Constitutive Androstane Receptor: A Peripheral and a Neurovascular Stress or Environmental Sensor

Fabiana Oliviero, Céline Lukowicz, Badreddine Boussadia, Isabel Forner-Piquer, Jean-Marc Pascussi, Nicola Marchi, Laila Mselli-Lakhal

cells

MDPI

Review

Constitutive Androstane Receptor: A Peripheral and a Neurovascular Stress or Environmental Sensor

Fabiana Oliviero [1,†], Céline Lukowicz [1,†], Badreddine Boussadia [2], Isabel Forner-Piquer [2], Jean-Marc Pascussi [2], Nicola Marchi [2,*] and Laila Mselli-Lakhal [1,*]

1 Toxalim (Research Centre in Food Toxicology), Université de Toulouse, INRAE, ENVT, INP-Purpan, UPS, 31027 Toulouse, France; fabiana.oliviero@inrae.fr (F.O.); celine.lukowicz@unil.ch (C.L.)

2 Cerebrovascular and Glia Research, Institute of Functional Genomics (UMR 5203 CNRS–U 1191 INSERM, University of Montpellier), 34094 Montpellier, France; badreddine.boussadia@gmail.com (B.B.); Isabel.Forner-Piquer@igf.cnrs.fr (I.F.-P.); jean-marc.pascussi@inserm.fr (J.-M.P.)

* Correspondence: Nicola.Marchi@igf.cnrs.fr (N.M.); laila.lakhal@inrae.fr (L.M.-L.); Tel.: +33-4-34-35-92-20 (N.M.); +33-5-61-19-39-15 (L.M.-L.)

† These authors contributed equally to this work.

Received: 6 October 2020; Accepted: 2 November 2020; Published: 6 November 2020

Abstract: Xenobiotic nuclear receptors (NR) are intracellular players involved in an increasing number of physiological processes. Examined and characterized in peripheral organs where they govern metabolic, transport and detoxification mechanisms, accumulating data suggest a functional expression of specific NR at the neurovascular unit (NVU). Here, we focus on the Constitutive Androstane Receptor (CAR), expressed in detoxifying organs such as the liver, intestines and kidneys. By direct and indirect activation, CAR is implicated in hepatic detoxification of xenobiotics, environmental contaminants, and endogenous molecules (bilirubin, bile acids). Importantly, CAR participates in physiological stress adaptation responses, hormonal and energy homeostasis due to glucose and lipid sensing. We next analyze the emerging evidence supporting a role of CAR in NVU cells including the blood–brain barrier (BBB), a key vascular interface regulating communications between the brain and the periphery. We address the emerging concept of how CAR may regulate specific P450 cytochromes at the NVU and the associated relevance to brain diseases. A clear understanding of how CAR engages during pathological conditions could enable new mechanistic, and perhaps pharmacological, entry-points within a peripheral–brain axis.

Keywords: constitutive androstane receptor; liver; brain; neurovascular unit; blood-brain barrier, stress sensor; environmental contaminants

1. Introduction: CAR Governs Detoxification Mechanisms

The Constitutive Androstane Receptor (CAR), a key nuclear receptor (subfamily 1, group I, member 3 (NR1i3)), displays a prominent functional expression in peripheral organs and an emerging role in the brain. Here, we examine CAR as an element responding to environmental or stress challenges, preserving cellular and multi-organ homeostasis. CAR was originally defined as a xenobiotic nuclear receptor that controls the hepatic detoxification of foreign chemicals and endogenous bile acids [1]. CAR is the mediator of phenobarbital-induced cytochrome P450 enzymes expression in the liver [2,3]. CAR directly regulates the expression of an array of phase I and II xenobiotic metabolism enzymes and multi-drug transporters (Table 1) [4,5]. Specifically, CAR controls the inductive expression of the CYP phase I enzymes CYP2B, CYP3A, CYP2C, contributing to the detoxification of numerous drugs and environmental chemicals. Furthermore, CAR activation results in the upregulation of phase II enzymes such as uridine diphosphate glucuronosyltransferase (UGT), sulphotransferases

(SULT), and efflux and uptake transporters such as multidrug resistance mutation 1 (MDR1), multidrug resistance proteins (MRPS), and organic-anion-transporting polypeptides (OATP) [6,7]. Via these enzymes and transporters, CAR governs the detoxification of endogenous bile acids and bilirubin, which can cause hepato-toxicity if accumulated [8,9]. This evidence outlines CAR as a player regulating key metabolic and transporter machineries involved in a myriad of endogenous and protective cellular processes, applicable to peripheral organs and the brain.

Table 1. Constitutive Androstane Receptor (CAR) target genes involved in detoxification processes [4,5].

	Mice	Human
Phase I	*Cyp1a1*, *Cyp1a2*, *Cyp2a4*, *Cyp2b10*, *Cyp2c29*, *Cyp2c37*, *Cyp2c55*, *Cyp3a11*, *Nqo1*, *Aldh1a1*, *Aldh1a7*, *Akr1b7*, *Ces6*	*CYP1A1*, *CYP1A2*, *CYP2B6*, *CYP2C8*, *CYP2C9*, *CYP2C19*, *CYP3A4*, *CYP3A5*
Phase II	*Ugt1a1*, *Ugt1a9*, *Ugt2b34*, *Ugt2b35*, *Ugt2b36*, *Sult1e1*, *Sult2a1*, *Sult2a2*, *Sult3a1*, *Sult5a1*, *Gsta1*, *Gsta4*, *Gstm1*, *Gstm2*, *Gstm3*, *Gstm4*, *Gstp*, *Gstt1*	*UGT1A1*, *SULT2A1*
Transporters	*Mrp2*, *Mrp3*, *Mrp4*, *Oatp1a4*	*MDR1*, *PTGS2*, *GCK*, *PTPRN*, *ATP2B2*

Importantly, microarray analyses identified additional sets of CAR target genes involved in hepatocyte proliferation, glucose and lipid metabolism [10,11]. The latter was confirmed in functional studies revealing that selective activation of CAR alleviates high fat diet-induced obesity and type 2 diabetes [12,13]. Furthermore, CAR is activated by cellular stress as induced by fasting, caloric restriction [14,15] or hypoxia [16]. CAR regulatory pathways include AMP-activated protein kinase (AMPK) [17], a key player maintaining intracellular homoeostasis, and stress activated protein kinase (SAPK) [18]. Based on this evidence, we here review how CAR, through key peripheral and central functions, acts as a stress sensor engaging and responding to toxic, environmental, or metabolic insults.

2. CAR Has a Particular Mechanism of Action: Direct and Indirect Activation

The crystal structure of CAR, published in 2004 [19,20], outlined the sites responsible for its constitutive activity. CAR contains a single-turn helix X located before the C-terminal AF2 helix that favors an active conformation of the receptor. The intrinsic constitutive nature of CAR necessitates specific mechanisms of regulation aside from ligand binding. Specifically, CAR is sequestered in the cytoplasm in a phosphorylated active conformation, forming a complex with chaperone proteins: Cytoplasmic CAR retaining protein (CCRP), Heat shock protein (HSP90) and PPP1R16A (the membrane subunit of protein phosphatase 1β) [21,22]. TCPOBOP (murine form, 1,4-Bis-[2-(3,5-dichloropyridyloxy)]benzene) or CITCO (human form, 6-(4-Chlorophenyl)imidazo[2,1-b][1,3]thiazole-5-carbaldehyde O-(3,4-dichlorobenzyl)oxime) are synthetic CAR agonist interacting with the ligand-binding pocket of CAR to induce its nuclear translocation (Figure 1) [23]. This translocation requires the recruitment of phosphatase protein A2 (PP2A) responsible for dephosphorylating the threonine 38 (human form) or 48 (murine form) [24], thus releasing CAR from its cytosolic complex [21,22].

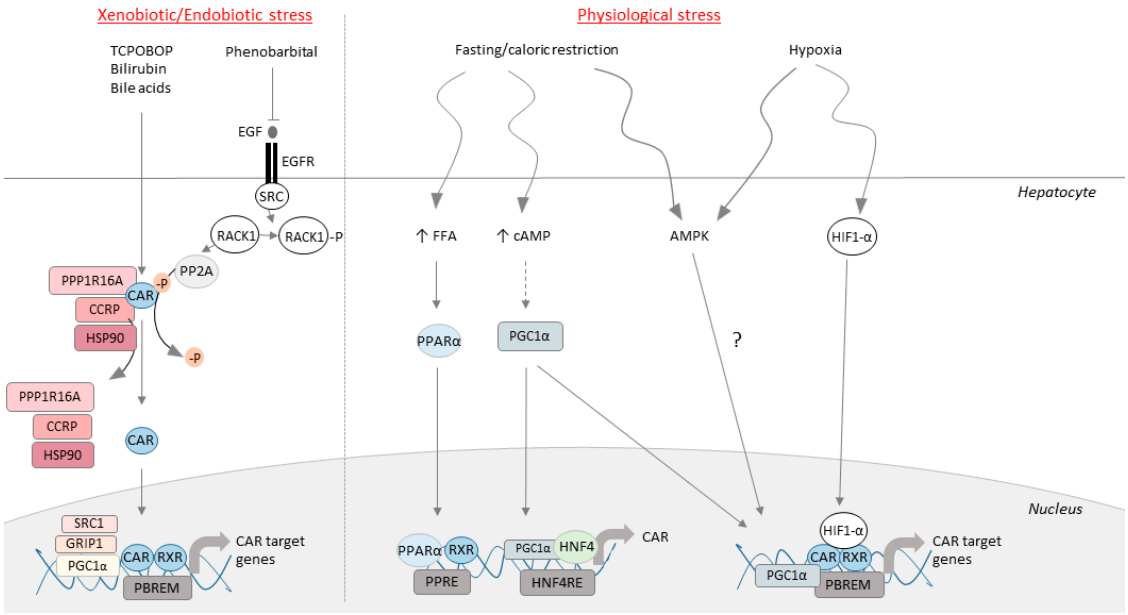

Figure 1. CAR is a sensor for xenobiotic/endobiotic and physiological stress. CAR is maintained in the cytoplasm by a complex of chaperone proteins (PP1R16A, CCRP, HSP90) and can be activated through direct or indirect processes by a xenobiotic or endogenous molecule. Dephosphorylation of CAR allows it to be free from its chaperone complex, to migrate to the nucleus, heterodimerize with RXR, recruit co-activator factors and allow transcription of its target genes. Gene expression of CAR is induced in response to fasting and caloric restriction through nuclear receptors PPARa and HNF4. Hypoxia induces nuclear translocation of CAR and expression of its target genes through HIF1.

