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Themed Issue: Emerging Fields for Therapeutic Targeting of the Aldosterone-Mineralocorticoid Receptor Signaling Pathway

THEMED ISSUE REVIEW

Mineralocorticoid receptors in non-alcoholic fatty liver disease

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Liver diseases are the fourth common death in Europe responsible for about 2 million death per year worldwide. Among the known detrimental causes for liver dysfunction are virus infections, intoxications and obesity.

The mineralocorticoid receptor (MR) is a ligand-dependent transcription factor activated by aldosterone or glucocorticoids but also by pathological milieu factors. Canonical actions of the MR take place in epithelial cells of kidney, colon and sweat glands and contribute to sodium reabsorption, potassium secretion and extracellular volume homeostasis. The non-canonical functions can be initiated by inflammation or an altered micro-milieu leading to fibrosis, hypertrophy and remodelling in various tissues. This narrative review summarizes the evidence regarding the role of MR in portal hypertension, non-alcoholic fatty liver disease, liver fibrosis and cirrhosis, demonstrating that inhibition of the MR in vivo seems to be beneficial for liver function and not just for volume regulation. Unfortunately, the underlying molecular mechanisms are still not completely understood.

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KEYWORDS
aldosterone, cirrhosis, hepatic stellate cell, hepatocytes, liver, mineralocorticoid receptor, NAFL

Abbreviations: 11β-HSD1, 11-β-hydroxysteroid dehydrogenase 1; 11β-HSD2, 11-β-hydroxysteroid dehydrogenase 2; ACE2, angiotensin converting enzyme 2; Ang 1–7, angiotensin (1–7); CDAA, choline-deficient and amino-acid defined; CYP11B2, aldosterone synthase; DOC, deoxycorticosterone; ERα, oestrogen receptor α; G6Pase, glucose-6-phosphatase; GR, glucocorticoid receptors; HCC, hepatocellular carcinoma cells; HGF, hepatocyte growth factor; HOMA, Homeostasis Model Assessment; HSC, hepatic stellate cells; HVPG, hepatic venous pressure gradient; LSEC, liver sinusoidal endothelial cells; MAS, MAS1 proto-oncogene; MR, mineralocorticoid receptor; MrgD, Mas-related G protein-coupled receptor D; NAFL, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis,; NHE1, sodium-hydrogen antiporter 1; ob/ob, mutation of the leptin gene,; PDGF-BB, platelet-derived growth factor BB; RAAS, renin-angiotensin-aldosterone system; ROCK-2, Rho-associated protein kinase 2; SP1, specificity protein 1; TBARS, thiobarbituric acid reactive substance; VASP, vasodilator-stimulated phosphoprotein; VEGF, vascular endothelial growth factor.

1 | INTRODUCTION TO THE MINERALOCORTICOID RECEPTOR (MR)

Classically the **renin-angiotensin-aldosterone** system (RAAS) is conceived as a hormonal mechanism regulating blood pressure and electrolyte balance (Simoes E Silva et al., 2017). Renin is synthesized in the juxtaglomerular cells of the afferent arteriole and released upon glomerular hypoperfusion, reduced sodium intake and increased sympathetic tone (Hackenthal et al., 1990). In a cascade of partial proteolysis, activated renin cleaves the plasma protein angiotensinogen to form the decapeptide **angiotensin I**. **Angiotensin converting enzyme** (ACE), a membrane bound metalloproteinase of endothelial cells, cleaves angiotensin I to **angiotensin II** (Paul et al., 2006). Angiotensin II, for a long time considered the main effector peptide of the RAAS, induces vasoconstriction by binding to its G-protein coupled AT_1 receptors on vascular smooth muscle cells and induces the synthesis of aldosterone in the adrenal cortex (Paul et al., 2006).

Aldosterone exerts its effects via binding to the MR. The MR belongs to the steroid receptor superfamily together with **progesterone**, **estrogen**, **androgen** and **glucocorticoid receptors** (GR) (Meinel et al., 2014) and is nowadays considered an ubiquitously expressed receptor (Kuhn & Lombes, 2013). However, the canonical actions of the MR occur in epithelial cells from kidney, colon and sweat glands and contribute to sodium reabsorption, potassium secretion and extracellular volume homeostasis. Non-canonical MR functions can be initiated by inflammation or an altered micro-milieu leading to fibrosis, hypertrophy and remodelling (Meinel et al., 2014). Here the best-described mechanistic insights derive from cardiovascular diseases. In recent years, other effector organs, as well as diseases, related to the MR were identified. There is evidence that the MR plays a role in the immune system (van der Heijden et al., 2018), in adipose tissue (Feraco et al., 2013) and in the liver (Li et al., 2020; Luo et al., 2012; Schreier et al., 2018). Thereby, the MRs contribute to the consequences of diseases such as diabetes mellitus (Chen et al., 2015; Luther et al., 2011; Wang et al., 2019) metabolic syndrome (Long et al., 2013) or liver cirrhosis and portal hypertension (Garcia-Pagan et al., 1994; Katsuta et al., 1993; Queisser et al., 2014; Schreier et al., 2018; Tandon et al., 2010). An increase in aldosterone plasma concentrations in liver cirrhosis was recognized relatively early in the history of aldosterone (Conn, 1956). This secondary hyperaldosteronism leads to salt and water retention and is involved in the formation of ascites, hypertension and therefore decompensation of liver function. Additionally, there is more and more evidence that the effects of aldosterone and the MR during liver dysfunction is attributable not only to electrolyte and extracellular fluid balance.

