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ARTICLE

Maternal Cariprazine Exposure Effects on Lactating Offspring Sterol Biosynthesis

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ABSTRACT

In the developing brain cholesterol is synthesized by both neurons and glia, and sterol biosynthesis peaks in early postnatal life. Genetic disruptions of sterol biosynthesis genes lead to complex intellectual and developmental disabilities. In addition, multiple commonly prescribed medications can impede sterol homeostasis. Of these, cariprazine (CAR) is one of the strongest prescription medications with sterol biosynthesis inhibiting side effects. CAR inhibits the final steps in cholesterol biosynthesis mediated by the enzyme dehydrocholesterol reductase 7 (DHCR7). This inhibition leads to accumulations of sterol precursors, including 7-dehydocholesterol (7-DHC). 7-DHC is the most oxidizable lipid known in mammals, and the 7-DHC derived oxysterols are toxic. There is limited information on CAR effects during lactation. We exposed lactating mice to daily CAR injections of 0.2mg/kg CAR. At postnatal day 11 we found that CAR levels were similar in the brains of exposed pups and their lactating mothers. In addition, the exposed pup brains and livers had increased levels of 7-DHC and 8-DHC. This disruption of post-lanosterol sterol biosynthesis by CAR was not dependent on the sex of the pups or maternal genotype. However, CAR levels were genotype dependent, with *Dhcr7*$^{+/-}$ animals showing lower levels of CAR than their wild-type littermates. In summary, our current study fills a knowledge gap: CAR is excreted through milk, accumulates in the brain of the lactating pups, and disrupts sterol biosynthesis (and potentially many other physiological processes) in the developing postnatal brain.

INTRODUCTION

Cholesterol is an essential molecule of life and a critical structural building block for all mammalian cells (1, 2). In addition, the sterol biosynthesis pathway serves as a starting point for hundreds of homeostatic molecules (3, 4). Cholesterol biosynthesis starts during early development, and peaks in early postnatal life (2).

The sterol biosynthesis process is tightly regulated and involves many enzymatic steps that proceed through two parallel post-lanosterol pathways (Bloch and Kandutsch-Russell) (3). Two alleles of pathogenic variants in the last enzyme of the cholesterol biosynthesis pathway (dehydrocholesterol reductase 7 – DHCR7) give rise to a complex intellectual and developmental disability known as Smith-Lemli-Opitz syndrome (SLOS) (5). The underlying pathophysiology arises by two mechanisms – reduced cholesterol biosynthesis and accumulation of toxic precursors, including 7-dehydrocholesterol (7-DHC) (6).

Importantly, multiple commonly prescribed medications can also interfere with normal sterol biosynthesis (7). These medications encompass antipsychotic, antidepressant, cardiac and metabolic medications. While they do not share common indications, structure or mechanism of action, they all have a sterol biosynthesis inhibiting side effects. These effects have been described in *in vitro* cell culture and pregnant mice models and have been subsequently validated in human dermal fibroblasts, plasma/serum studies of psychiatric patients and pregnant women (8-13).

Cariprazine (CAR) is an atypical third-generation antipsychotic medication primarily used to treat mental health conditions like schizophrenia and bipolar disorder (14). CAR rebalances dopamine and serotonin levels in the brain. It is a partial agonist at dopamine D2 and D3 receptors and serotonin 5-HT1A receptors, but it is an antagonist at serotonin 5-HT2A receptors (15). CAR is long-lasting, with a half-life of 2-4 days, while its active metabolite, the equipotent didesmethylcariprazine (DDCAR) remains detectable up to 8 weeks post-dose (14).

It is less appreciated that CAR is one of the strongest prescription medications with a sterol biosynthesis inhibiting side effects (16). It strongly inhibits the final steps in cholesterol biosynthesis, which are the conversion of 7-DHC to CHOL in the Kandutsch-Russell pathway and 7-dehydrodesmosterol (7-DHD) to desmosterol (DES) (17). Both of these steps are mediated by a single enzyme, DHCR7 (18, 19). The result of this inhibition is the accumulation of the toxic sterol precursors 7-DHC and 8-DHC (20-22).

While there is strong evidence of sterol biosynthesis inhibition during intrauterine life in pregnant mouse models (23), there is limited information on CAR effects during early postnatal life. The FDA cariprazine prescriber label (14) states that administration of cariprazine to rats during the period of organogenesis caused malformations, lower pup survival, and

developmental delays at drug exposures less than the human exposure at the maximum recommended human dose (MRHD) of 6 mg/day. However, cariprazine was not teratogenic in rabbits at doses up to 4.6 times the MRHD of 6 mg/day. The same document also states that cariprazine is present in rat milk but points out that the effects of maternal CAR intake on the breastfed infant are unknown at the current time. The Texas Infant Risk Center has recently been made aware of a possible case of infant tardive dyskinesia secondary to breastfeeding from a mother taking cariprazine (24). Furthermore, it has been reported that CAR can adversely affect maternal milk supply (25).

Based on this combined information, our current study focused on several critical questions. First, we aimed to ascertain if CAR is detectable in the tissues of lactating offspring in a mouse model. Second, we wanted to assess the effects of maternal CAR exposure on sterol biosynthesis in the lactating offspring blood, liver and brain. Finally, we evaluated the effect of a single-allele *DHCR7* pathogenic variant on the above-mentioned processes.

MATERIAL AND METHODS

Ethics approval and consent to participate. All animal experiments were approved by UNMC IACUC 17-117-11-FC. All methods were performed in accordance with the relevant guidelines and regulations. The study did not utilize human biomaterials or patients.

Chemicals. Unless otherwise noted, all chemicals were purchased from Sigma-Aldrich Co (St. Louis, MO). HPLC grade solvents were purchased from ThermoFisher Scientific Inc. (Waltham, MA). CAR was obtained from Sigma Aldrich (St. Louis, MO) and dissolved in sterile water for the experiments. All sterol standards, natural and isotopically labeled, used in this study are available from Kerafast, Inc (Boston, MA).

Experimental animals. Adult male and female B6.129P2(Cg)-*Dhcr7*^{tm1Gst}/J stock # 007453 mice were purchased from Jackson Laboratories. Mice homozygous for the *Dhcr7*^{Ex8} allele lack the exon 8 coding sequence and flanking splice acceptor site of the targeted gene, resulting in the truncated DHCR7 mutation most frequently observed in SLOS patients (IVS8-1G>C) (26). Homozygous mice die shortly after birth. Heterozygous *Dhcr7*$^{+/-}$ mice are well, fertile, and indistinguishable from control, wild type mice. Mice were maintained by breeding within colony and refreshing twice a year with stock 000664 mice from Jackson Laboratories. Mice were housed under a 12 h light-dark cycle at constant temperature (25°C) and humidity with *ad libitum* access to food (Teklad LM-485 Mouse/Rat Irradiated Diet 7912) and water in Comparative Medicine at the UNMC, Omaha, NE.