CAR can be activated by endogenous and exogenous molecules without direct binding. Phenobarbital induces CAR translocation indirectly by competing with the epidermal growth factor (EGF) for binding on its receptor EGFR. This prevents activity of Src kinase and dephosphorylates Receptor of activated C kinase 1 (RACK1). RACK1 activation of PP2A leads to dephosphorylation and nuclear translocation of CAR (Figure 1) [24]. Once in the nucleus, CAR heterodimerizes with its partner Retinoid X Receptor (RXR), and binds to its response elements: Phenobarbital response element module (PBREM) [25]. PBREMs are located on the promoters of CAR-target genes such as *CYP2B6* for the human form of CAR, or *Cyp2b10* for murine CAR. The CAR/RXR heterodimer recruits specific co-activators allowing its interaction with the transcription machinery. Glucocorticoid receptor interacting protein-1 (GRIP-1), Proliferator activated receptor coactivator 1α (PGC1α), and Steroid receptor co-activator (SRC-1) allow the transcription of CAR-target genes [26–28].

3. Functional Roles of CAR in Peripheral Organs

CAR is expressed mainly in the liver, and also in the intestines and kidneys [29]. Most of the functions of CAR as a stress sensor occur in the liver, the main peripheral organ responsible for xenobiotics and metabolic stress responses [30]. The generation of CAR deficient mice represented a milestone to understand the complex roles of CAR in physiological and pathological settings [31]. CAR deletion induces sensitivity to toxins due to the disruption of detoxification enzymes regulation. Thus, CAR coordinates the expression of hepatic genes involved in xenobiotic catabolism, including phase I and II biotransformation enzymes and transporters [32]. Importantly, two main groups of xenobiotics are described as modulators of CAR activity: drugs and environmental pollutants (Tables 2 and 3). Hepatoprotection of CAR against xenobiotics does not only consist of induction of detoxification genes but also in specific gene repression. For instance, CAR prevents the induction of CYP4A, a major lipid peroxidation enzyme, by augmenting superoxide dismutase-3 (SOD) to limit oxidative stress [10].

Table 2. Environmental contaminants identified as CAR activators.

Contaminants	Species	References
Diphenamid (Pesticide)	Human	[33]
Phenothrin (Pesticide)	Human	[33]
Permethrin (Pesticide)	Rat	[34]
Perfluorocarboxylic acid, PFCA (Detergent)	Mice	[35,36]
Perfluorooctanoic acid, PFOA (Detergent)	Mice	[3,37]
Perfluorooctanesulfonic acid PFOS (Detergent)	Rat	[38]
Alachlor (Pesticide)	Mice	[39]
Arsenite (Chemical)	Mice	[39]
Azo dyes (Paint)	Mice/Rat	[40]
Bisphenol A (Chemical)	Mice	[39]
Butylate (Pesticide)	Mice	[39]
Chlorpropham (Pesticide)	Mice	[39]
Chlorpyrifos (Pesticide)	Mice	[39]
Cypermythrin (Pesticide)	Mice	[39]
Cyproconazole (Pesticide)	Mice	[41]
DBP, Di-n-butylphtalate (Plasticizer)	Rat	[42]
DDE, Dichlorodiphenyldichloroethylene (Pesticide)	Rat	[43]
Di-isononyl phthalate (DiBP) (Plasticizer)	Human	[44]
O,p-DDT,1,1,1-Tichloro-2-(2-chlorophenyl)2-(4-chlorophenyl)ethane (Pesticide)	Mice/Rat	[43,45]
DEHP (Plasticizer)	Mice/Human	[39,46]
Dieldrine (Pesticide)	Mice	[47]
Endosulfan (Pesticide)	Mice/Human	[39,48]
Fernitrothion (Pesticide)	Mice	[39]
Polycyclic aromatic hydrocarbons	Mice	[49]
Imazalil (Pesticide)	Mice	[39]
Kepone (Pesticide)	Mice	[39]
MEHP (Plasticizer)	Mice	[39]
Metolachlor (Pesticide)	Mice	[39]
Methoxychlor (Pesticide) and metabolites	Mice/Rat/Human	[39,48,50]
Monosodium methane arsenate	Mice	[39]
Nonylphenol (Plasticizer)	Human	[4]
Parathion (Pesticide)	Mice	[4]
PCB Polychlorobiphenyles (Chemical derivatives)	Mice	[45]
Propachlor (Pesticide)	Mice	[39]
2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD)	Mice	[51]
SSS-Tributylphosphorotithioate (Pesticide)	Mice	[39]
Triclopyr (Pesticide)	Mice	[39]

Table 3. Drugs presenting activation or repression action on CAR.

Drugs	Species	Action	References
Neticonazole	Human	Activator	[33]
Rimcazole	Human	Activator	[33]
Sorafenib	Human	Inhibitor	[52]
Rimonabant	Human	Inhibitor	[52]
DL5050	Human	Activator	[53]
Valproic Acid	Human	Activator	[54]
Acetaminophen	Mice	Activator	[55,56]
Triazole Antifungals	Mice	Activator	[41,57]
Artemisinin	Mice/Human	Activator	[58,59]
Benzodiazepines	Human	Inhibitor	[60]
Clotrimoxazole	Human	Inhibitor	[31]
Cocaine	Human	Inhibitor	[61]
Dexamethasone	Human	Activator	[62,63]
Ketoconazole	Human	Inhibitor	[64]
Meclizine	Mice/Human	Activator (Mice) Inhibitor (Human)	[65]
Metamizole	Human	Activator	[66]
Methotrexate	Mice	Inhibitor	[67,68]
Orphenadrine	Rat	Activator	[69]
Phenobarbital	Mice, Rat	Activator	[70,71]
Phenytoin	Human	Activator	[72–74]
Statins	Human	Activator	[75,76]

3.1. CAR as an Endobiotic Stress Sensor

CAR controls the metabolism of endogenous molecules. The degradation product of heme, bilirubin, is a potentially highly neurotoxic endogenous compound in case of extended accumulation. Glucuronidation by UGT1A1 enzyme is the main detoxification pathway of bilirubin, then secreted into the bile by MRP2 active transporter. CAR is involved in bilirubin clearance by inducing UGT1A1 and Glutathione S-transferase A1 (GSTa1) enzymes [77], as well as OATP2 and MRP2 transporters [78].

CAR activation in mice induces the expression of enzymes (CYP3A11, SULT2A1) and transporters (MRP3) involved in bile acid metabolism and elimination [56]. Bile acids, produced by the liver, are necessary for cholesterol elimination and dietary lipids absorption. Hepatic cholesterol is degraded in two primary bile acids, cholic acid (CA) and chenodeoxycholic acid (CDCA). In the intestine, these bile acids are hydroxylated by the microbiota into secondary bile acids, deoxycholic acid and lithocholic acid (LCA), reabsorbed and transported to the liver [79]. Wild type mice subjected to a diet containing 0.5% of LCA present Cyp2b10 induction which is not seen in CAR knock-out mice subjected to the same diet [56]. Furthermore, TCPOBOP-induced CAR activation protects the liver from cholestasis by allowing the production of non-toxic bile acids [80]. CAR seems to act independently from Farnesoid X Receptor (FXR) receptor, a known xenosensor of bile acids. In FXR and PXR deficient mice, elevated cholic acid levels induce expression of CAR and its target genes which metabolize potentially-toxic cholic acid [78].

3.2. CAR as a Regulator of Steroid and Thyroid Hormones

The involvement of CAR in hormone regulation was first suggested when androstanol and androstenol were identified as CAR ligands. These steroids inhibit CAR activity by inducing the dissociation of CAR from the co-activator SRC1 [2]. Progesterone and testosterone also inhibit CAR activity [59]. Steroid hormone levels are maintained by a dynamic balance between synthesis and inactivation due to limited storage capacity. Therefore, coordination between synthesis and biotransformation is necessary to maintain normal physiological functions. Many CYPs (CYP11, CYP17, CYP19, CYP21) are responsible for steroid hormone synthesis, catabolism and inactivation [81]. The liver is the main site of steroid catabolism where CAR plays an important role through regulation of CYPs and sulfotransferases expression. TCPOBOP activation of CAR induces estrogen catabolism to promote its excretion [82]. CAR also regulates estrogen sulfotransferase (EST) encoded by the *SULT1E1* gene which catalyzes the conjugation of a sulfate on estrogens, producing inactive forms [83].

Several studies outline a link between CAR and thyroid hormones activity. Phenobarbital chronic treatment leads to thyroid hypertrophy in rats and humans [84]. Other studies revealed that phenobarbital or phenytoin activation of CAR lowered circulating thyroxine (T4) levels [15,84,85]. CAR is involved in thyroid hormone catabolism through regulation of phase II enzymes UGT1A1 and SULT1A1 [4,86]. Experimental evidence demonstrated CAR regulation of the catabolism of the stress hormone corticosterone [87]. CAR knockout mice developed hypercorticism associated with obesity, glucose intolerance, insulin insensitivity, dyslipidemia and hepatic steatosis [87]. Remarkably, the latter modifications were absent, or minor, in CAR knockout females, developing similar metabolic disorders only when ovariectomized. Analysis of the hepatic transcriptome revealed a role of CAR in the catabolism of corticosterone [87]. CAR deletion resulted in down-regulation of enzymes involved in the hepatic catabolism of steroid hormones, specifically Hydroxy-Delta-5-Steroid Dehydrogenase, 3 Beta- And Steroid Delta-Isomerase 1 (Hsd3b1), Hydroxy-Delta-5-Steroid Dehydrogenase, 3 Beta- And Steroid Delta-Isomerase 5 (Hsd3b5), Hydroxy-Delta-5-Steroid Dehydrogenase, 11 Beta- And Steroid Delta-Isomerase 1 (Hsd11b1), Aldo-Keto Reductase Family 1 Member C14 (Akr1c14), Steroid 5 Alpha-Reductase 1 (Srd5a1) and Aldehyde Dehydrogenase 3 Family Member A2 (Aldh3a2) [87]. Altogether, these results highlight the important role of CAR in the maintenance of endocrine and metabolic equilibrium. The CAR-dependent regulation of hormone catabolism constitutes a lever for the maintenance of energy homeostasis.

3.3. CAR as a Sensor of Fasting and Caloric Restriction

The activity of CAR is modulated according to physiological and pathophysiological conditions (Figure 1). Resistance to weight-loss during extended fasting or caloric restriction requires the establishment of specific metabolic pathways. CAR deficient mice present a defect in extended-fasting resistance to weight loss [15]. Importantly, fasting activates CAR through interaction of PGC1α and Hepatocyte nuclear factor 4 α (HNF4α) with response elements that regulate expression of CAR [14]. Nuclear receptor Peroxisome proliferator-activated receptors α (PPARα) is essential in CAR induction during response to fasting [88]. The glucocorticoid receptor (GR) is also involved, as its response elements have been identified on the CAR promoter [89]. Finally, a study conducted on HepG2 cells revealed the involvement of SAPK and ETS Like-1 (Elk1) in regulating CAR expression [18]. Collectively, these data support CAR as a nuclear receptor that reacts to nutritional conditions such as fasting and caloric restriction.