Explaining the importance of RAAS, aldosterone or the MR on extracellular volume homeostasis, salt and water balance and for the control of blood pressure, is beyond the scope of this review and extensively covered elsewhere (Poulsen & Fenton, 2019; Sparks et al., 2014; Yamazaki et al., 2019). The same is true for the effect of the second RAAS axis consisting of **angiotensin converting enzyme 2** (ACE2), **angiotensin** (Ang 1–7), **alamandine** and their receptors **MAS1 proto-oncogene** (MAS) and **Mas-related G protein-coupled receptor D** (MrgD) (see Santos et al., 2017). Similarly, the roles of MRs in learning and memory, in neuronal differentiation, and in stress responses within the hippocampus and other areas of the brain, as evident from various studies in brain specific mutant mice, will not be covered here. This review will mainly focus on the effects of the MRs on liver physiology and pathophysiology.

2 | LIVER

The physiological functions of the liver include, among others, macronutrient metabolism, blood volume regulation, immune system support, endocrine control of growth signalling pathways, lipid and cholesterol homeostasis and breakdown of xenobiotic compounds (Trefts et al., 2017). Among the substrates metabolized in the liver are the corticosteroids. Aldosterone, for example, is metabolized to less polar metabolites and these are then mainly excreted in the bile (Egfjord et al., 1991). In liver cirrhosis, synthesis of aldosterone is increased and the metabolic clearance is reduced, both contributing to increased aldosterone plasma concentrations (Rosoff et al., 1975).

The liver consists of several different cell types, with the hepatocytes as the "parenchymal cells" and responsible for most of the synthetic and many of the metabolic functions (Nagy et al., 2020). Other important liver cells are hepatic stellate cells (HSC), Kupffer cells and liver sinusoidal endothelial cells (LSEC) (Trefts et al., 2017).

Endothelial cells of the sinusoids comprise about 3% of the parenchymal mass/volume. They are only 150–170 nm across in the normal liver and exhibit holes (fenestrae) 50–200 nm in diameter but lack a structured basal membrane (Nagy et al., 2020). Modifications in fenestrae properties, i.e. pseudo-capillarization, are associated with aging and hypoxia (McLean et al., 2003), while a complete loss of fenestrae, i.e. capillarization (Le Couteur et al., 2002) seems to precede the development of most chronic liver diseases (Schmucker, 1998; Wynne et al., 1989). One of the major factors involved in maintenance of the fenestrae is **vascular endothelial growth factor** (VEGF) (Iwakiri & Groszmann, 2020). HSCs – also known as *Ito* cells - represent 4–8% of cells of the healthy liver and are characterized by storage of retinyl esters in cytoplasmic lipid droplets (Lee & Friedman, 2020). HSCs are located in the space of Disse, between the hepatocytes and the endothelial cells. They are the principal source of extracellular matrix proteins (Ishibashi et al., 2009). Therefore, they play an important role in the development of liver fibrosis after injury (Lee & Friedman, 2020). Additionally, they act as pericytes of the liver sinusoids and regulate the sinusoidal blood flow (Nagy et al., 2020). Kupffer cells are the resident macrophages in the liver and play a major systemic anti-inflammatory role by preventing gut-derived, immuno-reactive substances from travelling past the hepatic sinusoid (Dixon et al., 2013). Reduced function of the Kupffer cells contributes to pathogen invasion and hence systemic inflammation. Enhanced activity contributes to chronic inflammatory liver diseases as NAFL/NASH or alcoholic liver disease (Dixon et al., 2013). The organizational principles of liver function have been recently reviewed (see Nagy et al., 2020).

Liver diseases account for about 2 million deaths per year, worldwide. Of these, 1 million people die due to complications of cirrhosis and 1 million due to viral hepatitis and hepatocellular carcinoma (HCC) (Asrani et al., 2019). In Europe, cirrhosis is the fourth most common cause of death with numbers rising (Tsochatzis et al., 2014). Different pathological alterations lead to liver cirrhosis in developed countries, with hepatitis C infection, alcohol misuse and non-alcoholic liver diseases as the main causes. However, infection with hepatitis B virus is the main cause in sub-Saharan Africa and the most parts of Asia (Tsochatzis et al., 2014).

Liver disease often starts with lipid accumulation in the hepatocytes and development of fibrosis. In the natural course, chronic liver disease progress into compensated cirrhosis and with development of complications, such as ascites, variceal bleeding, hepatic encephalopathy and icterus, to decompensated cirrhosis (D'Amico et al., 2006). The main driver of the most frequent complications, ascites and variceal haemorrhage, is portal hypertension (D'Amico, 2014; Zipprich et al., 2012). Patients with decompensated cirrhosis are at further risk of developing acute-on-chronic liver failure and subsequent death (Trebicka et al., 2021).

3 | RAAS IN THE LIVER

The function of the RAAS in the liver is still not completely understood (Simoes E Silva et al., 2017), although the liver is an important organ for this system because the main source of angiotensinogen are the hepatocytes. Cre-dependent deletion of angiotensinogen in mice revealed that 90% of the circulating angiotensinogen -which is the only precursor of all angiotensin peptides, including angiotensin II, Ang (1–7) or alamandine, is synthesized in hepatocytes (Lu et al., 2016). In advanced liver cirrhosis, the production of angiotensinogen is decreased, while the renin plasma activity is increased (Kuiper et al., 2008). Additionally, the liver is involved in renin clearance from the plasma (Kuiper et al., 2008), presumably contributing to an increase in plasma renin activity when liver function is restricted.

There is good evidence that angiotensinogen derived peptides are involved in liver diseases. For example, angiotensin II, as a vasoconstrictor substance, causes a rapid and pronounced rise in portal pressure, most probably by reducing the diameter of the post-sinusoidal venules (Simoes E Silva et al., 2017). Accordingly, **losartan** - an AT_1 receptor antagonist - reduced the portal pressure in patients with moderate to severe portal hypertension (Schneider et al., 1999). However, in a systematic review Tandon et al (Tandon et al., 2010) could not observe an overall beneficial effect of AT_1 receptor antagonists or decreased generation of angiotensin II (with ACE inhibitors) on portal pressure. By re-analyzing the patient data from three of the initial studies, the authors came to the conclusion that there is a beneficial effect of AT_1 receptor antagonists or ACE inhibitors in patients with less severe liver cirrhosis (Child Pugh A compared to Child Pugh B). The authors hypothesize that, in advanced cirrhosis, additional vasoactive pathways, such as increased **endothelin**, **thromboxane** or insufficient **NO** release, contribute to portal hypertension and that the effect of RAAS inhibitors might therefore be overcome (Tandon et al., 2010).