CAR exposure. In humans, CAR is prescribed at a dose of 1.5-3.0 mg/day. Thus, for our mouse experiments we chose the equivalent of 1 mg/day. Animal Equivalent dose (AED in mg/kg) was

calculated as = human dose (mg/kg) (1mg CAR/60 kg) x body surface area scaling (Km) method, defined as Km (human adult, 60-70 kg = 37)/Km (mouse =3) (12.3), resulting in a final mouse dose of 0.2 mg/kg/day (27). The therapeutic range of CAR is very narrow (1.5-3 mg/day), thus our experiments were performed using a single dose, as we were interested in querying if we can see the sterol-inhibiting effects of CAR even at the lowest dose. Due to the long-half-life of CAR and its metabolites we chose a single daily dose. Furthermore, our previously published data reported very strong sterol inhibition in the brains of maternally exposed pups (23). Intraperitoneal injection was chosen as a route of delivery for the ability to precisely control the dosage in the pregnant mice.

Sample size was chosen based on previously observed magnitude of sterol change in response to CAR exposure (23). *Dhcr7*$^{+/+}$ and *Dhcr7*$^{+/-}$ lactating female mice received i/p injections of vehicle (0.9% saline) or CAR (0.2 mg/kg/day) from P0 to P10 during lactation. This time-window of treatment was chosen based on the known developmental trajectory in the newborn mouse: this is the time window of the most active sterol biosynthesis in the brain (2). A total of 12 adult mothers were used in our study: 3 *Dhcr7*$^{+/+}$ vehicle-treated (23 pups); 3 *Dhcr7*$^{+/+}$ CAR-treated (22 pups); 3 *Dhcr7*$^{+/-}$ vehicle-treated (29 pups) 3*Dhcr7*$^{+/-}$ CAR-treated (19 pups). Details are shown in **Supplemental Material 1**. All procedures were performed in accordance with the Guide for the Humane Use and Care of Laboratory Animals. The use of mice in this study was approved by the Institutional Animal Care and Use Committee of UNMC. No animals or samples were excluded from our study. No randomization was performed, as we needed to know the genotype of the animals. All biochemical analyses were performed in a blinded fashion. Blinding was not possible in the analyses phase, as genotypes and CAR treatment were used to assign sample groups.

Tissue collection. Twenty-four hours after the last injection (day 11) pup and lactating dam brains and livers were dissected and blood collected. Brains were frozen in pre-chilled methyl-butane and stored at -80°C. Frozen brain and liver tissue samples were sonicated in ice-cold PBS containing butylated hydroxytoluene (BHT) and triphenylphosphine (PPh_3). An aliquot of homogenized tissue was used for sterol extraction with Folch solution. The second aliquot of homogenized tissue was used for protein measurements. The protein was measured using BCA assay (Pierce ThermoFisher Scientific Inc., Waltham, MA). Sterol levels were normalized to protein measurements and expressed as nmol/mg protein or in the case of blood, nmol/mL blood. The third aliquot of homogenized tissue was used for drug measurements.

LC-MS/MS (SRM) analyses. Sterols were extracted and derivatized with 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) as described previously (16) and placed in an Acquity UPLC system equipped with ANSI-compliant well plate holder coupled to a ThermoScientific TSQ Quantis mass spectrometer equipped with an APCI source. Then 10 µL was injected onto the column

(Phenomenex Luna Omega C18, 1.6 µm, 100 Å, 2.1 mm × 100 mm) with 100% MeOH (0.1% v/v acetic acid) mobile phase for 2.0 min runtime at a flow rate of 500 µL/min. Natural sterols were analyzed by using the following transitions: Chol 369 → 369, 7-DHC 560 → 365, DES 592 → 560, LAN 634 → 602, with retention times of 0.7, 0.4, 0.3 and 0.3 min, respectively. Internal standards were set to: d_7-Chol 376 → 376, d_7-7-DHC 567 → 372, $^{13}C_3$-desmosterol 595 → 563, $^{13}C_3$-lanosterol 637 → 605. Final sterol numbers are reported as nmol/mg of protein.

CAR, DCAR, DDCAR measurements. Medications were extracted from 100 µl aliquots using methyl *tert*-butyl ether and ammonium hydroxide as described previously (23). CAR levels were acquired in an Acquity UPLC system coupled to a Thermo Scientific TSQ Quantis mass spectrometer using an ESI source in the positive ion mode. Five µL of each sample was injected onto the column (Phenomenex Luna Omega C18, 1.6 µm, 100 Å, 2.1 × 50 mm^2) using water (0.1% v/v acetic acid) (solvent A) and acetonitrile (0.1% v/v acetic acid) (solvent B) as mobile phase. The gradient was: 10–40% B for 0.5 min; 40–95% B for 0.4 min; 95% B for 1.5 min; 95–10% B for 0.1 min; 10% B for 0.5 min. The SRM for the internal standards (d_8-aripiprazole and d_8-meta-chlorophenylpiperazine) were set to 456 → 293 and 204 → 157, respectively. Final drug levels are reported as ng/mg of protein or pg/mL blood.

Statistical analyses. Statistical analyses were performed using Graphpad Prism 10 for Windows. Data showed normal distribution based on Grubbs' method, and the variance was comparable between the experimental and control groups. Unpaired two-tailed t-tests were performed for individual comparisons between two groups. The Welch's correction was employed when the variance between the two groups was significantly different. Three-way ANOVA analyses were performed to assess the interaction between maternal genotype, embryonic genotype and drug treatment **(Supplemental Material 2)**. For sterol measurements pup data from *Dhcr7*$^{+/-}$ and *Dhcr7*$^{+/+}$ dams were combined, as ANOVA analyses did not reveal significant maternal genotype effects on sterol levels and CAR response. The p values for statistically significant differences are highlighted in the figure legends.

