ANNALS OF MEDICINE
2023, VOL. 55, NO. 1, 543–557
https://doi.org/10.1080/07853890.2022.2164047

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REVIEW ARTICLE

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Neuroimmunomodulation of adrenoblockers during liver cirrhosis: modulation of hepatic stellate cell activity

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ABSTRACT

The sympathetic nervous system and the immune system are responsible for producing neurotransmitters and cytokines that interact by binding to receptors; due to this, there is communication between these systems. Liver immune cells and nerve fibres are systematically distributed in the liver, and the partial overlap of both patterns may favour interactions between certain elements. Dendritic cells are attached to fibroblasts, and nerve fibres are connected via the dendritic cell-fibroblast complex. Receptors for most neuroactive substances, such as catecholamines, have been discovered on dendritic cells. The sympathetic nervous system regulates hepatic fibrosis through sympathetic fibres and adrenaline from the adrenal glands through the blood. When there is liver damage, the sympathetic nervous system is activated locally and systemically through proinflammatory cytokines that induce the production of epinephrine and norepinephrine. These neurotransmitters bind to cells through α-adrenergic receptors, triggering a cellular response that secretes inflammatory factors that stimulate and activate hepatic stellate cells. Hepatic stellate cells are key in the fibrotic process. They initiate the overproduction of extracellular matrix components in an active state that progresses from fibrosis to liver cirrhosis. It has also been shown that they can be directly activated by norepinephrine. Alpha and beta adrenoblockers, such as carvedilol, prazosin, and doxazosin, have recently been used to reverse CCl_4-induced liver cirrhosis in rodent and murine models.

KEY MESSAGES

- Neurotransmitters from the sympathetic nervous system activate and increase the proliferation of hepatic stellate cells.
- Hepatic fibrosis and cirrhosis treatment might depend on neurotransmitter and hepatic nervous system regulation.
- Strategies to reduce hepatic stellate cell activation and fibrosis are based on experimentation with α-adrenoblockers.

ARTICLE HISTORY
Received 6 October 2022
Revised 7 December 2022
Accepted 23 December 2022

KEYWORDS
Cirrhosis; hepatic cells; stellate cells; sympathetic nervous system; neuroimmunomodulation; adrenoblockers

Neuroimmunomodulation

The modulating effect of the nervous system on immunological processes is known as neuroimmunomodulation. This modulation considers the reciprocal communication of the immune and neurological systems. Because immune cells have neurotransmitter receptors (including those for norepinephrine and acetylcholine) and lymph nodes are innervated by sympathetic nervous system (SNS) fibres, neuroimmunomodulation is possible [1]. These innervating fibres impact immune cell migration and proliferation, promoting neuroimmunomodulation. The vagus nerve, which inhibits cytokine generation in peripheral monocytes *via* the alpha-7 nicotinic acetylcholine receptor, is a recently discovered alternative approach to neuroimmunomodulation [2]. Since the inflammatory response is the basis of severe chronic disease pathogenesis, such as cancer and coronary heart disease, the neuroimmunomodulating function of the vagus nerve may have clinical significance. Therefore, it is postulated that vagal activity might modulate disease progression [3,4], an issue currently under

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investigation. The cerebral hemispheres' influences on peripheral immunity is another way that neuroimmunomodulation manifests. According to studies, the right hemisphere has immunosuppressive effects, while the left hemisphere has immune-potentiating effects [5,6]. Since inhibiting beta-adrenergic receptors eliminated disparities in the immune response between the hemispheres, these effects were observed in animals and humans and mediated by the sympathetic response.

Although a change in activity from the left to the right hemisphere during stressful times was associated with an increased incidence of reported sickness [7], the neuroimmunomodulatory effects of the hemispheres may have clinical relevance. Additionally, in a matched prospective design, regardless of factors, those with right hemisphere lateralization had a substantially higher chance of reporting the common cold than those with left hemisphere lateralization [8].

Since the SNS, vagal nerve activity, and hemispheric lateralization are all connected to psychological factors, immunity, and the threat of liver injury, neuroimmunomodulation plays a key role in the function of medicine. It may help explain how psychological factors affect the likelihood of developing a disease. Understanding these neuromodulator interactions is key to potentially prevent or treat liver illnesses such as cirrhosis.