In the liver, angiotensin II induces the expression of **TGF-β1** in HSCs via AT_1 receptors, contributing to liver fibrosis (Yoshiji et al., 2001). Detrimental contributions of ACE and angiotensin II are not only reported for portal hypertension and liver fibrosis, but also for non-alcoholic fatty liver disease (NAFL) and chronic hepatitis B virus induced fibrosis (Simoes E Silva et al., 2017). Among liver diseases, NAFL is the most common worldwide and an important risk factor for non-alcoholic steatohepatitis (NASH), Type 2 diabetes and cardiovascular diseases (Musso et al., 2011, 2015).

In contrast to angiotensin II, Ang (1–7) acts anti-inflammatory and anti-fibrotic in liver tissue (Simoes E Silva et al., 2017). Accordingly, in rats with bile duct ligation, the induced liver cirrhosis was associated with an increase in plasma renin activity, angiotensin II and Ang (1–7) concentrations in the plasma. Upon treatment with the MAS receptor antagonist (**A-779**), fibrosis was significantly enhanced, indicating a protective role of the Ang (1–7) axis (Pereira et al., 2007). There seems to be a carefully maintained balance between the classical (ACE-angiotensin II-AT_1 receptor axis) and the non-classical ACE2-Ang (1–7)-MAS axis. While the former exerts pro-fibrotic effects, the latter acts as an anti-fibrotic system, not only in liver cirrhosis and hypertension but also in NAFL (Simoes E Silva et al., 2017).

One major drawback of all these studies is that they do not take into account the last part of the classical RAAS system, the aldosterone-MR interaction. For cardiovascular diseases, inhibition of the MRs has, at least, an additional, beneficial effect in patients treated with AT_1 receptor antagonists/ ACE inhibitors and β-adrenoceptor antagonists (Pitt et al., 1999, 2001). Therefore, it is of interest to have a closer look on the effects mediated by the MR and its ligand aldosterone, in liver tissue.

4 | FUNCTION OF THE MINERALOCORTICOID RECEPTOR AND ALDOSTERONE IN THE LIVER

MR activation in the cardiovascular tissue promotes hypertension, fibrosis and inflammation (Buonafine et al., 2018). These mechanisms are also involved in the development of liver diseases. Progression of liver dysfunction depends on the crosstalk of the different cell types within the liver but, while there is evidence that inhibition of the MR is beneficial for liver function (see below), little is known about the cellular mechanisms leading to this effect. In healthy rat livers, the main cell type expressing MRs, at mRNA and protein levels, is the hepatocytes (Schreier et al., 2018), although there are also MRs detectable in LSECs and Kupffer cells (Pizarro et al., 2015). At the moment, it is not clear if rat HSCs also express MRs, as we could detect the appropriate mRNA but not the protein (Schreier et al., 2018). Pizarro et al detected the mRNA (Pizarro et al., 2015), while Rombouts et al. could not detect mRNA for the MRs, but observed an increase of extracellular matrix proteins after treatment

with aldosterone, of freshly isolated rat hepatic stellate cells (Rombouts et al., 2001). As activation of the MRs might be cell type and micro-milieu specific, the effects in the different cells may vary and therefore a cell type-specific analysis is needed.

Unfortunately, little is known about the regulation of MR expression, e.g. is there a feedback from the ligand-activated MR on its own transcription or are there further transcription factors involved in the baseline MR expression. Zennaro et al. (Zennaro et al., 1997) demonstrated that there are at least two 5′-flanking regions of the MR leading to two functional MR promoters resulting in two distinct MR-mRNAs which result in the same protein. Both variants seem to have the same abundance in the tissues tested (Zennaro et al., 1997). In contrast to the tissue abundance, the promoters differ in their basal and hormone-regulated activity (Le Menuet et al., 2000; Zennaro et al., 1995, 1996). This might provide a tissue-specific, fine-tuning, control mechanism for MR expression and aldosterone action. It is possible that there are cell type-specific effects on MR expression, as in mice fed with a choline-deficient and amino-acid defined (CDAA) diet, an increase in MR mRNA was observed in HSCs but a reduction in hepatocytes (Pizarro et al., 2015). We also observed a reduction of MR mRNA content in freshly isolated hepatocytes from rats with decompensated liver cirrhosis (Schreier et al., 2018). If this reduced mRNA content is due to reduced transcription or enhanced mRNA degradation is still under investigation, as well as the underlying molecular pathways. This knowledge will provide relevant insight into the pathophysiological role of the MR in the liver.

The expression of different MR isoforms or splice variants is rarely taken into account for varying MR action. Besides the two variant exons 1, the human MR gene is composed of nine additional exons (Zennaro et al., 1995), with the translation start site located in exon 2. Bloem et al. (Bloem et al., 1995) identified a MR splice variant with a 12 base pair insertion between the two zinc fingers. This alteration leads to a four amino acid longer spacer between the two residues, presumably altering DNA binding of the MR. Additionally, a truncated version of the MR has been described lacking ten base pairs at the C-terminus resulting in a premature stop codon (Zhou et al., 2000). This deletion shortens the MR from 981 amino acids to 807 amino acids. The variant protein showed the same baseline activity as the wild type MR, but was not responsive to aldosterone. One of the tissues expressing this variant is the liver (Zhou et al., 2000). Furthermore, there is an isoform lacking exon five and six of the human MR. This isoform lacks the hinge region and the ligand-binding domain. This variant acts as a ligand-independent transcription factor and enhances with co-activators - differing from those of the wild type MR - the transcriptional potential (Zennaro et al., 2001). The expression of the isoform lacking the exons 5&6 in the hepatic cell line SK Hep1 was high (Zennaro et al., 2001). If this is true for the liver in vivo and for all liver cells has still to be evaluated. On the other hand, there are studies showing that loss of a part of the hormone-binding region of the GR generates a constitutively active molecule, indicating that neither the steroid binding domain, nor the steroid hormone itself, is needed for DNA binding or transcriptional enhancement (Evans, 1988).