RESULTS

CAR and metabolite measurements in maternal brain, liver, and blood

Previous intrauterine mice studies showed that both CAR levels and the resulting developmental sterol biosynthesis disruptions are *Dhcr7* genotype dependent (23). Thus, we used two models – wild-type *Dhcr7*$^{+/+}$ and *Dhcr7*$^{+/-}$ transgenic mice which had a single-allele pathogenic variant. CAR and its metabolites were measured in the three tissues of the lactating dams exposed to 0.2mg/kg i/p CAR for 10 days using LC-MS/MS. These analyses revealed a complex CAR pattern (**Figure 1**). CAR levels were genotype-dependent across the blood, liver

and brain, with *Dhcr7*$^{+/-}$ dams reporting lower levels of CAR 24 hours after the last injection. This was also observed in DCAR levels, which in *Dhcr7*$^{+/-}$ dam blood was in the non-measurable range. In contrast, the most stable, long-lasting and active metabolite of CAR, DDCAR was comparable across the Dhcr7$^{+/+}$ and *Dhcr7*$^{+/-}$ maternal livers and brains.

CAR and metabolite levels in lactating pups

Next, we wanted to establish if maternal CAR exposure through lactation reached the blood, liver, and brain of the lactating pups. The lower level of CAR and its metabolites were also observed in the liver and brain of *Dhcr7*$^{+/-}$ lactating pups, but not in the blood (**Figure 2**). CAR levels revealed a non-significant, 8.9% decrease in the blood of *Dhcr7*$^{+/-}$ pups compared to the littermates with *Dhcr7*$^{+/+}$ genotype ($p=0.5802$, $p>0.05$), and were significantly lower in the liver (52.4%, $p<0.0001$) and the brain (53.0%, $p<0.0001$). DCAR and DDCAR levels were not detectable in the blood, inconsistently observed in brain at low levels, and readily detected in the liver. However, the DCAR and DDCAR levels did not appear to be *Dhcr7* genotype dependent in the offspring liver. Notably, sex was not a significant variable in determining CAR and metabolite levels across the biomaterials.

CAR level measurements in i/p-exposed dams and lactating pups

In the following step we wanted to compare the levels and distribution of CAR between the dam and lactating offspring tissues. LC-MS/MS analysis revealed that maternal levels of CAR in the blood and liver samples were more than an order of magnitude higher in the maternal samples than samples originating from the pups (**Figure 3**). In contrast, we observed comparable levels between the CAR exposed dams and lactating pups in the brain (**Figure 3, right panel**). This suggests that in lactating offspring the CAR levels in blood and liver are poor predictors of potential unwanted side effects in the developing brain. It appears that CAR similarly accumulates within the brain tissue of the i/p-exposed mothers and their lactating, indirectly exposed offspring.

CAR alters sterol biosynthesis in lactating pup livers

The liver is one of the primary spots of cholesterol (CHOL) biosynthesis (28). As a result, we were interested in whether CAR exposure through lactation affects hepatic sterol biosynthesis (**Figure 4**). In both *Dhcr7*$^{+/-}$ and *Dhcr7*$^{+/+}$ pups CAR significantly increased 7-DHC and 8-DHC levels by 23.5%-102.5% (p-values ranging from $p<0.05$ to $p<0.001$; for data see **Supplemental Material 3**). Notably, sex was not a significant variable in predicting the magnitude of sterol changes in the lactating pup livers.

CAR alters sterol biosynthesis in lactating pup brains

CAR exposure through lactation disrupted the developing brain sterol profile in both *Dhcr7*$^{+/-}$ and *Dhcr7*$^{+/+}$ pups (**Figure 5**). This disruption consisted of elevation in 7-DHC and 8-DHC ranging from 16.0-33.6% ($p<0.0001$ for all). However, the *Dhcr7* pup genotype did not seem to be a significant factor in this sterol precursor elevation. Similarly, the altered levels of precursors were not dependent on the sex of pups (data not shown). Notably, CHOL levels were not changed, as CHOL is much more stable in the brain, with a long half-life (approximately 1 year in rodents and 5 years in human)(29-33). The combined liver and brain data of pups suggest that CAR exposure through lactation might have significant effects across the whole body during postnatal life, with unknown long term developmental consequences.

DISCUSSION

The main conclusions of our studies are that CAR, when maternally utilized, reaches the lactating pups' tissues. In particular, brains of i/p-injected CAR mothers and indirectly exposed pups through lactation had similar concentrations of CAR in the brain. As a result, pups exposed through lactation had elevated 7-DHC and 8-DHC in the liver and brain, suggesting that lactational CAR intake can inhibit the last step of developmental CHOL biosynthesis.

The early postnatal period is the time of the highest cholesterol accumulation and sterol biosynthesis (2). Myelination, axonal growth, membrane synthesis, signaling molecule secretion, molecular precursor production, and many other critical processes depend on the output of the sterol biosynthesis pathway (3, 34). CAR is one of the strongest disruptors of this process by acting as a DHCR7 inhibitor (16). Previous studies have shown that CAR elevates circulating 7-DHC levels in human blood, and this elevation was strongly dose-dependent (23). Furthermore, antipsychotic use during the third trimester of pregnancy has a risk for developing extrapyramidal symptoms and/or withdrawal symptoms in newborns following delivery (35, 36). This would suggest that CAR exposure through breastfeeding has potential to produce similar effects. Thus, we believe that the current findings have significant implications for clinical care of psychiatric patients.

7-DHC is the most oxidizable lipid known in mammals, and the 7-DHC derived oxysterols are toxic (37, 38). The potential severity of the sterol inhibition is likely dependent on the elevation level of 7-DHC, and the accumulation of oxysterols that arise from it (38-40). In previous studies the disruption of sterol biochemical profile by CAR in the developing mouse brain has been extensively documented during intrauterine life (23). Offspring of pregnant mice receiving 0.2 mg/kg CAR showed detectable levels of CAR and metabolites, coupled with elevated 7-DHC were observed in the brain of newborn pups 14 days after intrauterine maternal drug exposure. Furthermore, this sterol disruption was not only elevated in the brain tissue of pups, but also in liver, spleen, heart, kidney and lungs. In addition, the same studies also

revealed that the highest accumulation of CAR and its metabolites were found in the liver, while the 7-DHC elevation was most robust in the brain of the exposed pups.

The observation of comparable levels between the CAR exposed dams and lactating pups in the brain (but not in other tissues) is both intriguing and puzzling at the same time. We propose that this might be due to three factors: the lipophilic nature of CAR (41), the high sterol content of the brain (2), and the high concentration of receptors in the brain that bind CAR (42). Thus, we hypothesize that any potential deleterious effects of CAR during development would likely be primarily brain related.