Sympathetic nervous system

The sympathetic nervous system consists of multiple pathways that interact with different organ systems in multiple ways. The thoracic and lumbar portions of the spinal cord (T1 to L2) are the source of the preganglionic neurons of the SNS. The cell bodies are symmetrically and bilaterally distributed in four areas of the gray matter of the spinal cord [9]. The first-order neurons of the sympathetic nervous system (SNS) synapse with postsynaptic neurons within the sympathetic ganglia, but they are shorter than the parasympathetic nervous system. Acetylcholine is the neurotransmitter at this junction, similar to the parasympathetic nervous system (PNS). The nicotinic and muscarinic receptors in acetylcholine are activated.

In contrast to the sympathetic innervation of sweat glands and arrector pili—the small muscles attached to hair follicles, which use acetylcholine as their postganglionic neurotransmitter—these postganglionic neurons travel to their effector sites and release the neurotransmitters epinephrine (EPI) or norepinephrine (NE) [10]. These neurotransmitters regulate adrenergic receptors. Amid the adrenergic receptors are alpha-1 (coupled to a Gq and activating through the IP3/Ca^{2+} pathway), alpha-2 (coupled to Gi and acting by decreasing the cAMP pathway), and beta-1 and beta-2 (coupled to Gs and working by increasing the cAMP pathway) [11]. Depending on the tissue in which they are situated, adrenergic receptors can either be excitatory or inhibitory.

Immunomodulatory function of the sympathetic nervous system

Modulation of immune and inflammatory processes by the sympathetic nervous system

Primary and secondary lymphoid organs have noradrenergic sympathetic innervation. When there is extensive stimulation, NE is released, and immune cells express adrenoceptors. Through the stimulation of these receptors, locally released NE or catecholamines such as epinephrine modify lymphocyte trafficking, circulation, and proliferation and modulate cytokine production and Kupffer cell activity. There is evidence that NE and epinephrine, through the beta(2)-adrenoreceptor-cAMP-protein kinase A pathway, can inhibit the production of type-1 proinflammatory cytokines, such as IL-12, TNF-α, IFN-γ through antigen-presenting cells and helper T cells (Th)1. In contrast, the production of type-2 anti-inflammatory cytokines such as IL-10 and TGF-β is stimulated. Through this mechanism, endogenous catecholamines can systemically cause a selective suppression of Th1 responses and cellular immunity and a Th2 shift toward the domain of humoral immunity [12]. NA activates immune cell functions, primarily NK cells, macrophages, and T and B lymphocytes. In humans, catecholamine injection causes an increase in NK cell migration in the first 2 to 4 h. However, over time, it causes a decline in their functionality and granulocytes to be attracted to specific sites [12]. By preventing neutrophils from releasing lysosomal enzymes and participating in phagocytosis, catecholamines also affect innate immunity [13]. They also prevent the degranulation-related neutrophil respiratory burst at low doses [14].

Additionally, at nanomolar adrenaline concentrations, the production of superoxide and the creation of oxygen radicals is reduced. The stimulation of beta-adrenergic receptors (β-2) is what causes these effects. Contrarily, catecholamines are also known to activate and alter the effects on innate and acquired immunity when they interact with alpha-adrenergic receptors. Beta receptor stimulation also prevents human neutrophil chemotaxis when leukotriene B4 and formyl-methionyl-leucyl-phenylalanine, two potent chemoattractants, are present [12].

Catecholamine synthesis blockers are used to investigate the effects of the SNS. Their function is to cause reversible atrophy of the noradrenergic terminals through a loss of membrane integrity brought on by a reduction in the generation of hydroxyl radicals and hydrogen peroxide [15]. The immune cells that depend on this system's function are altered because the lymphocytes' adrenergic receptors are not activated [16]. According to authors [17], afferent nerves to the liver enter the parenchyma *via* the bile duct, hepatic artery, or portal vein. Somatic nerves come from the spinal cord segments T-7 to T-10 and innervate the liver through the celiac ganglion. Parasympathetic fibres come from the vagus nerve and innervate the liver.