3.4. CAR as a Glucose Sensor

A role of CAR in glucose homeostasis was first hypothesized as a result of clinical observations obtained from phenobarbital-treated diabetic patients who presented improved insulin sensitivity and decreased glycaemia levels [90,91]. Experimentally, diabetic mice present improved glucose tolerance following treatment with the CAR agonist TCPOBOP [12]. Improvement of glucose tolerance is mainly

due to the suppression of hepatic glucose production. CAR activation represses the gluconeogenesis limiting enzymes Phosphoenolpyruvate carboxykinase (PEPCK) and Glucose 6-phosphatase (G6Pase). A number of mechanisms were suggested, including competition of CAR with Forkhead box protein O1 (FoxO1) and HNF4α for binding on Iron-responsive element (IRE) and Hepatocyte nuclear factor 4 α responsive element (HNF4RE), respectively located on promoters of PEPCK and G6Pase [92]. Furthermore, CAR could bind to SRC2/GRIP1 and PGC1α which are two co-activators of HNF4α, lowering expression of gluconeogenesis genes [93]. Additional evidence suggests that nuclear translocation of CAR allows physical interaction with PGC1α, allowing the recruitment of E3 Culline Ligase and interaction to Promyelocytic leukemia (PML) nuclear bodies. This leads to PGC1α degradation by the proteasome and consequent repression of gluconeogenesis genes [94]. Finally, data suggest the action of CAR through SULT2b1 regulation on HNF4α deacetylation, which could prevent CAR nuclear translocation and action on gluconeogenesis genes [95]. CAR repression of gluconeogenesis genes was confirmed on human hepatocyte primary cultures [96]. Overall, this reveals a glucose sensing action of CAR through regulation of hepatic gluconeogenesis.

3.5. CAR as a Lipid Sensor

The role of CAR in the regulation of lipid metabolism remains controversial, with studies reporting both anti-lipogenic [12,13] and pro-lipogenic functions [97,98]. Chronic treatment with CAR activators, such as phenobarbital or valproic acid, is associated with hepatic metabolic disorders [99,100]. These clinical observations were confirmed using animal models, revealing a CAR-dependent control of fatty acid catabolism and hepatic lipogenic genes. CAR acts as an anti-lipogenic factor by interfering with PPARα on β-oxydation of fatty acids [101]. In ob/ob obese mice subjected to a high fat diet, CAR activation leads to a decreased hepatic steatosis by inhibiting de novo lipogenesis via Stearoyl-CoA desaturase-1 (Scd1), Fatty acid synthase (Fas), Acetyl coa carboxylase (Acc), and SREBP-1c repression [12,13]. Furthermore, CAR may act on de novo lipogenesis genes through the LXR nuclear receptor, regulator of hepatic lipogenesis genes. CAR could contribute to the inactivation of oxysterols which are endogenous ligands of LXR through regulation of Sult2B1b sulfotransferase expression. Oxysterol inactivation leads to decreased LXR activity and reduction of the LXR–SREBP pathway [102]. Accordingly, Sult2B1b deficient mice treated with TCPOBOP do not present repression of de novo lipogenesis genes [12].

However, recent data reported a prolipogenic effect of CAR, inducing hepatic lipid accumulation upon its activation [98]. This occurs through the induction of hepatic lipogenic genes, including patatin-like phospholipase domain-containing protein 3 (*Pnpla3*), a gene whose polymorphism is associated with the pathogenesis of non-alcoholic fatty liver diseases (NAFLD). The underlying mechanism involves the transcription factor Carbohydrate-responsive element-binding protein (ChREBP), a master regulator of hepatic carbohydrate-lipid metabolism [98]. The same prolipogenic effect was reported on human hepatocytes primary cultures, revealing that Thyroid hormone responsive protein (*Spot14*), a CAR target gene, is an important modulator of hepatic lipogenesis [97].

The contradictory effect of CAR on lipid metabolism may be explained considering the dissimilar physiological settings across studies. CAR appears to inhibit lipogenesis in a situation of metabolic stress induced by a high-fat diet, while activating it when a chemical stress is caused by the presence of a pharmacological agonist. Lipid droplet accumulation following activation of CAR by a xenobiotic could allow the neutralization of the xenobiotic before elimination from the cell. This hypothesis remains to be verified. Overall, these data indicate CAR as a stress sensor, responding in a stress-depend manner to allow cell homeostasis.

3.6. CAR as a Hypoxia Sensor

CAR was reported to cross-talk with Hypoxia inductible factor (HIF1) [16]. Hypoxia is a pathologic condition that activates HIF1 transcription and AMPK in the same way as energetic depletion and oxidative stress [103]. HIF1 is degraded during normoxic conditions and it is stabilized by hypoxia to

regulate transcription of its target genes: Vascular Endothelial Growth Factor (*VEGF*), erythropoietine (*EPO*) and glycolytic enzymes. Interestingly, treatment of mice with a HIF1 activator induces nuclear translocation of CAR and the expression of Cyp2b10. Furthermore, CAR can interact with HIF1 when binding on PBREMs [16]. This initial evidence suggests the engagement of CAR during reduced oxygen levels as an attempt to maintain cell homeostasis.

3.7. CAR Intestinal Response to Inflammatory Stress

CAR is down-regulated in intestinal biopsies obtained from Crohn's disease or Ulcerative Colitis patients and in colitis mouse tissues [104]. Consistently, CAR activation accelerates intestinal mucosal healing both in vitro and in vivo, suggesting that CAR plays a role in the maintenance of intestinal mucosal integrity, while CAR dysfunction could contribute to the pathogenesis of inflammatory bowel diseases. In addition, a link between CAR and the gut microbiota was reported. In mice, pharmacological activation of CAR by its ligand TCPOBOP impacted the microbiome composition and down-regulated bile-acid-metabolizing bacteria in the intestine [105]. A deficiency of CAR also modified the microbiota, increasing the pro-inflammatory bacteria and cytokines [106]. CAR may act on immune surveillance to prevent the colonization of harmful bacteria [106]. These data suggest that CAR regulates microbiota composition and responds to intestinal inflammatory stresses.

3.8. CAR Protects from Acute Kidney Injury

A role of CAR was recently demonstrated in mediating a kidney-liver cross-talk in Acute kidney injury (AKI) which is characterized by the sudden impairment of kidney function [107]. CAR activation by its agonist prevented the development of AKI-induced fatty liver and liver injury, and improved kidney function [107]. The protective effect of CAR agonist was abolished in CAR knockout mice. These results suggest that CAR could be a target in the management of hepatic steatosis and kidney function in patients with AKI.

4. Functional Roles of CAR in the Brain: Focus on the Neurovascular Unit

The brain integrates multiple inputs from and to the periphery, providing the adequate adaptive response to environmental changes. This includes the regulation of energy homeostasis based on highly coordinated interactions between the brain and peripheral metabolic organs [108]. Here, we examine the available evidence indicating expression of CAR in the brain, then extending to its potential role in a peripheral–brain interplay.

4.1. Brain Expression, Regulation and Function of CAR

While studied in peripheral organs, it is only recently that the functional expression of CAR was examined in the brain, in healthy and pathological conditions. Outing its expression patterns at the neurovascular unit (NVU) is important to unveil novel functional aspects at a key physiological brain–peripheral interface and within a multi-cellular neuronal, glial, and cerebrovascular structure [109–111]. Within the NVU, the blood–brain barrier (BBB) represents a key dynamic interface functioning as a protective brain gatekeeper [109,111] and as a hindrance for the delivery of systemically administered brain xenobiotics [112].

Early reports described mRNA and protein levels expression of CAR in the brain. In humans, analysis of mRNA in whole tissue homogenates obtained from one adult brain specimen showed detectable, although low as compared to liver and intestine, expression of CAR [113]. Others reported CAR mRNA in brain areas, specifically in the nucleus accumbens, caudate nucleus, and putamen [114,115]. In rodents, the expression of CAR was demonstrated at the mRNA or protein levels in the cerebral cortex, hippocampus, midbrain and the cerebellum [116–119]. An available human protein ATLAS dataset outlines the expression of CAR in the brain, further indicating levels in the cerebral cortex, hippocampus, amygdala, hypothalamus and the basal ganglia [120]. To date, no specific studies have examined the impact of gender and aging on brain CAR expression.

Supporting a possible role at the cerebrovascular interface, CAR mRNA and protein expression were shown in an in vitro BBB model, using human-derived cerebral endothelial cells [121]. The functional expression of CAR, and other cognate nuclear receptors, at the BBB was demonstrated by quantifying specific downstream P450 cytochromes or MDR gene targets [19,122–126]. Interestingly, acetaminophen treatment in mice increased the functional expression of Abcb1 transporter (P-gp) at the BBB by a CAR-dependent mechanism [126]. These results are significant, considering the strategic expression of xenobiotic nuclear receptors at the NVU interface. In other brain cell types, the role of CAR was examined in the settings of chemotherapy and pesticide-induced neurotoxicity [127]. In neuroblastoma (SH-SY5Y) and glioblastoma (U373-MG) cell lines, up-regulation of CAR mRNA and specific P450 cytochromes (CYP3A4, CYP2C8, etc.) was reported following treatment with cyclophosphamide, also increasing reactive oxygen species (ROS) production, and upregulating the expression of pro-apoptotic markers caspase-3, caspase-9, Bax, and p53 [127].

Modulation of CAR directly impacts the expression of biotransformation transporters and enzymes, possibly affording neuroprotection [7,124,128–130]. Available evidence supports a use for CITCO, a CAR agonist, as a potential therapy for gliomas. CITCO inhibits the growth and expansion of cancer stem cells by inducing cell cycle arrest and apoptosis, without affecting primary astrocytes [129]. Additional evidence indicated that stimulation of primary cultures of porcine brain capillary endothelial cells with CITCO provoked a significant up-regulation of Abcb1 (P-glycoprotein) and Abcg2 (breast cancer resistance protein) efflux-transporters at the RNA, protein and transport levels [131]. Another study showed that exposure to Triclocarban (3,4,4′-trichlorocarbanilide), an antibacterial, induced apoptosis of embryonic neuronal cells. The mechanism encompassed a caspase-3 dependent process with a CAR-mediated signaling activation. Furthermore, triclocarban induced CAR hypomethylation along with a disruption of the epigenetic status of neuronal cells and inhibiting post-translational protein modifications [118]. Collectively, this initial evidence supports the continuous investigation of the varying roles of CAR in brain cells.