The current lactation study and previous intrauterine studies of CAR exposure share similarities - but also differences in outcome. Both prenatal and postnatal studies reported altered sterol metabolism in all animals analyzed. However, in prenatal exposure studies the strongest effect of CAR was on the brain of *Dhcr7*$^{+/-}$ pups born to *Dhcr7*$^{+/-}$ dams. In our current study, this was not the case: the alterations in the sterol profile by CAR were not strongly dependent on the genotype of the CAR-exposed dam or pup. This suggests that the timing of exposure modulates genotype sensitivity. The lactation and intrauterine CAR studies showed another important similarity. Both the current study and our previous study revealed that *Dhcr7*$^{+/-}$ dams and *Dhcr7*$^{+/-}$ pups had lower levels of CAR in the tissues. That previous study revealed that reduced levels of CAR and metabolites in tissues from *Dhcr7*$^{+/-}$ animals were a result of increased levels of Cyp2d6 (43).

It should also be recognized that elevated drug levels in the pup brains might not only act through altering sterol levels. The accumulation of CAR in the lactating pups' brains might disrupt or delay other critical developmental processes in addition to the changes in the sterol profile and 7-DHC levels (44, 45). These effects are likely to be mediated through the primary action of CAR, affecting neurotransmitter and neuromodulatory systems (46). One of such systems is mitochondrial energy homeostasis. A previous study revealed that mitochondrial complex I activity was significantly affected by CAR and reduced cellular respiration by approximately 30% (47). In addition, at high concentrations CAR slightly but significantly decreased ATP production. These effects on energy homeostasis together might lower the energy available for cellular processes and disrupt neuronal functions, especially in the developing brain. The authors of the study concluded that lack of energy and higher oxidative stress by CAR (and other similar medications) would probably lead to neuronal damage at very high drug concentrations (47).

Notably, more than 50% of postpartum women (breastfeeding or not) require at least one medication, but data on their breastfeeding practices are not available at the current time (48). Our recent study revealed that approximately 4% of pregnant women had detectable serum levels of one or more of 30 prescription medications known to inhibit cholesterol

synthesis (9). These data suggest that the continuous use of the same medications during lactation is also likely. Importantly, both preclinical and human biomaterial studies suggest that the magnitude of developmental sterol biosynthesis is polypharmacy dependent. Simultaneous utilization of 2 or more medications with sterol biosynthesis inhibiting side effects lead to synergistic effects across *in vitro, in vivo* and human biomaterial studies (49, 50). As a result, maternal utilization of CAR with statins during lactation, which are found in low levels in breast milk (51, 52), might further exacerbate unwanted sterol inhibition in lactating infants. In addition, it is also notable that use of antidepressant drugs during lactation, including sertraline and fluoxetine (both medications with sterol biosynthesis inhibiting side effects), is widespread due to postpartum depression (53-55). In addition, Drugs.com lists 103 major pharmaceutical interactions with CAR, including many highly utilized medications such as bupropion, clarithromycin, dexamethasone and others (56). Unfortunately, there is virtually no lactation-related data on effects of such polypharmacy. Thus, CAR-including polypharmacy and sterol-inhibiting interactions should be considered when prescribing to lactating women.

In summary, our current study fills a knowledge gap: CAR is excreted through milk, accumulates in the brain of the lactating pups, and can affect sterol synthesis in developing postnatal brain. Thus, the impact of DHCR7 inhibition by CAR in early postnatal life should not be overlooked. If DHCR7 inhibition during the first trimester in humans is teratogenic (57), it is likely that elevated 7-DHC levels during the newborn period can potentially lead to long-lasting, more functional consequences. Finally, it remains to be determined if CAR levels in the brain can disrupt other critical developmental mechanisms beyond sterol biosynthesis, especially when coupled with polypharmacy. In the overall context of our current findings and previous studies we believe that CAR utilization by lactating mothers might have deleterious impact on the brain development of newborns. We suggest that its utilization should be limited in this population until conclusive human data are obtained.

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Data Availability Statement: Data generated in this series of experiments will be deposited to the NCBI database at the time of acceptance to publication. CAR and sterol measurements are also available in Supplemental Material 3.

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Conflicts of Interest: The authors declare no conflicts of interest.

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FIGURE LEGENDS:

Figure 1. Maternal CAR and metabolite levels in the blood, liver and brain. Only data from CAR-exposed dams are plotted. X axis denotes maternal genotype, while normalized CAR, DCAR and DDCAR levels are plotted on the Y axis. Each data point depicts a single lactating mother. CAR was detectable in all samples from *Dhcr7*$^{+/+}$ dams, while DCAR and DDCAR were not detected in every sample studied. **Note** that CAR and DCAR levels were lower in *Dhcr7*$^{+/-}$ dams across all three tissues compared to the *Dhcr7*$^{+/+}$ animals. Due to undetectable levels for multiple *Dhcr7*$^{+/-}$ samples the results were only statistically significant for CAR in the brain and liver at **p<0.01(t-test).

