percentage of control (mean values with minimum and maximum in brackets). Samples with normalized count < 50 were excluded. Low count values (<50) were obtained for three or more samples of *ABCC1*, *ABCC2*, *ABCC3*, and *ABCC5* (multidrug resistance-associated proteins 1, 2, 3, and 5, respectively) and *SLC22A4* (organic cation/carnitine transporter 1). These analyses are not shown. p_{total} indicates *p*-value across all groups by Kruskal–Wallis test. For *SLC19A3*, the post hoc Dunn multiple comparison test did not identify differences between pairs of groups. A statistically significant difference was found between lacosamide 10 μg/ml and controls in *SLC19A1* expression ($p < .05$).

Abbreviations: AHR, aryl hydrocarbon receptor; BCRP, breast cancer resistance protein; CTL, choline transporter-like; DPYSL, collapsin response mediator protein; ENT, equilibrative nucleoside transporter; FATP, fatty acid transporting protein; FCGRT, IgG Fc gamma receptor and transporter; FOLR, folate receptor; GLUT, glucose transporter; GR, glucocorticoid receptor; HCAT, cationic amino acid transporter; INSR, insulin receptor; LAT, L-type amino acid transporter; MCT, monocarboxylate transporter; NADC, sodium/dicarboxylate cotransporter; NET, norepinephrine transporter; OAT, organic anion transporter; OATP, organic anion transporting polypeptide; OCT, organic cation transporter; OCTN, novel organic cation transporter; PCFT, proton-coupled folate transporter; P-gp, P-glycoprotein; PPARG, peroxisome proliferator-activated receptor gamma; RFC, reduced folate carrier; SERT, serotonin transporter; SMVT, sodium-dependent multivitamin transporter; SNAT, sodium-coupled neutral amino acid transporter; TAUT, taurine transporter; TCN2R, transcobalamin II receptor; THTR, thiamine transporter; URLC, sodium-coupled neutral amino acid transporter; VDR, vitamin D receptor; ZNT, zinc transporter.

[a]One sample was excluded from the analysis due to low normalized count value.

[b]Statistically significant values.

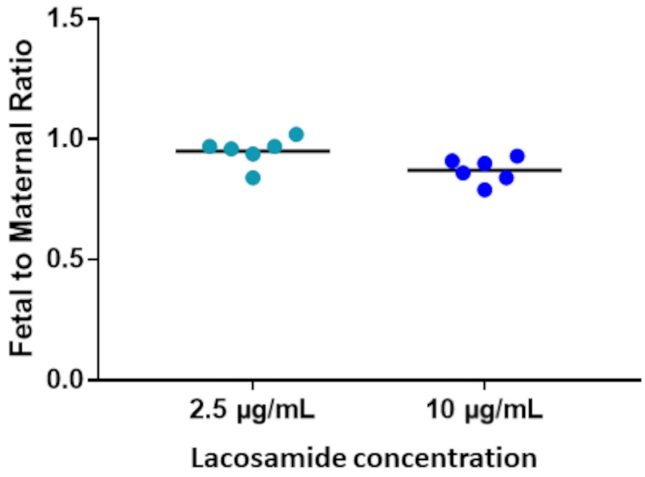

FIGURE 3 Lacosamide transfer across the placental barrier. Lacosamide concentrations were determined in perfusate collected after 3-h perfusion by high-performance liquid chromatography analysis

between-group differences. One common finding for both lacosamide (current study) and valproate (previous study and a trend in the current one) was downregulation of the key folate carrier RFC1 (Figure 2A,B). This effect is unlikely to be mediated by histone hyperacetylation, because previous studies provided hints that histone hyperacetylation is likely to upregulate RFC1 and not downregulate it.[21] Regardless of the putative mechanism, RFC1 downregulation might lead to decreased fetal folate with poorer pregnancy outcomes.[22–25] In addition to RFC1, the pharmacological treatment(s) significantly downregulated the expression of the thiamine carrier. Thiamine is a vitamin B essential for maintaining homeostasis and optimal metabolic processes whose deficiency can lead to neuronal dysfunction in the fetus.[26]

Lacosamide effects on the expression of placental carriers appeared to be concentration-dependent, manifesting at the higher end of the therapeutic range. These findings stress the need in therapeutic drug monitoring of lacosamide levels in pregnant women, particularly because dose modifications may be required along pregnancy. A recent study demonstrated that the dose-normalized concentrations of lacosamide were 40% lower during pregnancy as compared with postpartum levels,[27] similar to earlier observations.[28,29] In this context, our findings support therapeutic monitoring while adjusting lacosamide doses during pregnancy.