In vivo, the MR is exposed to different circulating steroids including **cortisol**, **cortisone**, **corticosterone** (the main active glucocorticoid in most rodents) and progesterone. The MR shows the same affinity for aldosterone, corticosterone and cortisol, while the GRα shows low affinity for aldosterone, **deoxycorticosterone** and the sex steroids but high affinity for dexamethasone and modest affinity for cortisol and corticosterone (Funder, 1997; Reul & Kloet, 1985). Therefore, the MR is often considered a high-affinity corticosteroid receptor. Nonetheless, aldosterone and deoxycorticosterone are recognized as the physiological MR ligands. The concentration of glucocorticoids in the plasma varies on a diurnal basis with low nanomolar concentrations during sleep and low micromolar concentrations during severe stress/illness (Chapman et al., 2013); thereby exceeding the plasma aldosterone concentrations up to 1,000 fold. Interestingly, the **aldosterone synthase** (CYP11B2) can be found in rat HSC and the expression of this enzyme is upregulated after chronic liver injury (Caligiuri et al., 2003), indicating a local RAAS which could affect liver function in an autocrine or paracrine fashion.

In certain cells, **11-β-hydroxysteroid dehydrogenase 2 (11β-HSD2)** converts cortisol to the inactive cortisone (Chapman et al., 2013), but not aldosterone. When this enzyme is not expressed or inhibited, e.g. by licorice, cortisol can bind to the MR and activate it (Funder, 1997). In the kidney, the 11β-HSD2 is expressed in collecting duct cells and protects the MR from activation by cortisol (Edwards et al., 1988; Funder et al., 1988). In the liver, adipose tissue and the adult brain this enzyme is absent, therefore activation by cortisol is possible if not likely (Chapman et al., 2013). Additionally, **11β-HSD1** regenerates cortisol from inactive cortisone. Among other locations, this enzyme is expressed in the liver, adipose tissue and the brain (Anagnostis et al., 2009). Interestingly, deletion of the 11β-HSD1 in hepatocytes did improve glucose tolerance but not insulin resistance or steatosis in mice fed a high-fat diet for 18 weeks (Lavery et al., 2012), indicating that cortisol might be the active ligand for the MR in liver and adipose tissue (Kuhn & Lombes, 2013) but regeneration of cortisol does not contribute substantially to steatosis. Unfortunately, little is known regarding the ligand activating the MR in the liver. Further studies are needed to identify if the effects elicited by MR inhibition in vivo are induced by aldosterone or glucocorticoids.

In the unliganded state, both MR and GR are associated with chaperone proteins, such as heat shock protein (HSP) 90 and immunophilin (HSP56). These proteins ensure that the receptors stay in their inactive form, with high affinity for the hormone (Funder, 1997). Upon ligand binding, the chaperone proteins are partly released from the complex and the receptor translocates – together with HSP90 - to the nucleus (Gekle et al., 2014), enabling its action as a transcription factor (Funder, 1997). The expression of chaperones, co-activators or co-repressors can be cell type or micro-milieu specific. For example, there is a change in transcriptional activity of the aldosterone-activated MR under hypoxic conditions in HEK cells, where the activity via the NFκB -response element is enhanced and activation of the glucocorticoid receptor response element is reduced (Schreier et al., 2018). The GR and the MR share 94% homology in the DNA binding domain and thus bind to the same palindromic 15-nucleotide sequence either as homodimers or heterodimers (Funder, 1997).

TABLE 1 Summary of the knowledge for the different factors potentially affecting MR actions in various liver cells

	Hepatocytes	LSEC	Kupffer cells	Hepatic stellate cells
MR expression				
Health	+	+	+	?
Disease	↓	?	?	↑
MR isoform	Δ5&6	?	?	?
CYP11B2	?	?	?	+
11β-HSD1	+	?	?	?
11β-HSD2	(–)	(–)	(–)	(–)
Aldosterone degradation	+			

However, from a systemic and clinical point of view, both receptors and hormones – glucocorticoids vs. mineralocorticoids – show different effects. Therefore, the identification of MR-specific response elements is of high scientific value. Meinel et al. (Meinel et al., 2013) identified a MR-, but not GR-responsive, DNA fragment within the promoter of the **epidermal growth factor receptor**. This element lacked the classical GR response element characteristics and gene transcription by the MR depended on the specificity protein 1 (SP1).

Considering the beneficial effects of MR inhibition for liver function in vivo, the following questions need to be answered: i) which liver cells are responsible for the beneficial effect of MR inhibition? ii) How does the alteration of the signalling cascade in one cell affect the other cell types? iii) Is the MR activated by aldosterone or by glucocorticoids in liver diseases, or are the micro-milieu changes sufficient to increase the transcriptional activity of the MR? iv) What are the effects of MR activation on liver function and which cofactors are needed to induce them? We tried to summarize the knowledge about the potential MR action modulating factors in the different liver cells in Table 1.

5 | MR IN LIVER DISEASES

5.1 | NASH (non-alcoholic steatohepatitis) & NAFL (non-alcoholic fatty liver)

NAFL has a global prevalence of 25% and is a leading cause for cirrhosis and hepatocellular carcinoma (Powell et al., 2021). NAFL enhances the risk of developing Type 2 diabetes, cardiovascular and cardiac diseases, as well as chronic kidney disease (Byrne & Targher, 2015). In patients with Type 2 diabetes, NAFL can be observed in 47.3–63.7% of patients, in people with obesity that number is even higher with 70–80%. Although less than 10% of people with NAFL develop liver associated complications, it is now known to be the most rapidly increasing cause of liver-related mortality worldwide (Powell et al., 2021).