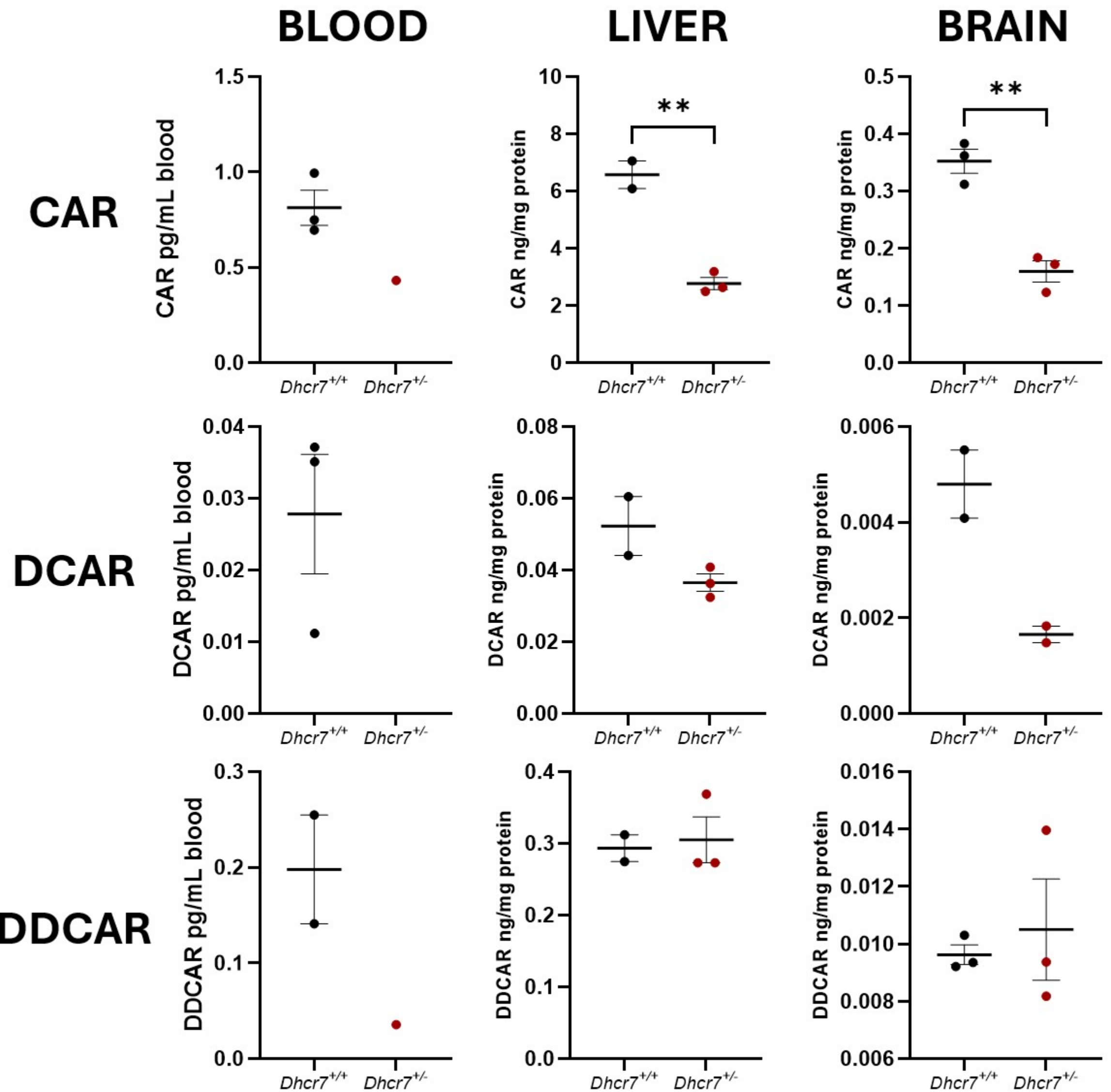
Figure 2. Lactating pup CAR and metabolite levels in the blood, liver and brain. Only data from CAR-exposed lactating pups are plotted. X axis denotes lactating pup genotype, while normalized CAR, DCAR and DDCAR levels are plotted on the Y axis. Each data point depicts a single pup biomaterial. Blue diamonds denote male, black dots denote female pups. CAR was detectable in the majority of samples, while DCAR and DDCAR were not detected in the blood of pups and could be measured only in a few brain samples. **Note** that CAR levels were lower in *Dhcr7*$^{+/-}$ pups in the liver and brain (****p<0.0001 (t-test).

Figure 3. Comparison of CAR levels across the tissues of lactating dams and their pups. Only data from CAR-exposed dams (i/p injections) and pups (lactation exposure) are plotted. X axis denotes dams and their lactating pups, while normalized CAR levels are plotted on the Y axis. CAR levels were normalized to ng/mg of protein from brain and liver or pg/mL for blood (Y axis).

Data points denote individual samples from a single animal. Red symbols denote *Dhcr7*$^{+/-}$ animals, black symbols correspond to *Dhcr7*$^{+/+}$ animals. **Note** that the concentration of CAR in the pup brains was high, comparable to those seen in the lactating dams' brains. In contrast, both CAR-exposed *Dhcr7*$^{+/+}$ and *Dhcr7*$^{+/-}$ pups had negligible levels of CAR in the peripheral tissues.

Figure 4. Pup post-lanosterol profile in response to CAR exposure through lactation in the liver. X axes denote VEH or CAR treatment of pups through lactation, Y axis denote normalized sterol intermediate levels. Red symbols denote pups born to mothers with *Dchr7*$^{+/-}$ genotype, black symbols correspond to pups born to *Dhcr7*$^{+/+}$ mothers. **Note** the consistent, statistically significant elevation in both *Dhcr7*$^{+/+}$ (upper row) and *Dhcr7*$^{+/-}$ pups (lower row) in 7-DHC and 8-DHC levels.

Figure 5. Pup post-lanosterol profile in response to CAR exposure through lactation in the brain. X axes denote VEH or CAR treatment, Y axis denote normalized sterol intermediate levels. Red symbols denote pups born to mothers with *Dchr7*$^{+/-}$ genotype, black symbols correspond to pups born to *Dhcr7*$^{+/+}$ mothers. **Note** the consistent, statistically significant elevation in both *Dhcr7*$^{+/+}$ (upper row) and *Dhcr7*$^{+/-}$ pups (lower row) in 7-DHC and 8-DHC levels.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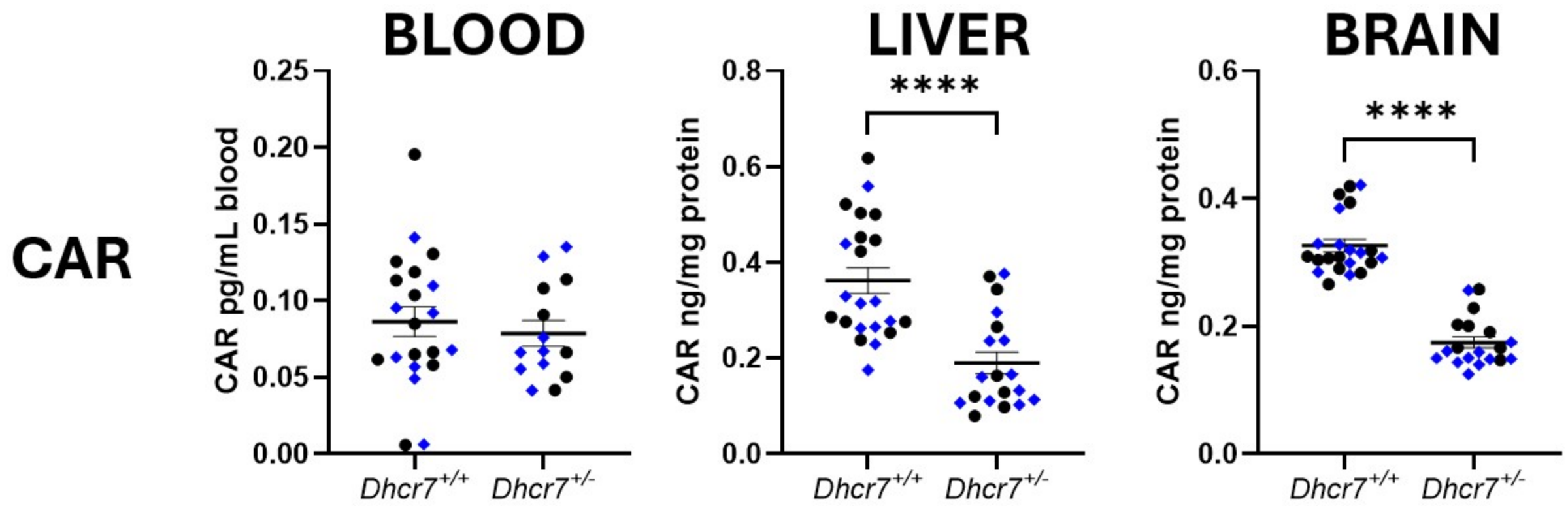
LIVER
BRAIN
CAR
DCAR
DDCAR
CAR pg/mL blood
CAR ng/mg protein
DCAR pg/mL blood
DCAR ng/mg protein
DDCAR pg/mL blood
DDCAR ng/mg protein
**
Dhcr7+/+
Dhcr7+/-