4.1 | Clinical translation

Our data suggest that lacosamide is well transferred to the fetus, which is not surprising given that it is a small, amphiphilic molecule that is likely to easily cross biological barriers. In addition, its volume of distribution is similar to the volume of total body water.[30] The concentrations of lacosamide in cord blood have not yet been reported, but are likely to be similar to those in maternal circulation. From a pharmacokinetic point of view, there is no reason to assume that lacosamide effects on the human placenta in vivo would differ significantly from those obtained ex vivo at similar concentrations. However, other factors, including gestational age, placental blood flow, and effects of concomitant medications and food supplements should be considered as well, complicating extrapolation to human pregnancies.

4.2 | Study strengths and limitations

Several limitations should be considered for this study in addition to the above-mentioned variability among and within placentas. First, the perfusions were performed using term placentas to enable efficient catheterization, complicating the extrapolation to earlier pregnancy stages in pregnant women. Nonetheless, changes in the activities of carriers of compounds that are involved in the development of the central nervous system and fetal growth (e.g., choline, glucose) are relevant during late pregnancy as well. Second, we performed placental perfusion over 3 h, which corresponds only to early changes in gene expression, to avoid decay in placental viability.[10,20,31] Our previous studies in placental BeWo cells have already predicted that longer exposure to lacosamide would have a modest effect, if any, on the expression of choline and heterodimeric transporters.[11,13] The results in the current study align with those findings. Third, our chromatographic methodology was not validated for body fluids other than serum or for tissues. Therefore, we report the findings of lacosamide concentrations in the perfusate semiquantitatively. For the same reason, we did not measure the placental concentrations of lacosamide. Nonetheless, the equilibrium in lacosamide concentrations across the placenta suggests that lacosamide may regulate carrier gene expression at both its maternal and fetal sides. Lastly, we did not evaluate the effects of lacosamide metabolites on carrier gene expression.

Despite the study limitations, our model has several advantages: the ex vivo studies were performed under controlled conditions that best mimic the exposure to lacosamide during pregnancy; we analyzed several samples from each placenta, thus partially overcoming the variability within placental tissue; we evaluated the effects of lacosamide at both the low and high therapeutic concentrations and in comparison with valproate; and analyses were nonbiased, conducted by laboratories external to those of the principle investigators (S.E. and M.K.).

5 | CONCLUSIONS

Human placentas exposed to lacosamide, even for 3 h, show considerable changes in the expression of genes encoding carriers of compounds essential for fetal growth and development. A similar phenomenon was previously demonstrated by us with valproate, although its scope was wider as compared with the effects of lacosamide. Lacosamide has been on the market for more than a decade and is being increasingly prescribed to women of childbearing age. Our findings support its cautious use in pregnant women, given the current absence of safety data. Overcoming the knowledge gap with regard to the outcomes of lacosamide administration to pregnant women is pivotal. In our ex vivo model, all lacosamide effects on carrier expression were observed at its high therapeutic concentrations, suggesting that dose adjustment during pregnancy should be made with caution, while monitoring lacosamide plasma concentrations.

AUTHOR CONTRIBUTIONS

E.B., M.K., and S.E. conceived and designed the work; E.B., E.K., and M.B. acquired, analyzed, and interpreted the data; E.B. drafted the work; all authors revised the work critically.

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CONFLICT OF INTEREST

S.E. has received speaker honoraria from Megapharm, Israel. None of the other authors has any conflict of interest to disclose.

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