NAFL is defined by the presence of steatosis – accumulation of triglycerides in the hepatocytes - together with metabolic risk factors like obesity and Type 2 diabetes but in the absence of excessive alcohol consumption or other chronic liver diseases (Powell et al., 2021). Different diseases are summarized under the term NAFL: i) steatosis with or without mild inflammation (non-alcoholic fatty liver, NAFL) and ii) steatosis with necro-inflammation and hepatocellular injury (NASH). In NASH fibrosis develops more rapid than in NAFL, presumably due to necro-inflammation (Powell et al., 2021). The underlying pathomechanism is – to state it simply – over-nutrition. Over-nutrition induces the expansion of adipose tissue, subsequent infiltration of macrophages in the fat tissue leads to insulin resistance. These changes mean that glucose uptake is reduced while lipolysis is induced inappropriately in adipose tissue. The resulting increased plasma lipid concentrations lead to an increased lipid uptake in the liver with a subsequent imbalance enabling the formation of lipotoxic lipids that contribute to cellular stress (i.e. oxidative stress and endoplasmic reticulum stress), inflammasome activation and apoptotic cell death, and subsequent stimulation of inflammation, tissue regeneration, and fibrogenesis in the liver (Powell et al., 2021). The lipid accumulation in the hepatocytes impairs key components of the insulin-signalling pathway, increasing the risk of Type 2 diabetes. Additionally insulin resistance is not only restricted to adipose tissue but takes also place in the liver (Rinella, 2015).

To our knowledge, liver-specific or rather, hepatocyte-specific MR mutant mouse models have not yet been characterized. There is some evidence from pharmacological inhibitor studies, that blockade of the MR is beneficial against steatohepatitis. Treatment of mice with 60% high-fat diet combined with 30% high-fructose water for 8 weeks results – besides other alterations - in the accumulation of lipid droplets in the hepatocytes, this phenotype was ameliorated by spironolactone (Wada et al., 2010). Because high fat/high fructose diet fed mice upon spironolactone treatment demonstrated reduced epididymal fat weight, circulating free fatty acids and leptin levels, it is possible that spironolactone suppresses hepatic steatosis and the expression of pro inflammatory cytokines by preventing hepatic influx of adipocytokines or free fatty acids from enlarged adipose tissue (Wada et al., 2010). Consistent with this, the main source of accumulated triglyceride in the liver is from serum free fatty acids (Donnelly et al., 2005).

Additionally, C57Bl6J mice given a CDAA diet (a rodent model for NASH), developed a severe steatosis, inflammatory cell infiltration, hepatocyte ballooning and development of hepatic fibrosis. **Eplerenone** treatment reduced liver steatosis and fibrosis but not liver inflammation (Pizarro et al., 2015). The cell types involved are difficult to identify. MR expression in isolated hepatocytes from CDAA mice

was reduced but increased in hepatic stellate cells (Pizarro et al., 2015). The interpretation of these results is difficult, as hepatocytes are the main cell type responsible for metabolic substrate turnover, while HSCs are the main source of extracellular matrix in the liver.

In genetically altered mouse models for obesity and diabetes (ob/ob mice with mutation of the leptin gene, db/db mice with mutation in the leptin receptor gene) Robinson et al. (2000) showed that eplerenone reduced the HOMA index (Homeostasis Model Assessment index) – a measure for the endogenous insulin resistance - and triglyceride levels in the plasma (Guo et al., 2008). Unfortunately, these effects were only attributed to changes in the adipose tissue and evaluation of the liver was not published until now. Interestingly, in the obese db/db mice, urinary aldosterone/ creatinine ratio was increased at 25 weeks of age (Guo et al., 2008), indicating an increased plasma aldosterone level.

Although MR antagonists effectively ameliorate insulin resistance in vivo, studies in vitro indicated that the effects of aldosterone on the metabolic signalling cascade of insulin in hepatocytes and adipocytes are mediated via the GR (Guo et al., 2008; Hirata et al., 2009; Wada et al., 2009; Yamashita et al., 2004). In primary mouse hepatocytes, aldosterone stimulated the gene expression of glucose-6-phosphatase, beginning at a concentration of 1 nM, with a maximum effect at 1 μM (Yamashita et al., 2004). Interestingly in HepG2 cells, human hepatocellular carcinoma cells mimicking human hepatocytes, the effect could be obtained at ∼100 fold higher concentrations, for the lowest effective concentration and for the highest effect (Yamashita et al., 2004). The results regarding the receptor mediating this effect are still conflicting. While the effect was inhibited in HepG2 cells by **RU-486**, a GR antagonist, but not by **spironolactone** (Yamashita et al., 2004), indicating a MR-independent effect. Liu et al., 2006 (Liu et al., 2006) demonstrated that RNAi-mediated MR silencing as well as the MR antagonists spironolactone, eplerenone and **RU-28318** led – among other effects - to a decreased expression of glucose-6-phosphatase in HepG2 cells. If MRs or GRs are involved in the de novo glucose synthesis in hepatocytes needs to be investigated further.

Although this review focuses mainly on the liver, in the context of NAFL the effect of the MR in adipocytes and immune cells has to be mentioned, at least briefly. The influence of adipocyte MRs on metabolic syndrome-related pathophysiological changes is still under debate. In adipose individuals, the expression of MRs in adipose tissue was increased (Hirata et al., 2009; Urbanet et al., 2015). Deletion of the MR in adipocytes did not induce major changes in weight gain, glucose tolerance or insulin tolerance after 16 weeks of high fat/high sucrose diet (Hayakawa et al., 2018). In contrast to this, overexpression of MRs in the adipocytes induced weight gain, as well as impaired insulin tolerance in mice (Urbanet et al., 2015). The insulin resistance in these mice was prevented by canrenoate treatment (Urbanet et al., 2015), indicating a MR-dependent effect not located in adipocytes. In obese db/db mice eplerenone reduced the expression of the chemokine **CCL2**, **TNF-α**, serpin-1, CD 68 and **leptin** in adipose tissue, while the expression of **adiponectin** and **PPAR-γ** increased to levels similar to those in lean mice (Guo et al., 2008). These findings suggest that endocrine inter-organ crosstalk needs to be taken into consideration in order to fully understand the effects of the MR in NAFL.