The innervation patterns differ in the livers of diverse species, as described in previous research in this issue. The hepatic pedicle and periportal areas of rodents contain a high concentration of nerve fibres of all types. A few are found along the hepatic veins, but only a rare fibre is identified inside the lobules. On the other hand, primates exhibit considerable intralobular innervation [18]. When analysing results from mouse investigations, the simple absence of intralobular innervation creates some difficulties because it suggests that sympathetic nerve fibre expression and neuronal influence on inflammatory processes in the liver are only present in the portal area. Humans, in contrast, express markers of efferent sympathetic fibres that terminate on liver parenchymal cells and extend deep into connective tissue and hepatic lobules [19].

Another concern is the contradiction between the abundance of functional evidence for cholinergic liver innervation [20,21] and the lack of morphological evidence, at least in rodents, for cholinergic intrahepatic nerve fibres [18]. Recent reports on the inflammatory reflex, which is thought to use cholinergic vagal routes to liver macrophages, are even more puzzling by this conundrum [22]. However, the distribution of nerve fibres and immune cells in the liver is not random, and the partial overlap of these patterns may promote interactions between some aspects. Others, however, disagree [17].

Liver cirrhosis

Cirrhosis was previously defined morphologically as anomalous liver architecture with fibrous bands around regenerative nodules [23]. It is important to emphasize that fibrosis and cirrhosis, frequently used synonymously, are clinically separate entities. It could be argued that fibrosis in and of itself in a pre-cirrhotic liver has little clinical significance because the hepatic reserve is still relatively intact. The increased risk of HCC is linked to liver cirrhosis of all aetiologies with one caveat that some liver illnesses have been shown to raise the risk of HCC in patients who are not yet cirrhotic.

The definition of cirrhosis should incorporate at least three important factors: physiological disruption of the vasculature, which contributes to the emergence of portal hypertension; an alteration in hepatic function, which may ultimately result in decompensated liver disease; and an increased risk of neoplastic transformation, a phenomenon relevant to cirrhosis of all aetiologies; all should be included in the definition of cirrhosis. These variables have a significant clinical impact that contributes to liver-related mortality and morbidity [24].

Types of cells that influence liver cirrhosis (cell involvement)

Hepatic stellate cells

HSCs are converted from a quiescent to an activated state by inflammatory cytokines, such as platelet-derived growth factor (PDGF), transforming growth factor (TGF)-β, tumour necrosis factor (TNF)-α, and interleukin (IL-1). HSC activation is a critical step in the progression of liver fibrosis and a key factor in collagen deposition (Figure 1) [25]. Activated HSCs change their phenotype to myofibroblast and initiate the production of collagen and extracellular matrix (ECM) components [26].

HSCs are primarily responsible for fibrosis in zone 3, known as perisinusoidal fibrosis. On the other hand, fibrosis in zone 1, known as portal fibrosis, is associated with the progression of damage in steatohepatitis and viral hepatitis. Periportal fibrosis has not been studied extensively, and it is unclear how and why portal fibrosis develops in chronic liver disease where the initial primary insult is within the lobules. In cholestatic liver disorders, it is common to observe the development of portal fibrosis in response to ductular morphological change. Studies in humans with biliary diseases and animal models of biliary fibrosis have shown that reactive or deteriorating ductal epithelium can express profibrogenic proteins, such as PDGF and TGF-β, and chemotactic proteins that activate both inflammatory cells and fibrogenic cells developing a periportal fibrosis process [27–30].

Hepatic progenitor cells (HPCs)

HPCs exist in normal liver tissue in the progenitor cell compartment and reside in the canals of Hering in