4.2. CAR and Brain Disease Conditions: Initial Clinical and Experimental Clues

In humans, a genetic association study identified a mutation of CAR (NR1I3) in a cohort of pediatric subjects affected by the Kleefstra syndrome (KS) (OMIM#610253), a condition characterized by neurodevelopmental delay, dysmorphic features, behavioral and intellectual disabilities. However, the pathophysiology of CAR mutation in KS patients remains understudied [132]. From a pre-clinical stand point, loss of CAR in mice was associated with memory defects and anxiety-like behavior [133]. Electroencephalographic changes in CAR−/− mice during sleep or awake periods were found to correlate with memory outcome. This phenotype was accompanied by morphologic glial modifications suggestive of a mild neuro-inflammatory processes. Moreover, expression of the tight junction protein ZO-1 was reduced in isolated brain capillaries, pointing to BBB permeability [133]. Taken together, this initial indication suggests that pharmacological, or genetic, modulation of CAR could be one element perhaps contributing to neurological dysfunctions [118,133]. Understanding the functional relevance of CAR expression in brain cells may be significant to unravel new molecular mechanisms involved in neurodevelopmental diseases.

The memory defects and anxiety-like behavior displayed by the CAR knock-out mice could be linked with the endocrine and metabolic disorders reported in this model [87,133]. A similar link was suggested in another study, indicating that CAR selective activation alleviates high fat diet-induced obesity. The authors suggested that the hypothalamic and pituitary functions of CAR may have contributed to the hepatic phenotype [13]. Although CAR is not expressed in brown and white adipose tissues (BAT, WAT), the authors observed increased BAT energy expenditure, and activation of adipose triglyceride lipase gene expression in WAT upon CAR activation. This suggests an indirect effect of CAR activation in tissues outside the adipose tissue [108]. Tissue-specific CAR knockout mice (e.g, hepatic) could constitute a tool to further elucidate the varying roles of CAR in physiological and pathological settings.

5. Conclusions: Can We Integrate CAR within a Peripheral–Brain Axis?

Existing evidence supports a multi-facet role of CAR, capturing the physiological state of varying cell types and contributing to organs homeostasis. Available data support the hypothesis that CAR functions may extend to a dialogue between multiple organs, perhaps including the central nervous system (Figure 2). The role of CAR could differ according to brain regions as suggested [134]. Furthermore, in the brain, CAR may be involved in the control of energy homeostasis through a cross-talk with the liver or the adipose tissue [13,87,133]. These associations are supported by clinical and experimental data revealing a link between obesity, cognitive impairment and BBB dysfunction. Rats fed with a high fat/sugar diet present with hippocampal BBB permeability, contingent to weight gain and concomitant to hippocampal-dependent learning defects [135]. Pathological conditions such as inflammatory bowel diseases (IBD; e.g., ulcerative colitis (UC); Crohn's disease (CD)) [136,137] can present extra-intestinal, brain symptoms. Approximately 3% of subjects suffering from IBD display neurological symptoms [137] and cerebrovascular disorders occur in 0.12–4% of cases [138]. The latter is important as BBB breakdown is emerging as a participant mechanism of dysregulated peripheral–CNS interplay, promoting or contributing to brain diseases [110,139].

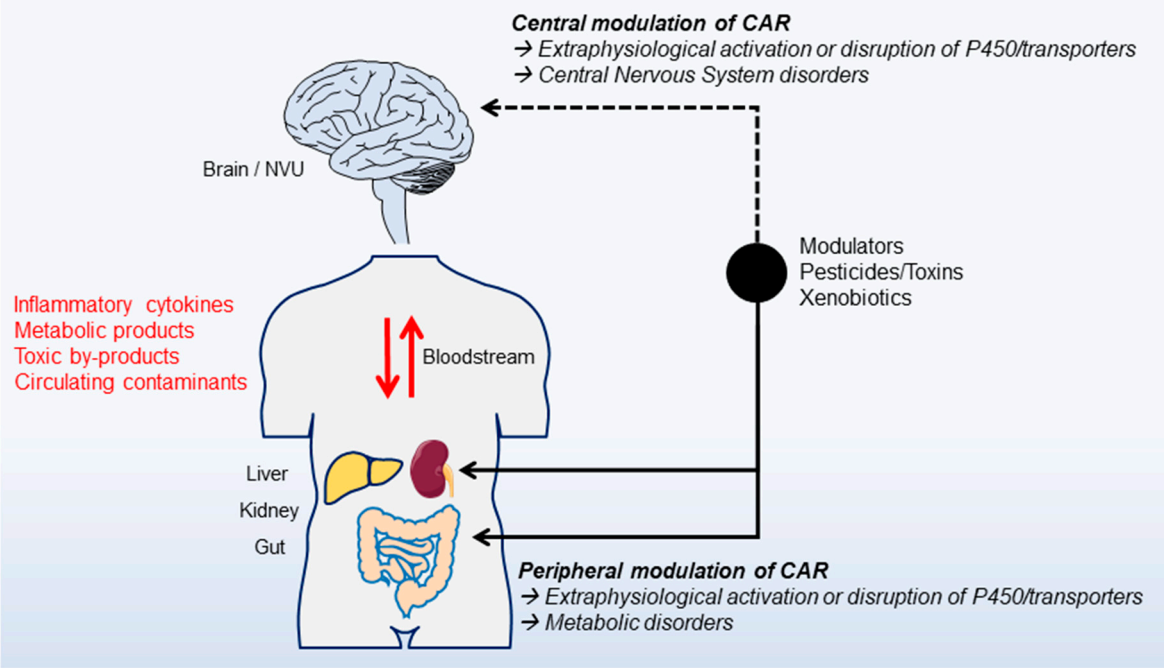

Figure 2. Modulation of CAR activity and a brain-peripheral dialogue. Peripheral or central activities of CAR can be modulated by endogenous or exogenous molecules (e.g., pesticides, toxins, xenobiotics), leading to a disruption of detoxifying p450 cytochromes and transporters regulation. A pathological brain-peripheral dialogue may enable disease conditions via soluble circulating blood factors, such as pro-inflammatory cytokines, metabolic or toxic by-products.

The exact role of nuclear receptors within the peripheral–brain axis needs to be fully deciphered. Experimentally, a CAR mediated microbiota–gut–brain communication was suggested [140] given the emerging role of this receptor in the brain [133] and in microbiota–gut interaction [104]. Experimentally, lack of CAR expression in mice was associated with metabolic disruptions including obesity, diabetes and hepatic steatosis [87] Concomitantly to BBB permeability, impairment in recognition memory and increased anxiety-like behavior were observed [133]. These studies support the hypothesis of a multi-organ pathological impact of CAR deletion. Further studies are required to understand whether the peripheral metabolic disorders lead to brain dysregulations or whether NVU cells damage in specific brain areas is the initiator of peripheral pathology. In summary, a holistic role of CAR fits

within the accumulating evidence indicating a peripheral–brain interplay, as occurring in metabolic and CNS diseases. Modulating CAR during pathological conditions could represent a new strategy to prevent or target metabolic modifications impacting the periphery and the brain.

Author Contributions: All authors have read and agreed to the published version of the manuscript. Conceptualization: L.M.-L., N.M., J.-M.P.; writing-original drat preparation: L.M.-L., N.M., F.O., C.L., B.B., I.F.-P.; writing—review and editing: L.M.-L., N.M., F.O.

Funding: This research was funded by ANR-Hepatobrain, PNRPE Synepest, ANSES Epidemicmac, MUSE-iSite University of Montpellier, ANSES Xenomix.

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

References

1. Wei, P.; Zhang, J.; Egan-Hafley, M.; Liang, S.; Moore, D.D. The nuclear receptor CAR mediates specific xenobiotic induction of drug metabolism. *Nature* **2000**, *407*, 920–923. [CrossRef] [PubMed]
2. Forman, B.M.; Tzameli, I.; Choi, H.S.; Chen, J.; Simha, D.; Seol, W.; Evans, R.M.; Moore, D.D. Androstane metabolites bind to and deactivate the nuclear receptor CAR-beta. *Nature* **1998**, *395*, 612–615. [CrossRef] [PubMed]
3. Kawamoto, T.; Sueyoshi, T.; Zelko, I.; Moore, R.; Washburn, K.; Negishi, M. Phenobarbital-responsive nuclear translocation of the receptor CAR in induction of the CYP2B gene. *Mol. Cell. Biol.* **1999**, *19*, 6318–6322. [CrossRef] [PubMed]
4. Hernandez, J.; Mota, L.; Baldwin, W. Activation of CAR and PXR by Dietary, Environmental and Occupational Chemicals Alters Drug Metabolism, Intermediary Metabolism, and Cell Proliferation. *Curr. Pharm. Person. Med.* **2009**, *7*, 81–105. [CrossRef] [PubMed]
5. Li, D.; Mackowiak, B.; Brayman, T.G.; Mitchell, M.; Zhang, L.; Huang, S.; Wang, H.; Spring, S. Genome-wide Analysis of Human Constitutive Androstane Receptor (CAR) Transcriptome in Wild-type and CAR-knockout HepaRG cells. *Biochem. Pharmacol.* **2015**, *98*, 190–202. [CrossRef]
6. Li, H.; Wang, H. Activation of xenobiotic receptors: Driving into the nucleus. *Expert Opin. Drug Metab. Toxicol.* **2010**, *6*, 409–426. [CrossRef]
7. Maglich, J.M.; Stoltz, C.M.; Goodwin, B.; Hawkins-Brown, D.; Moore, J.T.; Kliewer, S.A. Nuclear pregnane X receptor and constitutive androstane receptor regulate overlapping but distinct sets of genes involved in xenobiotic detoxification. *Mol. Pharmacol.* **2002**, *62*, 638–646. [CrossRef] [PubMed]
8. Saini, S.P.S.; Sonoda, J.; Xu, L.; Toma, D.; Uppal, H.; Mu, Y.; Ren, S.; Moore, D.D.; Evans, R.M.; Xie, W. A Novel Constitutive Androstane Receptor-Mediated and CYP3A-Independent Pathway of Bile Acid Detoxification. *Mol. Pharmacol.* **2004**, *65*, 292–300. [CrossRef]
9. Sugatani, J.; Yamakawa, K.; Yoshinari, K.; Miwa, M.; Machida, T.; Takagi, H.; Mori, M.; Kakizaki, S.; Sueyoshi, T.; Negishi, M. Identification of a defect in the UGT1A1 gene promoter and its association with hyperbilirubinemia. *Biochem. Biophys. Res. Commun.* **2002**, *292*, 492–497. [CrossRef]
10. Ueda, A.; Hamadeh, H.K.; Webb, H.K.; Yamamoto, Y.; Sueyoshi, T.; Afshari, C.A.; Lehmann, J.M.; Negishi, M. Diverse roles of the nuclear orphan receptor CAR in regulating hepatic genes in response to phenobarbital. *Mol. Pharmacol.* **2002**, *61*, 1–6. [CrossRef]
11. Locker, J.; Tian, J.; Carver, R.; Concas, D.; Cossu, C.; Ledda-Columbano, G.M.; Columbano, A. A common set of immediate-early response genes in liver regeneration and hyperplasia. *Hepatology* **2003**, *38*, 314–325. [CrossRef] [PubMed]
12. Dong, B.; Saha, P.K.; Huang, W.; Chen, W.; Abu-Elheiga, L.A.; Wakil, S.J.; Stevens, R.D.; Ilkayeva, O.; Newgard, C.B.; Chan, L.; et al. Activation of nuclear receptor CAR ameliorates diabetes and fatty liver disease. *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 18831–18836. [CrossRef]
13. Gao, J.; He, J.; Zhai, Y.; Wada, T.; Xie, W. The constitutive androstane receptor is an anti-obesity nuclear receptor that improves insulin sensitivity. *J. Biol. Chem.* **2009**, *284*, 25984–25992. [CrossRef]
14. Ding, X.; Lichti, K.; Kim, I.; Gonzalez, F.J.; Staudinger, J.L. Regulation of constitutive androstane receptor and its target genes by fasting, cAMP, hepatocyte nuclear factor alpha, and the coactivator peroxisome proliferator-activated receptor gamma coactivator-1alpha. *J. Biol. Chem.* **2006**, *281*, 26540–26551. [CrossRef]