The obesity-related changes in vivo could be mimicked by aldosterone incubation of isolated, primary adipocytes and were inhibited by canrenoate indicating a MR-dependent effect (Guo et al., 2008). This is in agreement with data from Hirata et al. (2009), who demonstrated that in white adipose tissue of db/db and ob/ob mice, the adipocyte cell size distribution, the number of macrophages (F4/80 positive cells), the number of crown-like structures, as well as plasma thiobarbituric acid reactive substance (TBARS) was reduced by eplerenone. Crown-like structures in the adipose tissue are dead adipocytes surrounded by macrophages and could be causally related to the appearance of metabolic disorders (Murano et al., 2008). TBARS is a marker for lipid peroxidation and therefore for reactive oxygen stress, related to metabolic disease (Dasgupta & Klein, 2014; Ruiz-Ojeda et al., 2018). Aldosterone mimicked the effect of obesity on reactive oxygen species (ROS) producing enzyme expression in 3 T3-L1 adipocytes and the effect could be inhibited by eplerenone as well as by siRNAs against the MR (Hirata et al., 2009).

A more recent study focused on the effects of MR in white adipose tissue (Urbanet et al., 2015), revealing that aldosterone in primary murine adipocytes increased the expression of **lipocalin-type PGD_2 synthase**, which could be inhibited by incubation with spironolactone. The effect could not be mimicked by **dexamethasone**. Interestingly, deletion of this PGD_2 synthase in mice leads to dyslipidemia, altered expression of lipogenesis genes and the acceleration of NAFL and NASH (Kumar et al., 2020). Further studies are necessary to evaluate the crosstalk between adipose tissue and the liver, and the contribution of this crosstalk to the development of NAFL.

In the last few years, the function of the MRs in immune cells has been further elucidated (Belden et al., 2017; Bene et al., 2014; van der Heijden et al., 2018). As mentioned before, Kupffer cells are specialized macrophages that reside in the liver and make up the main part of the mononuclear phagocytic system (Thomson & Knolle, 2010). The importance of macrophages in NAFL and Type 2 diabetes has been acknowledged, but how these cells affect the hepatocytes is still not clear (Zhang et al., 2017). Knockout of myeloid MR and therefore also in Kupffer cells, improved glucose tolerance, insulin resistance and hepatic steatosis in obese mice (Zhang et al., 2017). Hepatic gene and protein expression indicates that the deletion of the MR in myeloid cells reduces hepatic lipogenesis and lipid storage. Zhang et al. (2017) further demonstrated, that the MR directly regulated the **estrogen receptor 1** (ERα) in macrophages, which thereby via **hepatocyte growth factor** (HGF)/Met signalling enhanced lipid accumulation and reduced insulin sensitivity of hepatocytes. These data are in agreement with a study from Munoz-Durango et al. (2020) demonstrating in a NASH model that mice with a myeloid cell-specific MR inactivation showed reduced hepatic inflammation and lower triglyceride content than controls. While the total number and percentage of liver inflammatory infiltrate cells were similar in both mutants and controls, expression of the co-stimulatory molecule **CD86** by

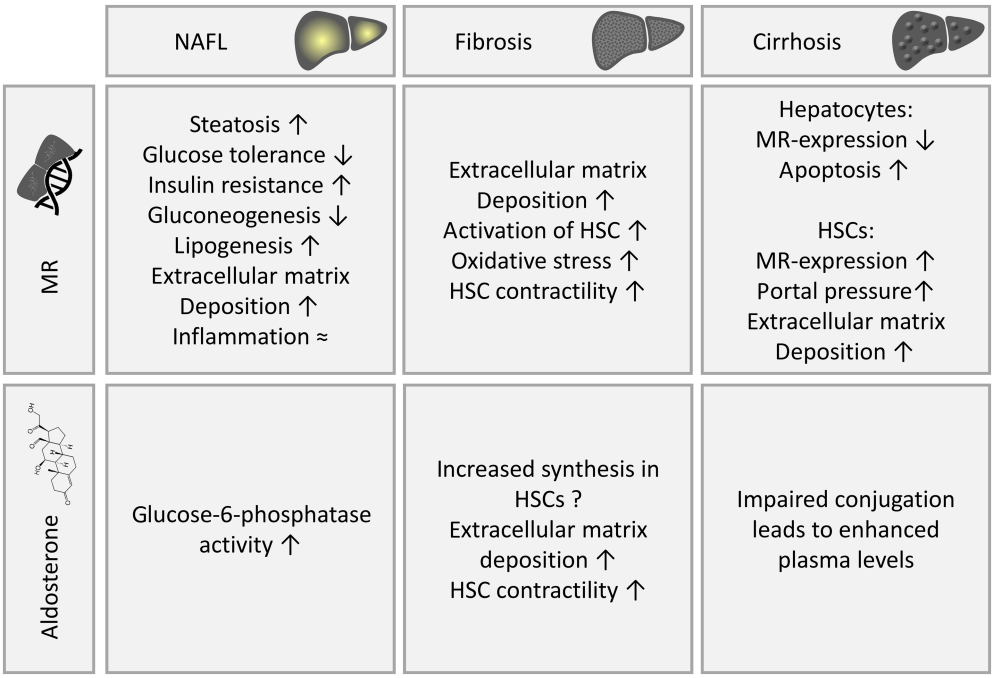

FIGURE 1 Effects mediated by the mineralocorticoid receptor (MR) and its endogenous agonist, aldosterone, in liver diseases. Data summarized from human and rodent model studies, as discussed in the text

dendritic cells and the **CD25** activation marker in $CD8^+$ T cells were significantly reduced in myeloid-specific mutant livers. It appears that myeloid MRs affect hepatic lipid accumulation, in part by modulating the adaptive immune response, and controlling pro inflammatory cells, which is important for the pathogenesis of steatosis (Munoz-Durango et al., 2020).