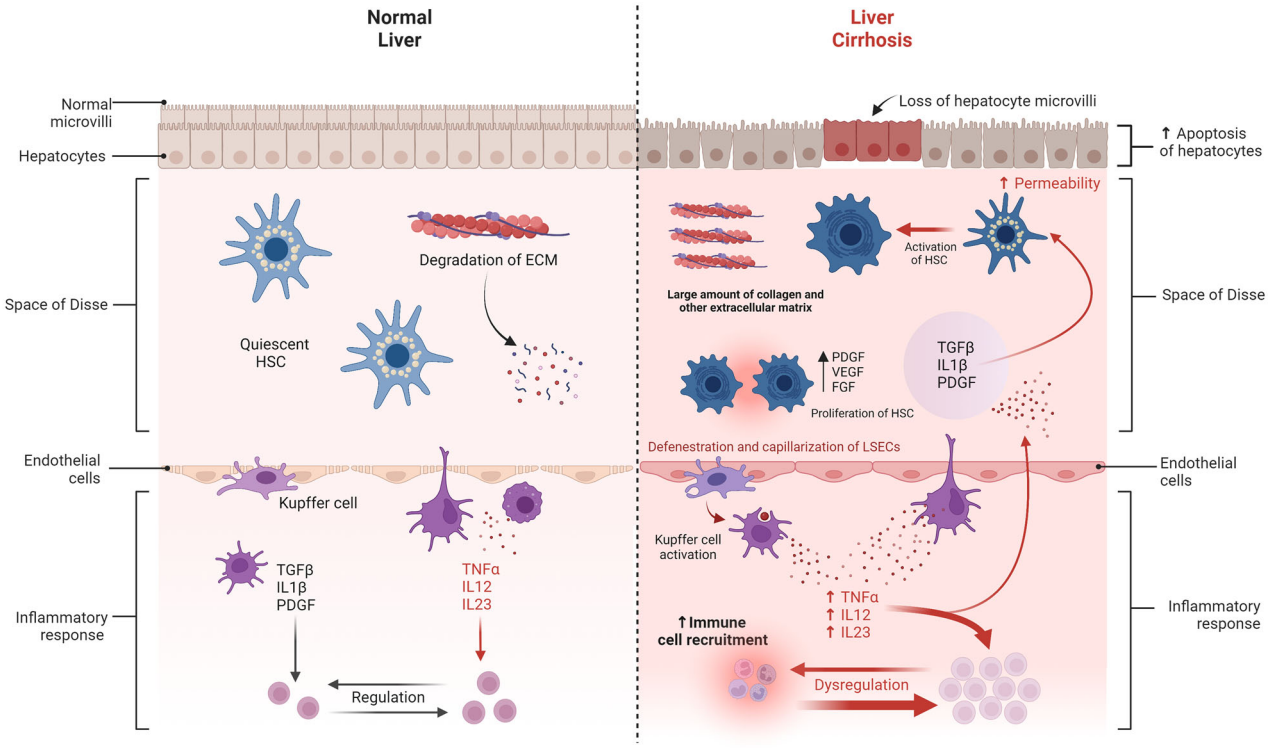


Figure 1. Hepatic stellate cell activation during liver injury and resolution.

bile ducts. HPCs are referred to as oval cells and possess the potential to differentiate toward the hepatocytic or biliary phenotype. Histologically, these cells adopt the appearance of small epithelial cells with an oval nucleus and scant cytoplasm. They express markers such as OV-6 and chromogranin A. As reservoir cells, HPCs were shown to be activated in a wide range of liver diseases and conditions, such as submassive necrosis, chronic viral hepatitis, and fatty liver disease [31].

Liver sinusoidal endothelial cells

Defenestration of the sinusoidal endothelium and a subendothelial basement membrane are frequent characteristics of the cirrhotic liver [32]. Retinol shortage can activate HSCs, transform them into myofibroblasts with increased ECM synthesis, and ultimately lead to cirrhosis [33]. Because of modifying retinol metabolism, it is thought that defenestration and capillarization of the hepatic endothelium are crucial for the onset of perisinusoidal cirrhosis. According to different studies, the defenestration of the liver sinusoidal endothelial cells, through impairment of substrate exchange, contributes to liver cirrhosis dysfunction [34].

Interleukin-33 (IL-33) expression is upregulated in human and murine hepatic fibrosis. This expression is related to stressed hepatocytes, which trigger the profibrogenic activation of hepatic stellate cells *via* mediators such as IL-13 [35].

Nevertheless, differentiated LSECs can promote regression and prevent the advancement of fibrosis by encouraging the reversal of activated HSCs to quiescence through VEGF-stimulated NO production [36].

Kupffer cells

Research using animal models has demonstrated that *Kupffer cells* (KCs) play a role in the aetiology of several liver disorders [37]. Liver damage and fibrosis are aggravated by KC-mediated hepatic inflammation [38]. HSC activation and fibrosis development are both aided by KCs. By inducing the expression of PDGF receptors in HSCs, *in vitro* studies have demonstrated that a KC-conditioned media can promote the activation of cultured rat HSCs with enhanced matrix synthesis and cell proliferation [39]. HSCs obtained from rats treated with a high-fat diet and ethanol are stimulated to proliferate and produce collagen by KC-derived TGF-β1 [40]. By degrading collagen type IV, gelatinase released by activated KCs causes the phenotypic change in HSCs (Figure 1) [41]. Inflammation and fibrogenesis are facilitated by KCs' consumption of apoptotic bodies and the production of death ligands like TNF-α and the Fas ligand [42]. In both normal and fibrotic livers, KCs

triggered by β-glucans raise portal pressure by releasing thromboxane A2 [43].