15. Maglich, J.M.; Watson, J.; McMillen, P.J.; Goodwin, B.; Willson, T.M.; Moore, J.T. The nuclear receptor CAR is a regulator of thyroid hormone metabolism during caloric restriction. *J. Biol. Chem.* **2004**, *279*, 19832–19838. [CrossRef]
16. Shizu, R.; Shindo, S.; Yoshida, T.; Numazawa, S. Cross-talk between constitutive androstane receptor and hypoxia-inducible factor in the regulation of gene expression. *Toxicol. Lett.* **2013**, *219*, 143–150. [CrossRef]
17. Shindo, S.; Numazawa, S.; Yoshida, T. A physiological role of AMP-activated protein kinase in phenobarbital-mediated constitutive androstane receptor activation and CYP2B induction. *Biochem. J.* **2007**, *401*, 735–741. [CrossRef]
18. Osabe, M.; Sugatani, J.; Takemura, A.; Kurosawa, M.; Yamazaki, Y.; Ikari, A.; Miwa, M. Up-regulation of CAR expression through Elk-1 in HepG2 and SW480 cells by serum starvation stress. *FEBS Lett.* **2009**, *583*, 885–889. [CrossRef]
19. Xu, R.X.; Lambert, M.H.; Wisely, B.B.; Warren, E.N.; Weinert, E.E.; Waitt, G.M.; Williams, J.D.; Collins, J.L.; Moore, L.B.; Willson, T.M.; et al. A structural basis for constitutive activity in the human CAR/RXRα heterodimer. *Mol. Cell* **2004**, *16*, 919–928. [CrossRef]
20. Shan, L.; Vincent, J.; Brunzelle, J.S.; Dussault, I.; Lin, M.; Ianculescu, I.; Sherman, M.A.; Forman, B.M.; Fernandez, E.J. Structure of the murine constitutive androstane receptor complexed to androstenol: A molecular basis for inverse agonism. *Mol. Cell* **2004**, *16*, 907–917. [CrossRef]
21. Yoshinari, K.; Kobayashi, K.; Moore, R.; Kawamoto, T.; Negishi, M. Identification of the nuclear receptor CAR:HSP90 complex in mouse liver and recruitment of protein phosphatase 2A in response to phenobarbital. *FEBS Lett.* **2003**, *548*, 17–20. [CrossRef]
22. Sueyoshi, T.; Moore, R.; Sugatani, J.; Matsumura, Y.; Negishi, M. PPP1R16A, the membrane subunit of protein phosphatase 1beta, signals nuclear translocation of the nuclear receptor constitutive active/androstane receptor. *Mol. Pharmacol.* **2008**, *73*, 1113–1121. [CrossRef]
23. Tzameli, I.; Pissios, P.; Schuetz, E.G.; Moore, D.D. The xenobiotic compound 1,4-bis[2-(3,5-dichloropyridyloxy)] benzene is an agonist ligand for the nuclear receptor CAR. *Mol. Cell. Biol.* **2000**, *20*, 2951–2958. [CrossRef]
24. Mutoh, S.; Osabe, M.; Inoue, K.; Moore, R.; Pedersen, L.; Perera, L.; Rebolloso, Y.; Sueyoshi, T.; Negishi, M. Dephosphorylation of threonine 38 Is required for nuclear translocation and activation of human xenobiotic receptor CAR (NR1I3). *J. Biol. Chem.* **2009**, *284*, 34785–34792. [CrossRef] [PubMed]
25. Mäkinen, J.; Frank, C.; Jyrkkärinne, J.; Gynther, J.; Carlberg, C.; Honkakoski, P. Modulation of mouse and human phenobarbital-responsive enhancer module by nuclear receptors. *Mol. Pharmacol.* **2002**, *62*, 366–378. [CrossRef]
26. Min, G.; Kemper, J.K.; Kemper, B. Glucocorticoid receptor-interacting protein 1 mediates ligand-independent nuclear translocation and activation of constitutive androstane receptor in vivo. *J. Biol. Chem.* **2002**, *277*, 26356–26363. [CrossRef]
27. Shiraki, T.; Sakai, N.; Kanaya, E.; Jingami, H. Activation of orphan nuclear constitutive androstane receptor requires subnuclear targeting by peroxisome proliferator-activated receptor γ coactivator-1α: A possible link between xenobiotic response and nutritional state. *J. Biol. Chem.* **2003**, *278*, 11344–11350. [CrossRef]
28. Wright, E.; Vincent, J.; Fernandez, E.J. Thermodynamic characterization of the interaction between CAR-RXR and SRC-1 peptide by isothermal titration calorimetry. *Biochemistry* **2007**, *46*, 862–870. [CrossRef]
29. Baes, M.; Gulick, T.; Choi, H.S.; Martinoli, M.G.; Simha, D.; Moore, D.D. A new orphan member of the nuclear hormone receptor superfamily that interacts with a subset of retinoic acid response elements. *Mol. Cell. Biol.* **1994**, *14*, 1544–1552. [CrossRef]
30. Zmrzljak, U.P.; Rozman, D. Circadian regulation of the hepatic endobiotic and xenobitoic detoxification pathways: The time matters. *Chem. Res. Toxicol.* **2012**, *25*, 811–824. [CrossRef]
31. Moore, L.B.; Parks, D.J.; Jones, S.A.; Bledsoe, R.K.; Consler, T.G.; Stimmel, J.B.; Goodwin, B.; Liddle, C.; Blanchard, S.G.; Willson, T.M.; et al. Orphan nuclear receptors constitutive androstane receptor and pregnane X receptor share xenobiotic and steroid ligands. *J. Biol. Chem.* **2000**, *275*, 15122–15127. [CrossRef]
32. Hernandez, J.P.; Mota, L.C.; Huang, W.; Moore, D.D.; Baldwin, W.S. Sexually dimorphic regulation and induction of P450s by the constitutive androstane receptor (CAR). *Toxicology* **2009**, *256*, 53–64. [CrossRef]
33. Lynch, C.; Mackowiak, B.; Huang, R.; Li, L.; Heyward, S.; Srilatha, S.; Wang, H.; Xia, M. Identification of Modulators that Activate the Constitutive Androstane Receptor from the Tox21 10K Compound Library. *Toxicol. Sci.* **2019**, *1*, 282–292. [CrossRef] [PubMed]

34. Fujino, C.; Watanabe, Y.; Sanoh, S.; Nakajima, H.; Uramaru, N.; Kojima, H.; Yoshinari, K.; Ohta, S.; Kitamura, S. Activation of PXR, CAR and PPARα by pyrethroid pesticides and the effect of metabolism by rat liver microsomes. *Heliyon* **2019**, *5*, e02466. [CrossRef]
35. Abe, T.; Takahashi, M.; Kano, M.; Amaike, Y.; Ishii, C.; Maeda, K.; Kudoh, Y.; Morishita, T.; Hosaka, T.; Sasaki, T.; et al. Activation of nuclear receptor CAR by an environmental pollutant perfluorooctanoic acid. *Arch. Toxicol.* **2017**, *91*, 2365–2374. [CrossRef] [PubMed]
36. Cheng, X.; Klaassen, C.D. Perfluorocarboxylic acids induce cytochrome P450 enzymes in mouse liver through activation of PPAR-α and CAR transcription factors. *Toxicol. Sci.* **2008**, *106*, 29–36. [CrossRef]
37. Oshida, K.; Vasani, N.; Jones, C.; Moore, T.; Hester, S.; Nesnow, S.; Auerbach, S.; Geter, D.R.; Aleksunes, L.M.; Thomas, R.S.; et al. Identification of chemical modulators of the constitutive activated receptor (CAR) in a gene expression compendium. *Nucl. Recept. Signal.* **2015**, *13*, e002. [CrossRef]
38. Elcombe, C.R.; Elcombe, B.M.; Foster, J.R.; Chang, S.C.; Ehresman, D.J.; Butenhoff, J.L. Hepatocellular hypertrophy and cell proliferation in Sprague-Dawley rats from dietary exposure to potassium perfluorooctanesulfonate results from increased expression of xenosensor nuclear receptors PPARα and CAR/PXR. *Toxicology* **2012**, *293*, 16–29. [CrossRef]
39. Baldwin, W.S.; Roling, J.A. A Concentration Addition Model for the Activation of the Constitutive Androstane Receptor by Xenobiotic Mixtures. *Toxicol. Sci.* **2009**, *107*, 93–105. [CrossRef]
40. Pakharukova, M.Y.; Smetanina, M.A.; Kaledin, V.I.; Kobzev, V.F.; Romanova, I.V.; Merkulova, T.I. Activation of constitutive androstane receptor under the effect of hepatocarcinogenic aminoazo dyes in mouse and rat liver. *Bull. Exp. Biol. Med.* **2007**, *144*, 338–341. [CrossRef]
41. Peffer, R.C.; Moggs, J.G.; Pastoor, T.; Currie, R.A.; Wright, J.; Milburn, G.; Waechter, F.; Rusyn, I. Mouse liver effects of cyproconazole, a triazole fungicide: Role of the constitutive androstane receptor. *Toxicol. Sci.* **2007**, *99*, 315–325. [CrossRef]
42. Wyde, M.E.; Kirwan, S.E.; Zhang, F.; Laughter, A.; Hoffman, H.B.; Bartolucci-Page, E.; Gaido, K.W.; Yan, B.; You, L. Di-n-butyl phthalate activates constitutive androstane receptor and pregnane X receptor and enhances the expression of steroid-metabolizing enzymes in the liver of rat fetuses. *Toxicol. Sci.* **2005**, *86*, 281–290. [CrossRef] [PubMed]
43. Wyde, M.E.; Bartolucci, E.; Ueda, A.; Zhang, H.; Yan, B.; Negishi, M.; You, L. The environmental pollutant 1,1-Dichloro-2,2-bis (p-chlorophenyl)ethylene induces rat hepatic cytochrome P450 2B and 3A expression through the constitutive androstane receptor and pregnane X receptor. *Mol. Pharmacol.* **2003**, *64*, 474–481. [CrossRef]
44. Laurenzana, E.M.; Coslo, D.M.; Vigilar, M.V.; Roman, A.M.; Omiecinski, C.J. Activation of the Constitutive Androstane Receptor by Monophthalates. *Chem. Res. Toxicol.* **2016**, *29*, 1651–1661. [CrossRef]
45. Sueyoshi, T.; Kawamoto, T.; Zelko, I.; Honkakoski, P.; Negishi, M. The repressed nuclear receptor CAR responds to phenobarbital in activating the human CYP2B6 gene. *J. Biol. Chem.* **1999**, *274*, 6043–6046. [CrossRef]
46. DeKeyser, J.G.; Stagliano, M.C.; Auerbach, S.S.; Prabhu, K.S.; Jones, A.D.; Omiecinski, C.J. Di(2-ethylhexyl) phthalate is a highly potent agonist for the human constitutive androstane receptor splice variant CAR2. *Mol. Pharmacol.* **2009**, *75*, 1005–1012. [CrossRef] [PubMed]
47. Wei, P.; Zhang, J.; Dowhan, D.H.; Han, Y.; Moore, D.D. Specific and overlapping functions of the nuclear hormone receptors CAR and PXR in xenobiotic response. *Pharm. J.* **2002**, *2*, 117–126. [CrossRef]
48. Savary, C.C.; Jossé, R.; Bruyère, A.; Guillet, F.; Robin, M.A.; Guillouzo, A. Interactions of endosulfan and methoxychlor involving CYP3A4 and CYP2B6 in human HepaRG cells. *Drug Metab. Dispos.* **2014**, *42*, 1234–1240. [CrossRef]
49. Zhang, X.J.; Shi, Z.; Lyv, J.X.; He, X.; Englert, N.A.; Zhang, S.Y. Pyrene is a novel constitutive androstane receptor (CAR) activator and causes hepatotoxicity by CAR. *Toxicol. Sci.* **2015**, *147*, 436–445. [CrossRef]
50. Blizard, D.; Sueyoshi, T.; Negishi, M.; Dehal, S.S.; Kupfer, D. Mechanism of Induction of Cytochrome P450 Enzymes by the Proestrogenic Endocrine Disruptor Pesticide-Methoxychlor: Interactions of Methoxychlor Metabolites with the Constitutive Androstane Receptor System. *Drug Metab. Dispos.* **2001**, *29*, 781–785.
51. Prokopec, S.D.; Watson, J.D.; Lee, J.; Pohjanvirta, R.; Boutros, P.C. Sex-related differences in murine hepatic transcriptional and proteomic responses to TCDD. *Toxicol. Appl. Pharmacol.* **2015**, *284*, 188–196. [CrossRef]