As summarized in Figure 1, there is evidence that the MR is involved in the development of NAFL and NASH. However, there are still questions to be answered: Is the beneficial effect of MR antagonists due to an intra-hepatic effect or due to a change in inter-organ crosstalk? Moreover, which cells are responsible for the beneficial effect: hepatocytes, hepatic stellate cells (Ito cells) or Kupffer cells?

5.2 | Liver fibrosis

Liver fibrosis is a dynamic, highly integrated molecular, cellular and tissue process responsible for driving the excess accumulation of extracellular matrix components by myofibroblasts (Parola & Pinzani, 2019). Chronic liver injury, chronic inflammation and progressive fibrogenesis is leading often to liver cirrhosis, a process which usually takes between 15–20 years (Parola & Pinzani, 2019). In liver fibrosis, the progressive accumulation of extracellular matrix destroys the physiological architecture of the liver (Iredale, 2007). The starting point of liver fibrosis is often toxic, metabolic or viral damage of hepatocytes. This promotes immune cell infiltration further by activating the trans-differentiation of HSCs to collagen-producing myofibroblasts (Elpek, 2014; Zhou et al., 2014). Although, on the short term, pro-fibrotic and anti-fibrotic processes are balanced, persistent activation of proliferating, contractile and migrating myofibroblasts causes the excessive production of extracellular matrix (Elpek, 2014; Zhou et al., 2014). Hepatocyte death is an important driver of liver disease etiologies. One of the main causes for hepatotoxicity is lipid overload, as accumulation of toxic lipid intermediates cause oxidative and endoplasmic reticulum stress, mitochondrial dysfunction and induce apoptosis (Musso et al., 2018). Quiescent HSCs are characterized as non-proliferative, peri-sinusoidal cells, characterized by their star-like morphology and their cytoplasmic retinyl ester droplets (Ito cells) (Testerink et al., 2012). Upon liver injury, HSCs become activated, loose their lipid droplets and produce collagen I, III, IV, fibronectin and pro inflammatory mediators (Affo et al., 2017; Kisseleva et al., 2012; Tsuchida & Friedman, 2017). Aldosterone, via the MRs, contributes to tissue fibrosis in the heart, the kidney or blood vessels (Azibani et al., 2013; Brown, 2013; Shrestha et al., 2019), but if they also contribute to liver fibrosis is less clear.

There are only a few studies of the effects of aldosterone or the MRs on liver fibrosis. In patients with liver fibrosis, there was no significant increase in serum aldosterone levels but an increase in aldosterone levels in the liver tissue, per se, to about 700 pg g^{-1} in patients, from about 250 pg g^{-1} in healthy subjects (Li et al., 2020). The mechanism leading to the increased aldosterone concentration in the liver tissue is not known, there could either be an increase in aldosterone synthesis – as in the rat brain (Albiston et al., 1994) or a reduced aldosterone clearance from the liver (Rosoff et al., 1975). In a model of hepatic fibrosis in rats, induced by i.p. injection of pig serum over 12 weeks, treatment with spironolactone reduced the accumulation of fibrotic material and the number of cells positive for α-smooth muscle actin, indicating a reduced activation of HSCs (Fujisawa et al., 2006). This model did not show increased plasma aldosterone concentrations but the expression of CYP11B2 protein in hepatocytes and HSCs was increased.

In rats, infusion of aldosterone and 1% salt in the drinking water induced systemic hypertension and liver fibrosis after 28 days of treatment (Queisser et al., 2014). The effect was mediated by MR and oxidative stress, as it was reduced by tempol – a ROS scavenger – and spironolactone. Presumably, oxidative stress induced hepatic cell damage, adding to the pro-fibrotic capacity of aldosterone. In a model of bile duct ligation-induced liver cirrhosis in rats, spironolactone reduced deposition of extracellular matrix and portal pressure (Luo et al., 2012). This was accompanied by an increase in phosphorylation and activity of endothelial NOS, indicated by enhanced phosphorylation of the vasodilator-stimulated phosphoprotein, as well as a decrease of ROCK-2 (**Rho-associated protein kinase 2**) activity, measured as increased moesin phosphorylation (Luo et al., 2012).

In an additional study, high physiological concentrations of aldosterone (1 nM) induced a contraction of activated HSCs, determined by hydrated collagen gel contraction (Ji et al., 2011). This was mediated most probably by interaction of the MRs with AT_1 receptors activating ROCK-2, which is a key regulator of actin cytoskeleton and cell polarity and subsequently an increase in myosin light chain phosphorylation, necessary for smooth muscle cell like contraction (Ji et al., 2011). Apart from the contractile function of the HSCs, activated MRs seem to enhance the pro-fibrotic effects of activated HSCs. **Platelet-derived growth factor BB** (PDGF-BB) induced cell proliferation and cell migration in human HSCs, effects inhibited by canrenone. PDGF-BB also enhanced the activity of the **sodium-hydrogen antiporter, NHE1**, by activating **PI3K** and this effect was reduced by canrenone, as well as the de novo synthesis of collagen I, collagen IV and fibronectin (Caligiuri et al., 2003). Aldosterone in physiological concentrations stimulates the secretion of collagen IV from freshly isolated HSCs, but after sub-culture, leading to an activated phenotype of these cells, this effect was abolished (Rombouts et al., 2001).

Taken together (Figure 1), there seems to be a pro-fibrotic action of aldosterone and the MR in the liver, presumably in interaction with enhanced reactive oxygen or nitrogen species. Further investigations are needed to elucidate if the effect of aldosterone or the MRs is facilitated by increasing the ROS levels in hepatocytes, leading to an increased activation of the HSCs or if there is a direct effect on HSCs by aldosterone and the MRs.