Hepatocytes

Cirrhosis and other chronic liver diseases can stimulate hepatocyte regeneration in response to compensation or induce apoptosis. Hepatocyte damage results from the release of reactive oxygen species (ROS), profibrotic mediators, HSC activation, and stimulation of myofibroblast effects. As a result of this process, there is tissue inflammation and disease progression [44]. Hepatocyte apoptosis is induced in the early stages of CCl_4-induced liver injury, followed by constant proliferation, and if it persists, liver cirrhosis develops at a later stage [45]. Matrix metalloproteinases (MMP-2, MMP-3, and MMP-13) and tissue inhibitors of matrix metalloproteinases (TIMP-1 and TIMP-2) are primarily produced by hepatocytes. They are all involved in the aetiology of liver cirrhosis in rats with liver cirrhosis induced by CCl_4 [46]. Hypoxic hepatocytes become the main source of TGF-β1 in the last fibrotic stage of cirrhosis, aggravating hepatic fibrogenesis [47]. The pathophysiology of cirrhosis has recently been explained uniquely by the discovery that hepatocyte telomere shortening, and senescence can cause fibrotic scarring at the cirrhosis stage [48].

Role of growth factors and cytokines in liver cirrhosis (humoral involvement)

PDGF

Of all the polypeptide growth factors, PDGF is the strongest mitogen for HSCs. PDGF-A, PDGF-B, PDGF-C, and PDGF-D are the four members of the PDGF family [49]. In fibrous tissues, PDGF and its receptors are noticeably overexpressed, and the degree of liver fibrosis promotes the activity of these molecules [50]. Numerous factors, including viruses, drugs, or physical harm to the hepatocytes, can cause KCs to produce and release PDGF [51]. PDGF activates corresponding signal molecules and transcription factors upon binding to its receptor on the membrane of HSCs, which in turn causes the activation of its downstream target genes and HSCs [52]. According to research, PDGF increases MMP-2, MMP-9, and TIMP-1 expression and inhibits collagenase activity, which inhibits the degradation of the extracellular matrix (ECM) [49,52].

According to PDGFRβ autophosphorylation and activation of the ERK1/2, C-Jun N-terminal kinase (JNK), p38 mitogen-activated protein kinase (MAPK), and protein kinase (PK)B/Akt pathways, PDGF-B and PDGF-D are potent PDGF isoforms in PDGF receptor (PDGFR)β signalling within HSCs [53]. Although PDGF-D can activate HSCs and has mitogenic and fibrotic effects, it is essential for remodelling the matrix in liver fibrosis [54].

TGF-β

The strongest known inducer of fibrogenesis in cirrhosis and liver fibrosis is TGF-β. The liver's HSCs/myofibroblasts, KCs, LSECs, and hepatocytes are the principal producers of TGF-β. The TGF-β1 family includes 3 members. TGF-β1 has been demonstrated essential for developing and maintaining liver fibrosis [55]. TGF-β1 expression increases in the fibrotic liver and culminates at the stage of cirrhosis [47]. By suppressing the expression of MMPs and promoting TIMP, TGF-β1 induces the expression of the matrix-producing genes, prevents the degradation of ECM, and promotes liver fibrosis. This change causes an excessive accumulation of collagenous fibres [56]. Furthermore, it has been demonstrated that TGF-β1 inhibits DNA synthesis and induces apoptosis in hepatocytes. It is thought that tissue loss and a decrease in liver size in cirrhosis are caused by TGF-β1-induced apoptosis [57].