52. Mackowiak, B.; Li, L.; Lynch, C.; Ziman, A.; Heyward, S.; Wang, H.; States, U.; States, U.; States, U.; Technologies, I.V.; et al. High-content analysis of constitutive androstane receptor (CAR) translocation identifies mosapride citrate as a CAR agonist that represses gluconeogenesis. *Biochem. Pharmacol.* **2019**, *168*, 224–236. [CrossRef]
53. Liang, D.; Li, L.; Lynch, C.; Diethelm-Varela, B.; Xia, M.; Xue, F.; Wang, H. DL5050, a Selective Agonist for the Human Constitutive Androstane Receptor. *ACS Med. Chem. Lett.* **2019**, *10*, 1039–1044. [CrossRef] [PubMed]
54. Cerveny, L.; Svecova, L.; Anzenbacherova, E.; Vrzal, R.; Staud, F.; Dvorak, Z.; Ulrichova, J.; Anzenbacher, P.; Pavek, P. Valproic acid induces CYP3A4 and MDR1 gene expression by activation of constitutive androstane receptor and pregnane X receptor pathways. *Drug Metab. Dispos.* **2007**, *35*, 1032–1041. [CrossRef]
55. Zhang, J.; Huang, W.; Chua, S.S.; Wei, P.; Moore, D.D. Modulation of acetaminophen-induced hepatotoxicity by the xenobiotic receptor CAR. *Science* **2002**, *298*, 422–424. [CrossRef] [PubMed]
56. Zhang, J.; Huang, W.; Qatanani, M.; Evans, R.M.; Moore, D.D. The constitutive androstane receptor and pregnane X receptor function coordinately to prevent bile acid-induced hepatotoxicity. *J. Biol. Chem.* **2004**, *279*, 49517–49522. [CrossRef]
57. Goetz, A.K.; Bao, W.; Ren, H.; Schmid, J.E.; Tully, D.B.; Wood, C.; Rockett, J.C.; Narotsky, M.G.; Sun, G.; Lambert, G.R.; et al. Gene expression profiling in the liver of CD-1 mice to characterize the hepatotoxicity of triazole fungicides. *Toxicol. Appl. Pharmacol.* **2006**, *215*, 274–284. [CrossRef]
58. Burk, O.; Arnold, K.A.; Nussler, A.K.; Schaeffeler, E.; Efimova, E.; Avery, B.A.; Avery, M.A.; Fromm, M.F.; Eichelbaum, M. Antimalarial artemisinin drugs induce cytochrome P450 and MDR1 expression by activation of xenosensors pregnane X receptor and constitutive androstane receptor. *Mol. Pharmacol.* **2005**, *67*, 1954–1965. [CrossRef]
59. Swales, K.; Negishi, M. CAR, Driving into the Future. *Mol. Endocrinol.* **2004**, *18*, 1589–1598. [CrossRef] [PubMed]
60. Li, L.; Chen, T.; Stanton, J.D.; Sueyoshi, T.; Negishi, M.; Wang, H. The peripheral benzodiazepine receptor ligand 1-(2-chlorophenyl-methylpropyl)-3-isoquinoline-carboxamide is a novel antagonist of human constitutive androstane receptor. *Mol. Pharmacol.* **2008**, *74*, 443–453. [CrossRef]
61. Malaplate-Armand, C.; Ferrari, L.; Masson, C.; Visvikis-Siest, S.; Lambert, H.; Batt, A.M. Down-regulation of astroglial CYP2C, glucocorticoid receptor and constitutive androstane receptor genes in response to cocaine in human U373 MG astrocytoma cells. *Toxicol. Lett.* **2005**, *159*, 203–211. [CrossRef]
62. Pascussi, J.M.; Gerbal-Chaloin, S.; Fabre, J.M.; Maurel, P.; Vilarem, M.J. Dexamethasone enhances constitutive androstane receptor expression in human hepatocytes: Consequences on cytochrome P450 gene regulation. *Mol. Pharmacol.* **2000**, *58*, 1441–1450. [CrossRef]
63. Qatanani, M.; Wei, P.; Moore, D.D. Alterations in the distribution and orexigenic effects of dexamethasone in CAR-null mice. *Pharmacol. Biochem. Behav.* **2004**, *78*, 285–291. [CrossRef]
64. Duret, C.; Daujat-Chavanieu, M.; Pascussi, J.M.; Pichard-Garcia, L.; Balaguer, P.; Fabre, J.M.; Vilarem, M.J.; Maurel, P.; Gerbal-Chaloin, S. Ketoconazole and miconazole are antagonists of the human glucocorticoid receptor: Consequences on the expression and function of the constitutive androstane receptor and the pregnane X receptor. *Mol. Pharmacol.* **2006**, *70*, 329–339. [CrossRef]
65. Huang, W.; Zhang, J.; Wei, P.; Schrader, W.T.; Moore, D.D. Meclizine is an agonist ligand for mouse constitutive androstane receptor (CAR) and an inverse agonist for human CAR. *Mol. Endocrinol.* **2004**, *18*, 2402–2408. [CrossRef]
66. Saussele, T.; Burk, O.; Blievernicht, J.K.; Klein, K.; Nussler, A.; Nussler, N.; Hengstler, J.G.; Eichelbaum, M.; Schwab, M.; Zanger, U.M. Selective induction of human hepatic cytochromes P450 2B6 and 3A4 by metamizole. *Clin. Pharmacol. Ther.* **2007**, *82*, 265–274. [CrossRef]
67. Chen, X.; Maiti, S.; Zhang, J.; Chen, G. Nuclear receptor interactions in methotrexate induction of human dehydroepiandrosterone sulfotransferase (hSULT2A1). *J. Biochem. Mol. Toxicol.* **2006**, *20*, 309–317. [CrossRef]
68. Shibayama, Y.; Ushinohama, K.; Ikeda, R.; Yoshikawa, Y.; Motoya, T.; Takeda, Y.; Yamada, K. Effect of methotrexate treatment on expression levels of multidrug resistance protein 2, breast cancer resistance protein and organic anion transporters Oat1, Oat2 and Oat3 in rats. *Cancer Sci.* **2006**, *97*, 1260–1266. [CrossRef]
69. Murray, M.; Fiala-Beer, E.; Sutton, D. Upregulation of cytochromes P450 2B in rat liver by orphenadrine. *Br. J. Pharmacol.* **2003**, *139*, 787–796. [CrossRef]
70. Li, L.; Bao, X.; Zhang, Q.Y.; Negishi, M.; Ding, X. Role of Cyp2b in phenobarbital-induced hepatocyte proliferation in mice. *Drug Metab. Dispos.* **2017**, *45*, 977–981. [CrossRef]