BLOOD
LIVER
BRAIN
CAR
CAR pg/mL blood
CAR ng/mg protein
CAR ng/mg protein
0.25
0.20
0.15
0.10
0.05
0.00
0.8
0.6
0.4
0.2
0.0
0.6
0.4
0.2
0.0
****
****
Dhcr7+/+
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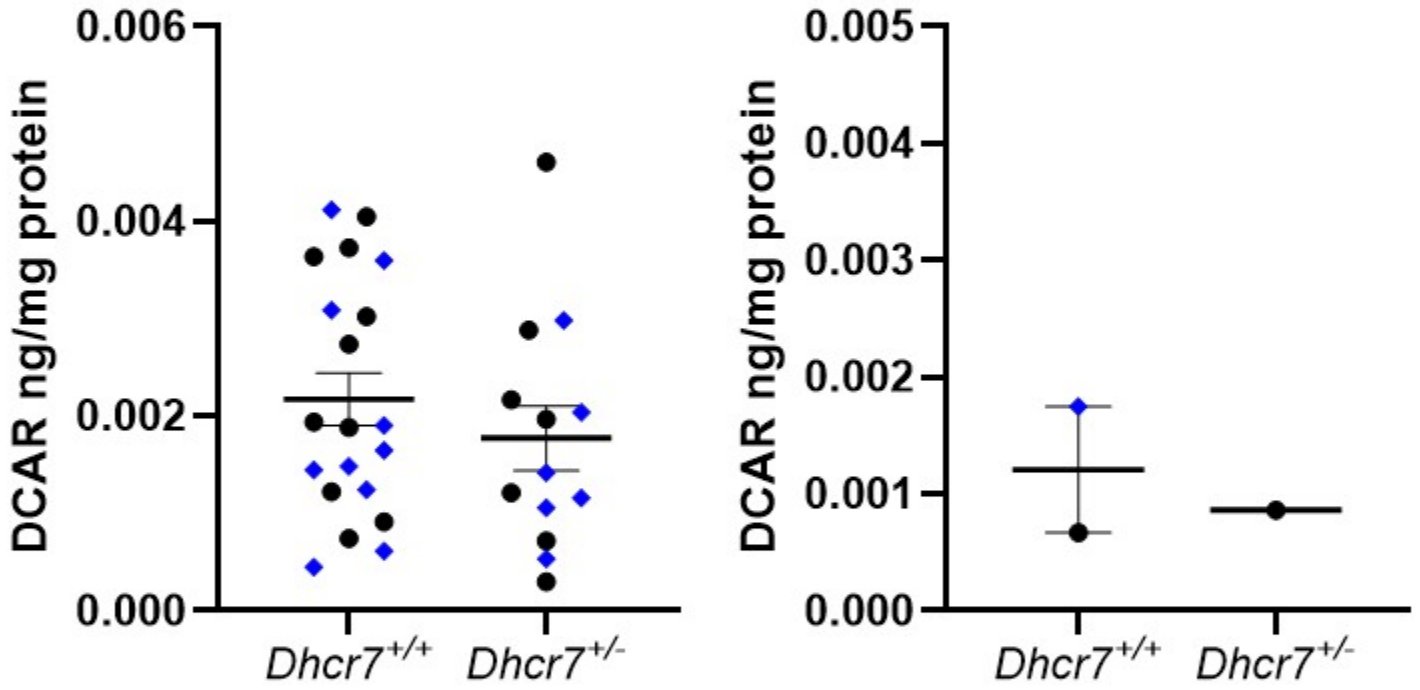
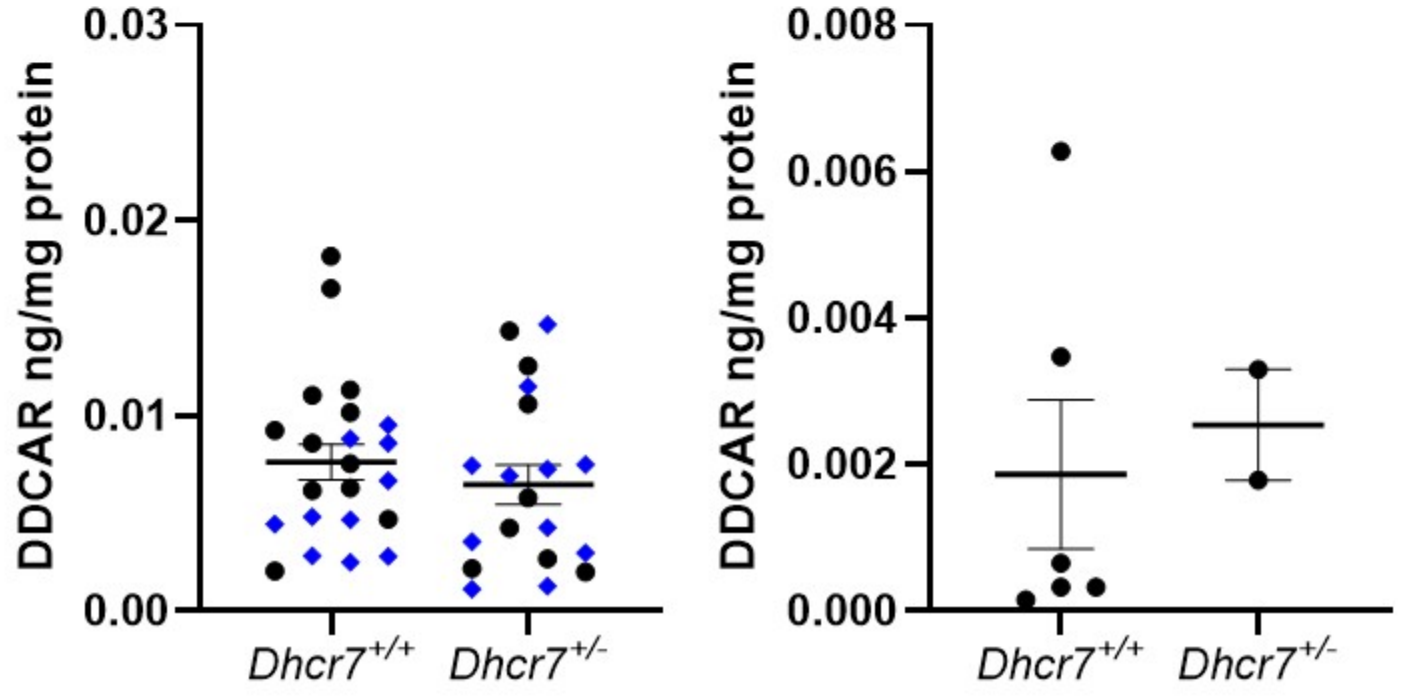
Dhcr7+/+
Dhcr7+/-
Dhcr7+/+
Dhcr7+/-