5.3 | Liver cirrhosis & portal hypertension

Portal hypertension is the main driver of complications in cirrhosis (Bosch et al., 2015). It results from an increased intrahepatic resistance and an increased splanchnic inflow (Bosch et al., 2015). The main cause for increased hepatic resistance is the distortion of the liver tissue by increased extracellular matrix formation, and microvascular thrombosis, accounting for 70–80% of increased resistance (named static resistance) (Bosch et al., 2015; Gunarathne et al., 2020; Iwakiri & Groszmann, 2020). 20–30% of the increased resistance is due to reversible, hyper-contractile phenotype of the hepatic microcirculation (dynamic resistance) (Bosch et al., 2015; Gunarathne et al., 2020; Iwakiri & Groszmann, 2020; Wiest & Groszmann, 2002). In the normal liver, 75% of the blood comes from the portal vein and 25% from the hepatic artery (Nagy et al., 2020). This circulatory situation leads to different important vascular necessities: i) the portal vein is not or only moderately auto regulated, as the liver has to take up all the blood draining from the gastro-intestinal tract. ii) The oxygen content of the portal venous blood is low while the supply with other nutrients is high (Bosch et al., 2015). Portal hypertension is characterized by an increase in portal venous pressure. In the clinical setting, this is determined by measuring the pressure gradient between the portal vein and the inferior vena cava – HVPG (hepatic venous pressure gradient). This gradient is normally not higher than 1–5 mmHg. Portal hypertension is clinically manifest if the gradient exceeds 10 mmHg (Bosch et al., 2015).

Hyperaldosteronism is a well-known feature of advanced liver cirrhosis. In one study, the plasma aldosterone concentration was three to four times higher than the normal upper reference value (Kuiper et al., 2008). The increase of plasma aldosterone level was only moderately correlated to plasma renin activity, indicating a deregulation of the RAAS. Tandon et al (Tandon et al., 2010) performed a systematic review analysing, if inhibition of the RAAS was beneficial in reducing portal hypertension. In this study, AT_1 receptor antagonists and ACE inhibitors were compared to aldosterone antagonists (at that time spironolactone). While AT_1 receptor antagonists and ACE inhibitors had no beneficial effect on HVPG, spironolactone reduced HVPG and neither **nitroglycerin** patches (NO-donor) nor β-adrenoceptor antagonists showed an additional effect or enhanced the effect. In the treatment guidelines from the European Association for the Study of the Liver (EASL, 2018), spironolactone is indicated as a potassium-sparing diuretic to reduce blood volume and thereby blood pressure. Therefore, a study performed comparing the effect of spironolactone and **furosemide**, a loop diuretic, is of special interest. Here, a significantly larger effect of spironolactone, compared with furosemide, on HVPG was observed, indicating an effect of MR blockade, above or independent of its effects on blood volume (Katsuta et al., 1993). In an additional study, Nevens et al. (Nevens et al., 1996) compared the change in variceal pressure – as a parameter for portal hypertension - in patients treated with placebo or spironolactone for six weeks. They subdivided the groups into **propranolol** or non-treated patients, ahead of spironolactone treatment. Regardless of the pre-treatment, spironolactone reduced the variceal pressure but not the mean arterial pressure. As expected, plasma renin activity was increased by spironolactone treatment.

The molecular mechanisms contributing to the beneficial effects of aldosterone-MR inhibition have not been resolved in detail. In a model of bile duct ligation induced liver cirrhosis in rats, spironolactone reduced deposition of extracellular matrix and portal pressure (Luo et al., 2012). This was accompanied by an increase in endothelial NO-synthase phosphorylation and activity - indicated by enhanced VASP phosphorylation - as well as a decrease of ROCK-2 activity, measured as increased moesin phosphorylation (Luo et al., 2012). We (Schreier et al., 2018) have found, in an animal study, that treatment with eplerenone (a more specific MR blocker) leads to

less development of fibrosis and less portal hypertension related complications (ascites and hypersplenism). Eplerenone treatment was started eight weeks after the beginning of cirrhosis induction in the rats, mimicking a clinically relevant situation. It was hypothesized that the effect of the MR was related to hypoxia and independent of the ligand aldosterone. Interestingly, **ursodeoxycholic acid** inhibits - at least in part - TGF-β1-induced apoptosis of hepatocytes, by ligand-independent activation of the MR, presumably by inducing MR-GR-heterodimers with the GR and subsequent expression of the transcription factor E2f-1 (Sola et al., 2004).

6 | CONCLUSIONS AND FUTURE PERSPECTIVES

In summary (Figure 1), inhibition of the MR in vivo seems to improve liver function, at least in the diseased state. Regrettably, not much is known about the mechanisms specific to the liver that underlie such actions. Nevertheless, it can be hypothesized that the known molecular mechanisms from "classical" non-target tissues of the MR (heart, blood vessels, immune cells) are at least partly involved in the actions of the MR in liver.

6.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, and are permanently archived in the Concise Guide to PHARMACOLOGY 2021/22 (Alexander, Christopoulos, Davenport, Kelly, Mathie, Peters, Veale, Armstrong, Faccenda, Harding, Pawson, Southan, Davies, et al., 2021; Alexander, Cidlowski, Kelly, Mathie, Peters, Veale, Armstrong, Faccenda, Harding, Pawson, Southan, Davies, Coons, et al., 2021; Alexander, Fabbro, et al., 2021a, 2021b; Alexander, Kelly, et al., 2021a, 2021b).

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

All authors have made substantial contributions to the conception of the manuscript. MG and BS have made substantial contributions to design, analysis, interpretation and presentation of data. AZ and HU have been involved in drafting the manuscript and revising it critically for important intellectual content.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article because no new data were created or analysed in this study.

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