71. Currie, R.A.; Peffer, R.C.; Goetz, A.K.; Omiecinski, C.J.; Goodman, J.I. Phenobarbital and propiconazole toxicogenomic profiles in mice show major similarities consistent with the key role that constitutive androstane receptor (CAR) activation plays in their mode of action. *Toxicology* **2014**, *321*, 80–88. [CrossRef] [PubMed]
72. Jackson, J.P.; Ferguson, S.S.; Moore, R.; Negishi, M.; Goldstein, J.A. The constitutive active/androstane receptor regulates phenytoin induction of Cyp2c29. *Mol. Pharmacol.* **2004**, *65*, 1397–1404. [CrossRef]
73. Wang, H.; Faucette, S.; Moore, R.; Sueyoshi, T.; Negishi, M.; LeCluyse, E. Human constitutive androstane receptor mediates induction of CYP2B6 gene expression by phenytoin. *J. Biol. Chem.* **2004**, *279*, 29295–29301. [CrossRef]
74. Jackson, J.P.; Ferguson, S.S.; Negishi, M.; Goldstein, J.A. Phenytoin Induction of the Cyp2c37 Gene is Mediated by the Constitutive Androstane Receptor. *Drug Metab. Dispos.* **2006**, *34*, 2003–2010. [CrossRef]
75. Howe, K.; Sanat, F.; Thumser, A.E.; Coleman, T.; Plant, N. The statin class of HMG-CoA reductase inhibitors demonstrate differential activation of the nuclear receptors PXR, CAR and FXR, as well as their downstream target genes. *Xenobiotica* **2011**, *41*, 519–529. [CrossRef]
76. Režen, T.; Hafner, M.; Kortagere, S.; Ekins, S.; Hodnik, V.; Rozman, D. Rosuvastatin and atorvastatin are ligands of the human constitutive androstane receptor/retinoid X receptor α complex. *Drug Metab. Dispos.* **2017**, *45*, 974–976. [CrossRef] [PubMed]
77. Sugatani, J.; Kojima, H.; Ueda, A.; Kakizaki, S.; Yoshinari, K.; Gong, Q.H.; Owens, I.S.; Negishi, M.; Sueyoshi, T. The phenobarbital response enhancer module in the human bilirubin UDP-glucuronosyltransferase UGT1A1 gene and regulation by the nuclear receptor CAR. *Hepatology* **2001**, *33*, 1232–1238. [CrossRef]
78. Guo, G.L.; Choudhuri, S.; Klaassen, C.D. Induction profile of rat organic anion transporting polypeptide 2 (oatp2) by prototypical drug-metabolizing enzyme inducers that activate gene expression through ligand-activated transcription factor pathways. *J. Pharmacol. Exp. Ther.* **2002**, *300*, 206–212. [CrossRef]
79. Ridlon, J.M.; Kang, D.J.; Hylemon, P.B. Bile salt biotransformations by human intestinal bacteria. *J. Lipid Res.* **2006**, *47*, 241–259. [CrossRef]
80. Beilke, L.D.; Aleksunes, L.M.; Holland, R.D.; Besselsen, D.G.; Beger, R.D.; Klaassen, C.D.; Cherrington, N.J. Constitutive androstane receptor-mediated changes in bile acid composition contributes to hepatoprotection from lithocholic acid-Induced liver injury in mice. *Drug Metab. Dispos.* **2009**, *37*, 1035–1045. [CrossRef] [PubMed]
81. Schenkman, J.B. Steroid metabolism by constitutive cytochromes P450. *J. Steroid Biochem. Mol. Biol.* **1992**, *43*, 1023–1030. [CrossRef]
82. Yamamoto, Y.; Moore, R.; Hess, H.A.; Guo, G.L.; Gonzalez, F.J.; Korach, K.S.; Maronpot, R.R.; Negishi, M. Estrogen receptor α mediates 17α-ethynylestradiol causing hepatotoxicity. *J. Biol. Chem.* **2006**, *281*, 16625–16631. [CrossRef]
83. Sueyoshi, T.; Green, W.D.; Vinal, K.; Woodrum, T.S.; Moore, R.; Negishi, M. Garlic Extract Diallyl Sulfide (DAS) Activates Nuclear Receptor CAR to Induce the Sult1e1 Gene in Mouse Liver. *PLoS ONE* **2011**, *6*, e21229. [CrossRef]
84. Curran, P.G.; DeGroot, L.J. The effect of hepatic enzyme-inducing drugs on thyroid hormones and the thyroid gland. *Endocr. Rev.* **1991**, *12*, 135–150. [CrossRef]
85. Qatanani, M.; Zhang, J.; Moore, D.D. Role of the Constitutive Androstane Receptor in Xenobiotic-Induced Thyroid Hormone Metabolism. *Endocrinology* **2005**, *146*, 995–1002. [CrossRef]
86. Visser, T.J.; Kaptein, E.; Glatt, H.; Bartsch, I.; Hagen, M.; Coughtrie, M.W.H. Characterization of thyroid hormone sulfotransferases. *Chem. Biol. Interact.* **1998**, *109*, 279–291. [CrossRef]
87. Lukowicz, C.; Ellero-Simatos, S.; Régnier, M.; Oliviero, F.; Lasserre, F.; Polizzi, A.; Montagner, A.; Smati, S.; Boudou, F.; Lenfant, F.; et al. Dimorphic metabolic and endocrine disorders in mice lacking the constitutive androstane receptor. *Sci. Rep.* **2019**, *9*, 20169. [CrossRef]
88. Wieneke, N.; Hirsch-Ernst, K.I.; Kuna, M.; Kersten, S.; Püschel, G.P. PPARα-dependent induction of the energy homeostasis-regulating nuclear receptor NR1i3 (CAR) in rat hepatocytes: Potential role in starvation adaptation. *FEBS Lett.* **2007**, *581*, 5617–5626. [CrossRef]
89. Pascussi, J.M.; Busson-Le Coniat, M.; Maurel, P.; Vilarem, M.J. Transcriptional analysis of the orphan nuclear receptor constitutive androstane receptor (NR1I3) gene promoter: Identification of a distal glucocorticoid response element. *Mol. Endocrinol.* **2003**, *17*, 42–55. [CrossRef]

90. Lahtela, J.T.; Arranto, A.J.; Sotaniemi, E.A. Enzyme inducers improve insulin sensitivity in non-insulin-dependent diabetic subjects. *Diabetes* **1985**, *34*, 911–916. [CrossRef]
91. Sotaniemi, E.A.; Arranto, A.J.; Sutinen, S.; Stengård, J.H.; Sutinen, S. Treatment of noninsulin-dependent diabetes mellitus with enzyme inducers. *Clin. Pharmacol. Ther.* **1983**, *33*, 826–835. [CrossRef]
92. Kodama, S.; Koike, C.; Negishi, M.; Yamamoto, Y. Nuclear receptors CAR and PXR cross talk with FOXO1 to regulate genes that encode drug-metabolizing and gluconeogenic enzymes. *Mol. Cell. Biol.* **2004**, *24*, 7931–7940. [CrossRef] [PubMed]
93. Miao, J.; Fang, S.; Bae, Y.; Kemper, J.K. Functional inhibitory cross-talk between constitutive androstane receptor and hepatic nuclear factor-4 in hepatic lipid/glucose metabolism is mediated by competition for binding to the DR1 motif and to the common coactivators, GRIP-1 and PGC-1alpha. *J. Biol. Chem.* **2006**, *281*, 14537–14546. [CrossRef] [PubMed]
94. Gao, J.; Yan, J.; Xu, M.; Ren, S.; Xie, W. CAR Suppresses Hepatic Gluconeogenesis by Facilitating the Ubiquitination and Degradation of PGC1α. *Mol. Endocrinol.* **2015**, *29*, 1558–1570. [CrossRef] [PubMed]
95. Shi, X.; Cheng, Q.; Xu, L.; Yan, J.; Jiang, M.; He, J.; Xu, M.; Stefanovic-Racic, M.; Sipula, I.; O'Doherty, R.M.; et al. Cholesterol Sulfate and Cholesterol Sulfotransferase Inhibit Gluconeogenesis by Targeting Hepatocyte Nuclear Factor 4. *Mol. Cell. Biol.* **2014**, *34*, 485–497. [CrossRef]
96. Lynch, C.; Pan, Y.; Li, L.; Heyward, S.; Moeller, T.; Swaan, P.W.; Wang, H. Activation of the constitutive androstane receptor inhibits gluconeogenesis without affecting lipogenesis or fatty acid synthesis in human hepatocytes. *Toxicol. Appl. Pharmacol.* **2014**, *279*, 33–42. [CrossRef]
97. Breuker, C.; Moreau, A.; Lakhal, L.; Tamasi, V.; Parmentier, Y.; Meyer, U.; Maurel, P.; Lumbroso, S.; Vilarem, M.J.; Pascussi, J.M. Hepatic expression of thyroid hormone-responsive spot 14 protein is regulated by constitutive androstane receptor (NR1I3). *Endocrinology* **2010**, *151*, 1653–1661. [CrossRef]
98. Marmugi, A.; Lukowicz, C.; Lasserre, F.; Montagner, A.; Polizzi, A.; Ducheix, S.; Goron, A.; Gamet-Payrastre, L.; Gerbal-Chaloin, S.; Pascussi, J.M.; et al. Activation of the Constitutive Androstane Receptor induces hepatic lipogenesis and regulates Pnpla3 gene expression in a LXR-independent way. *Toxicol. Appl. Pharmacol.* **2016**, *303*, 90–100. [CrossRef]
99. La Vecchia, C.; Negri, E. A review of epidemiological data on epilepsy, phenobarbital, and risk of liver cancer. *Eur. J. Cancer Prev.* **2014**, *23*, 1–7.
100. Verrotti, A.; Agostinelli, S.; Parisi, P.; Chiarelli, F.; Coppola, G. Nonalcoholic fatty liver disease in adolescents receiving valproic acid. *Epilepsy Behav.* **2011**, *20*, 382–385. [CrossRef]
101. Kassam, A.; Winrow, C.J.; Fernandez-Rachubinski, F.; Capone, J.P.; Rachubinski, R.A. The peroxisome proliferator response element of the gene encoding the peroxisomal beta-oxidation enzyme enoyl-CoA hydratase/3-hydroxyacyl-CoA dehydrogenase is a target for constitutive androstane receptor beta/9-cis-retinoic acid receptor-mediated transactivation. *J. Biol. Chem.* **2000**, *275*, 4345–4350.
102. Chen, W.; Chen, G.; Head, D.L.; Mangelsdorf, D.J.; Russell, D.W. Enzymatic Reduction of Oxysterols Impairs LXR Signaling in Cultured Cells and the Livers of Mice. *Cell Metab.* **2007**, *5*, 73–79. [CrossRef]
103. Lee, M.; Hwang, J.T.; Lee, H.J.; Jung, S.N.; Kang, I.; Chi, S.G.; Kim, S.S.; Ha, J. AMP-activated protein kinase activity is critical for hypoxia-inducible factor-1 transcriptional activity and its target gene expression under hypoxic conditions in DU145 cells. *J. Biol. Chem.* **2003**, *278*, 39653–39661. [CrossRef]
104. Hudson, G.M.; Flannigan, K.L.; Erickson, S.L.; Vicentini, F.A.; Zamponi, A.; Hirota, C.L.; Alston, L.; Altier, C.; Ghosh, S.; Rioux, K.P.; et al. Constitutive androstane receptor regulates the intestinal mucosal response to injury. *Br. J. Pharmacol.* **2017**, *174*, 1857–1871. [CrossRef]
105. Dempsey, J.L.; Wang, D.; Siginir, G.; Fei, Q.; Raftery, D.; Gu, H.; Yue Cui, J. Pharmacological Activation of PXR and CAR Downregulates Distinct Bile Acid-Metabolizing Intestinal Bacteria and Alters Bile Acid Homeostasis. *Toxicol. Sci.* **2019**, *168*, 40–60. [CrossRef]
106. Little, M.; Dutta, M.; Li, H.; Matson, A.; Shi, X.; Gu, H.; Mani, S.; Cui, J.Y. Understanding the Physiological Functions of the Host Xenobiotic-Sensing Nuclear Receptors PXR and CAR on the Gut Microbiome Using Genetically Modified Mice. Master's Thesis, University of Washington, Seattle, WA, USA, 2019.
107. Choi, Y.J.; Zhou, D.; Barbosa, A.C.S.; Niu, Y.; Guan, X.; Xu, M.; Ren, S.; Nolin, T.D.; Liu, Y.; Xie, W. Activation of constitutive androstane receptor ameliorates renal ischemia-reperfusion-induced kidney and liver injury. *Mol. Pharmacol.* **2018**, *93*, 239–250. [CrossRef]
108. Oh, E.; Kim, M.S. Brain regulation of energy metabolism. *Endocrinol. Metab.* **2016**, *31*, 519–524.