DCAR
ND
DCAR ng/mg protein
DCAR ng/mg protein
0.006
0.004
0.002
0.000
0.005
0.004
0.003
0.002
0.001
0.000
Dhcr7+/+
Dhcr7+/-
Dhcr7+/+
Dhcr7+/-


DDCAR
ND
DDCAR ng/mg protein
DDCAR ng/mg protein
0.03
0.02
0.01
0.00
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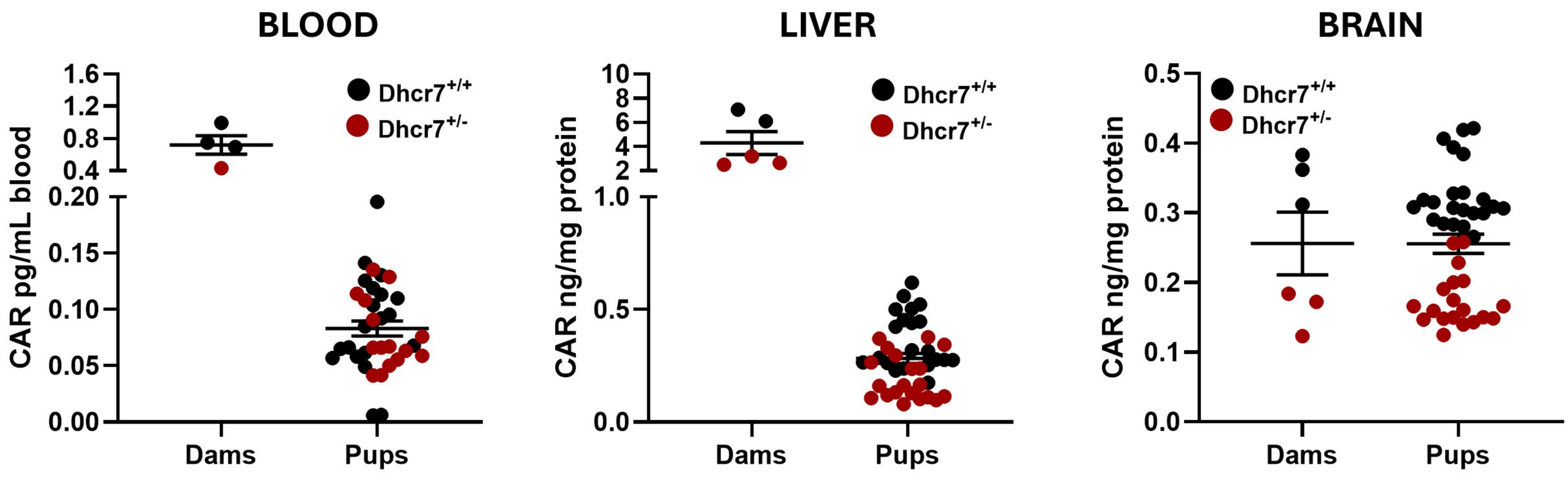
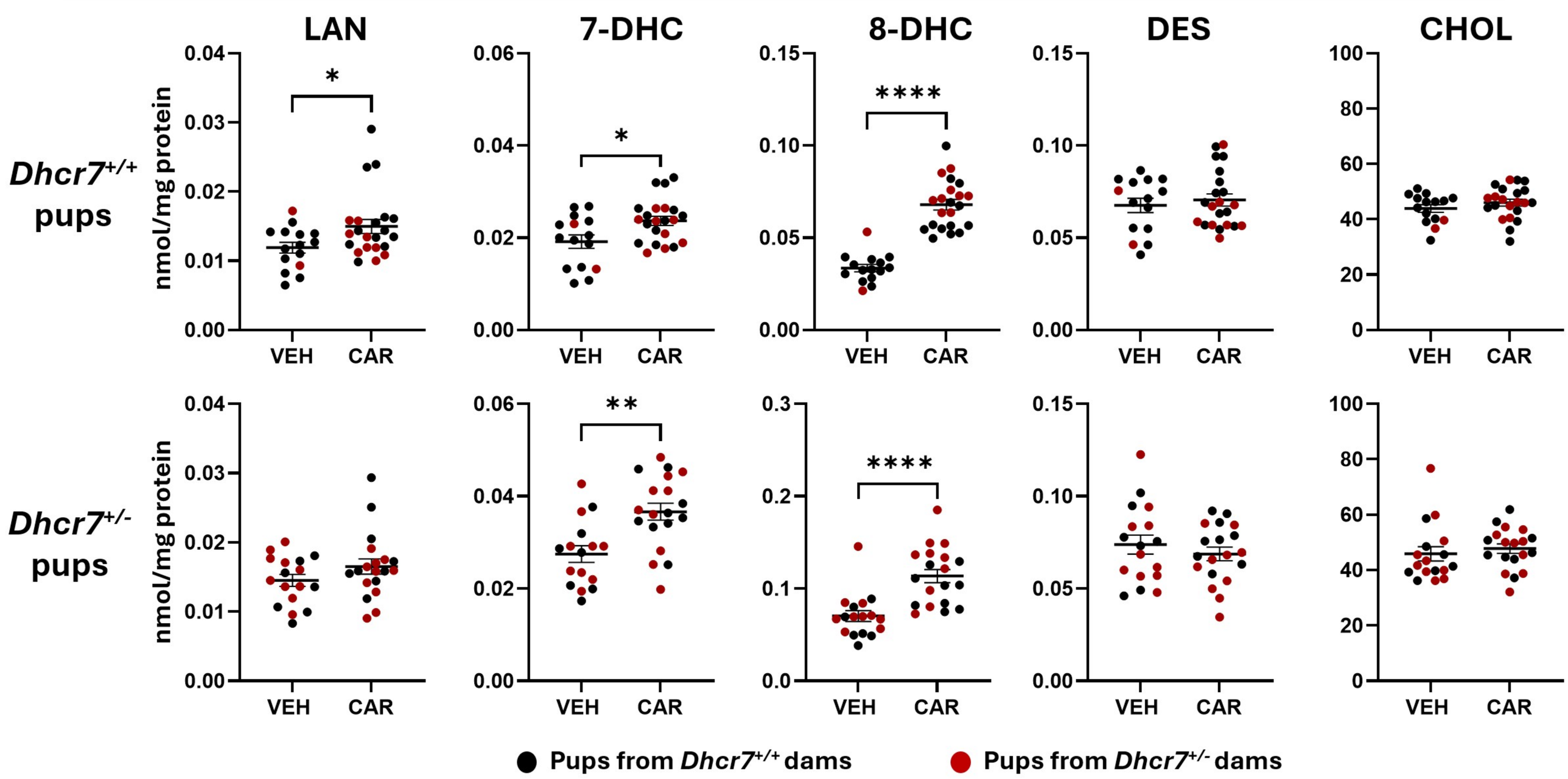
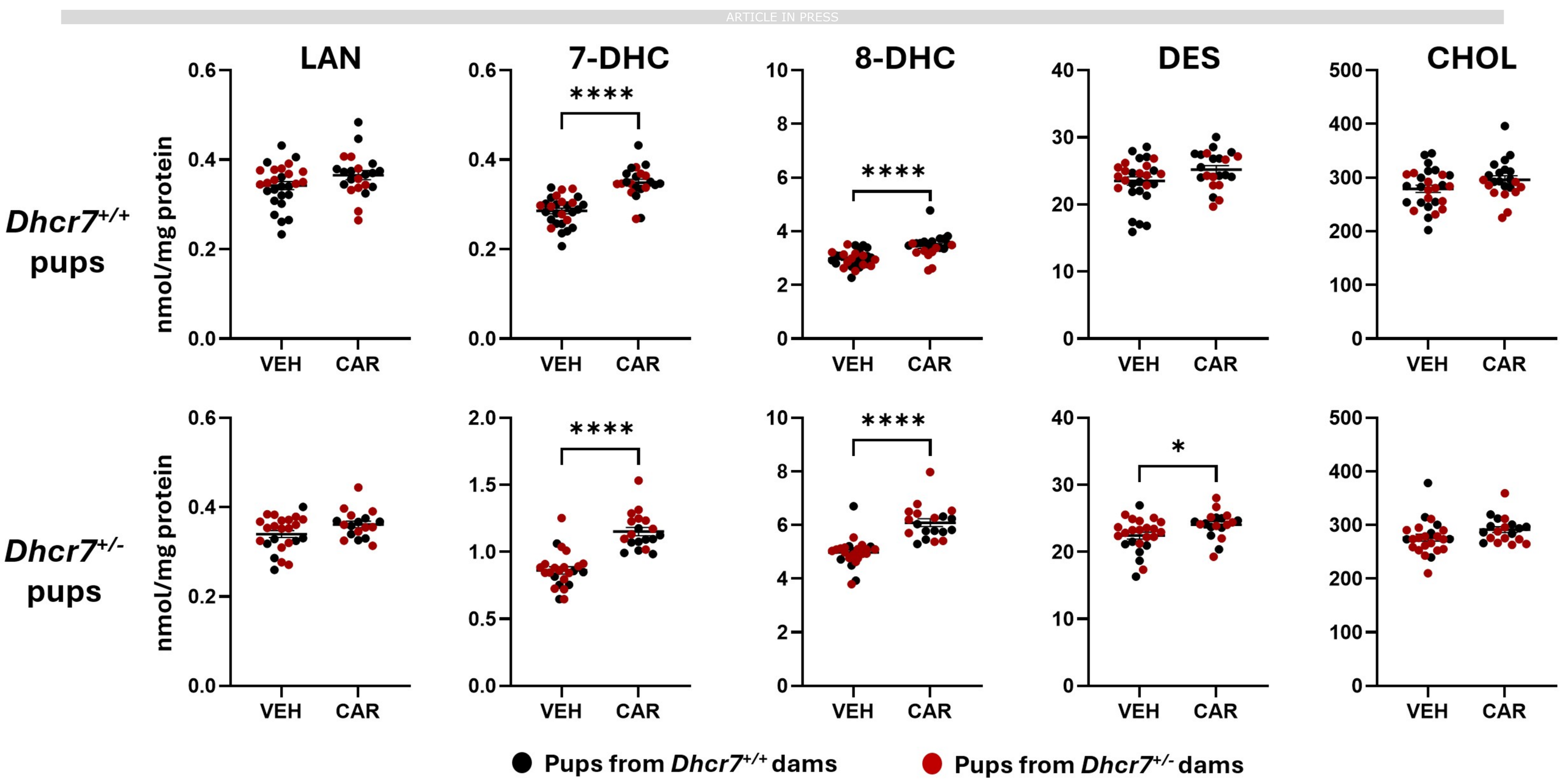
0.006
0.004
0.002
0.000
Dhcr7+/+
Dhcr7+/-
Dhcr7+/+
Dhcr7+/-


BLOOD
CAR pg/mL blood
1.6
1.2
0.8
0.4
0.20
0.15
0.10
0.05
0.00
Dhcr7+/+
Dhcr7+/-
Dams
Pups
LIVER
CAR ng/mg protein
10
8
6
4
2
1.0
0.5
0.0
Dhcr7+/+
Dhcr7+/-
Dams
Pups
BRAIN
CAR ng/mg protein
0.5
0.4
0.3
0.2
0.1
0.0
Dhcr7+/+
Dhcr7+/-
Dams
Pups


LAN
7-DHC
8-DHC
DES
CHOL
Dhcr7+/+ pups
Dhcr7+/- pups
nmol/mg protein
VEH
CAR
*
**
****
Pups from Dhcr7+/+ dams
Pups from Dhcr7+/- dams


LAN
7-DHC
8-DHC
DES
CHOL
Dhcr7+/+ pups
Dhcr7+/- pups
nmol/mg protein
VEH
CAR
****
*
Pups from Dhcr7+/+ dams
Pups from Dhcr7+/- dams