109. Giannoni, P.; Badaut, J.; Dargazanli, C.; De Maudave, A.F.H.; Klement, W.; Costalat, V.; Marchi, N. The pericyte-glia interface at the blood-brain barrier. *Clin. Sci.* **2018**, *132*, 361–374. [CrossRef]
110. Giannoni, P.; Claeysen, S.; Noe, F.; Marchi, N. Peripheral Routes to Neurodegeneration: Passing Through the Blood–Brain Barrier. *Front. Aging Neurosci.* **2020**, *12*, 3. [CrossRef]
111. Sweeney, M.D.; Zhao, Z.; Montagne, A.; Nelson, A.R.; Zlokovic, B.V. Blood-brain barrier: From physiology to disease and back. *Physiol. Rev.* **2019**, *99*, 21–78. [CrossRef]
112. Abbott, N.J.; Patabendige, A.A.K.; Dolman, D.E.M.; Yusof, S.R.; Begley, D.J. Structure and function of the blood-brain barrier. *Neurobiol. Dis.* **2010**, *37*, 13–25. [CrossRef]
113. Nishimura, M.; Naito, S.; Yokoi, T. Tissue-specific mRNA expression profiles of human nuclear receptor subfamilies. *Drug Metab. Pharmacokinet.* **2004**, *19*, 135–149. [CrossRef]
114. Lamba, J.K.; Lamba, V.; Yasuda, K.; Lin, Y.S.; Assem, M.; Thompson, E.; Strom, S.; Schuetz, E.G. Expression of constitutive androstane receptor splice variants in human tissues and their functional consequences. *J. Pharmacol. Exp. Ther.* **2004**, *311*, 811–821. [CrossRef]
115. Dutheil, F.; Dauchy, S.; Diry, M.; Sazdovitch, V.; Cloarec, O.; Mellottée, L.; Bièche, I.; Ingelman-Sundberg, M.; Flinois, J.P.; De Waziers, I.; et al. Xenobiotic-metabolizing enzymes and transporters in the normal human brain: Regional and cellular mapping as a basis for putative roles in cerebral function. *Drug Metab. Dispos.* **2009**, *37*, 1528–1538. [CrossRef]
116. Souidi, M.; Gueguen, Y.; Linard, C.; Dudoignon, N.; Grison, S.; Baudelin, C.; Marquette, C.; Gourmelon, P.; Aigueperse, J.; Dublineau, I. In vivo effects of chronic contamination with depleted uranium on CYP3A and associated nuclear receptors PXR and CAR in the rat. *Toxicology* **2005**, *214*, 113–122. [CrossRef] [PubMed]
117. Marini, S.; Nannelli, A.; Sodini, D.; Dragoni, S.; Valoti, M.; Longo, V.; Gervasi, P.G. Expression, microsomal and mitochondrial activities of cytochrome P450 enzymes in brain regions from control and phenobarbital-treated rabbits. *Life Sci.* **2007**, *80*, 910–917. [CrossRef]
118. Kajta, M.; Wnuk, A.; Rzemieniec, J.; Lason, W.; Mackowiak, M.; Chwastek, E.; Staniszewska, M.; Nehring, I.; Wojtowicz, A.K. Triclocarban Disrupts the Epigenetic Status of Neuronal Cells and Induces AHR/CAR-Mediated Apoptosis. *Mol. Neurobiol.* **2019**, *56*, 3113–3131. [CrossRef] [PubMed]
119. Litwa, E.; Rzemieniec, J.; Wnuk, A.; Lason, W.; Krzeptowski, W.; Kajta, M. RXRα, PXR and CAR xenobiotic receptors mediate the apoptotic and neurotoxic actions of nonylphenol in mouse hippocampal cells. *J. Steroid Biochem. Mol. Biol.* **2016**, *156*, 43–52. [CrossRef]
120. The Human Protein Atlas. Available online: https://www.proteinatlas.org/ENSG00000143257-NR1I3/brain (accessed on 1 September 2020).
121. Weksler, B.; Romero, I.A.; Couraud, P.O. The hCMEC/D3 cell line as a model of the human blood brain barrier. *Fluids Barriers CNS* **2013**, *10*. [CrossRef] [PubMed]
122. Wang, H.; LeCluyse, E.L. Role of Orphan Nuclear Receptors in the Regulation of Drug-Metabolising Enzymes. *Clin. Pharmacokinet.* **2003**, *42*, 1331–1357. [CrossRef]
123. Miller, D.S. Regulation of ABC Transporters Blood-Brain Barrier. The Good, the Bad, and the Ugly. In *Advances in Cancer Research*; Academic Press Inc.: Cambridge, MA, USA, 2015; Volume 125, pp. 43–70.
124. Chan, G.N.Y.; Hoque, M.T.; Cummins, C.L.; Bendayan, R. Regulation of P-glycoprotein by orphan nuclear receptors in human brain microvessel endothelial cells. *J. Neurochem.* **2011**, *118*, 163–175. [CrossRef]
125. Wang, X.; Sykes, D.B.; Miller, D.S. Constitutive androstane receptor-mediated up-regulation of ATP-driven xenobiotic efflux transporters at the blood-brain barrier. *Mol. Pharmacol.* **2010**, *78*, 376–383. [CrossRef] [PubMed]
126. Slosky, L.M.; Thompson, B.J.; Sanchez-Covarrubias, L.; Zhang, Y.; Laracuente, M.L.; Vanderah, T.W.; Ronaldson, P.T.; Davis, T.P. Acetaminophen modulates P-glycoprotein functional expression at the blood-brain barrier by a constitutive androstane receptor-dependent mechanism. *Mol. Pharmacol.* **2013**, *84*, 774–786. [CrossRef]
127. Tripathi, V.K.; Kumar, V.; Pandey, A.; Vatsa, P.; Dhasmana, A.; Singh, R.P.; Appikonda, S.H.C.; Hwang, I.; Lohani, M. Monocrotophos Induces the Expression of Xenobiotic Metabolizing Cytochrome P450s (CYP2C8 and CYP3A4) and Neurotoxicity in Human Brain Cells. *Mol. Neurobiol.* **2017**, *54*, 3633–3651. [CrossRef]
128. Ghosh, C.; Puvenna, V.; Gonzalez-Martinez, J.; Janigro, D.; Marchi, N. Blood-Brain Barrier P450 Enzymes and Multidrug Transporters in Drug Resistance: A Synergistic Role in Neurological Diseases. *Curr. Drug Metab.* **2011**, *12*, 742–749. [CrossRef]

129. Chakraborty, S.; Kanakasabai, S.; Bright, J.J. Constitutive androstane receptor agonist CITCO inhibits growth and expansion of brain tumour stem cells. *Br. J. Cancer* **2011**, *104*, 448–459. [CrossRef] [PubMed]
130. Maglich, J.M.; Parks, D.J.; Moore, L.B.; Collins, J.L.; Goodwin, B.; Billin, A.N.; Stoltz, C.A.; Kliewer, S.A.; Lambert, M.H.; Willson, T.M.; et al. Identification of a Novel Human Constitutive Androstane Receptor (CAR) Agonist and Its Use in the Identification of CAR Target Genes. *J. Biol. Chem.* **2003**, *278*, 17277–17283. [CrossRef] [PubMed]
131. Lemmen, J.; Tozakidis, I.E.P.; Bele, P.; Galla, H.J. Constitutive androstane receptor upregulates Abcb1 and Abcg2 at the blood-brain barrier after CITCO activation. *Brain Res.* **2013**, *1501*, 68–80. [CrossRef]
132. Koemans, T.S.; Kleefstra, T.; Chubak, M.C.; Stone, M.H.; Reijnders, M.R.F.; de Munnik, S.; Willemsen, M.H.; Fenckova, M.; Stumpel, C.T.R.M.; Bok, L.A.; et al. Functional convergence of histone methyltransferases EHMT1 and KMT2C involved in intellectual disability and autism spectrum disorder. *PLoS Genet.* **2017**, *13*. [CrossRef]
133. Boussadia, B.; Gangarossa, G.; Mselli-Lakhal, L.; Rousset, M.-C.; de Bock, F.; Lassere, F.; Ghosh, C.; Pascussi, J.-M.; Janigro, D.; Marchi, N. Lack of CAR impacts neuronal function and cerebrovascular integrity in vivo. *Exp. Neurol.* **2016**, *283*, 39–48. [CrossRef]
134. Torres-Vergara, P.; Ho, Y.S.; Espinoza, F.; Nualart, F.; Escudero, C.; Penny, J. The constitutive androstane receptor and pregnane X receptor in the brain. *Br. J. Pharmacol.* **2020**, *177*, 2666–2682. [CrossRef] [PubMed]
135. Davidson, T.L.; Monnot, A.; Neal, A.U.; Martin, A.A.; Horton, J.J.; Zheng, W. The effects of a high-energy diet on hippocampal-dependent discrimination performance and blood-brain barrier integrity differ for diet-induced obese and diet-resistant rats. *Physiol. Behav.* **2012**, *107*, 26–33. [CrossRef]
136. Ferro, J.M.; Oliveira, S.N.; Correia, L. Neurologic manifestations of inflammatory bowel diseases. In *Handbook of Clinical Neurology*; Elsevier B.V.: Amsterdam, The Netherlands, 2014; Volume 120, pp. 595–605.
137. Casella, G.; Tontini, G.E.; Bassotti, G.; Pastorelli, L.; Villanacci, V.; Spina, L.; Baldini, V.; Vecchi, M. Neurological disorders and inflammatory bowel diseases. *World J. Gastroenterol.* **2014**, *20*, 8764–8782.
138. Miehsler, W.; Reinisch, W.; Valic, E.; Osterode, W.; Tillinger, W.; Feichtenschlager, T.; Grisar, J.; Machold, K.; Scholz, S.; Vogelsang, H.; et al. Is inflammatory bowel disease an independent and disease specific risk factor for thromboembolism? *Gut* **2004**, *53*, 542–548. [CrossRef]
139. Varatharaj, A.; Galea, I. The blood-brain barrier in systemic inflammation. *Brain. Behav. Immun.* **2017**, *60*, 1–12. [CrossRef] [PubMed]
140. Duszka, K.; Wahli, W. Enteric Microbiota–Gut–Brain Axis from the Perspective of Nuclear Receptors. *Int. J. Mol. Sci.* **2018**, *19*, 2210. [CrossRef]