TNF-α

Kupffer cells, HSC, macrophages, and monocytes are the main producers of TNF-α; these cells have cytotoxic and proinflammatory actions. TNF-α is essential for HSC stimulation and ECM production throughout liver fibrosis [58]. Upregulating the antiapoptotic proteins NF-κB and Bcl-XL and downregulating the proapoptotic factor p53, TNF-α can decrease spontaneous apoptosis of activated rat HSCs [59]. TNF-α can cause HSC apoptosis, indicating that its effects on fibrosis are complicated and contradictory [60]. It has also been shown that TNF-α has an antifibrogenic effect in rat HSCs, the expression of which can decrease glutathione and prevent the production of pro-collagen 1 [61].

Interferon

In response to viral infection, leukocytes produce IFN-α and IFN-β, and T lymphocytes release IFN-γ after being stimulated by various mitogens and antigens. IFNs have antiviral activity, and their antiviral effects are well known [62]. Even in the absence of viral eradication, IFN-treated patients show a regression of liver fibrosis, demonstrating that IFN has an antifibrotic effect by inducing HSC apoptosis [63]. By inhibiting

the TGF-β and PDGF pathways, IFN-β might inactivate HSCs and reduce their synthesis of α-smooth muscle actin (SMA) and collagen [64]. Like this, it has been shown that IFN-γ inhibits HSC activation *via* TGF-β1/Smad3 signalling pathways, hence reducing ECM deposition *in vivo*. IFN-γ treatment for liver fibrosis in rats resulted in less collagen, laminin, fibronectin, and pro-collagen type I being produced and deposited [65].

Interleukins

Leukocytes were initially found to express a group of cytokines known as ILs; however, it was later discovered that a wide variety of other cells, including CD4 T lymphocytes, monocytes, macrophages, and endothelial cells, were also capable of producing ILs [66]. Profibrotic ILs: In response to liver tissue damage, KCs and SECs can quickly create ILs. As a result of IL-1's direct activation of HSCs and stimulation of their production of MMP-9, MMP-13, and TIMP-1, hepatic fibrogenesis occurs. In contrast, IL-1-receptor-deficient animals show reduced susceptibility to fibrosis development and liver injury [67]. Similarly, it was discovered that IL-1 receptor antagonists prevented dimethylnitrosamine-induced liver fibrosis in rats [68].

Hepatocytes' production of the pro-steatosis chemokine monocyte chemoattractant protein-1 and macrophages' Toll-like receptor (TLR4)-dependent amplification of inflammatory signaling were both reported increased by IL-1β [69]. Profibrotic cytokine IL-17 is expressed at higher levels in livers with more fibrosis, suggesting that IL-17 may contribute to the development and persistence of the illness [70]. Studies in mice have demonstrated that IL-17 induces liver fibrosis through various mechanisms, including the promotion of HSCs' myofibroblast-like change and upregulation of TNFα-, TGF-β, and collagen 1α. These mechanisms depend on the STAT3 signalling pathway and the upregulation of TNF-, TGF-, and collagen 1 [71].

Antifibrogenic ILs: IL-10 is a cytokine that modulates hepatic fibrogenesis and downregulates the proinflammatory response [72]. Exogenous IL-10 was shown to reverse CCl_4-induced hepatic fibrosis by reducing the production of TGF-β1, MMP-2, and TIMP-1 in a rat model, demonstrating that IL-10 has antifibrotic effects *via* inhibiting HSC activity [73,74].

IL-22 promotes antimicrobial immunity, inflammation, and tissue healing at barrier surfaces. In a mouse model, IL-22 has been demonstrated to cause HSC senescence, limit liver fibrosis, and hasten liver fibrosis resolution after recovery [75].

IL-6 is a pleiotropic cytokine that regulates immunological function, haematopoiesis, and inflammatory pathways. By promoting hepatocyte regeneration through NF-κB signalling and the Ras-MAPK pathway, it can attenuate apoptosis and lessen CCl_4-induced acute and chronic liver injury as well as fibrosis [76]. Improved liver injury following fibrosis results from pretreating the fibrotic liver with IL-6, which also enhances the hepatic microenvironment and prepares it for mesenchymal stem cell transplantation [77].

Adrenoreceptors on immune cells and liver stellate cells

As described above, there is an anatomical mismatch between the distribution of nerve fibres to KCs and hepatocytes, the non-neuronal component of the liver. T cells and dendritic cells are located in the periportal area, so they can easily contact nerve fibres and be influenced by neurotransmitters. Most KCs, and hepatocytes, except those found in the periphery, are far from the nerve fibres due to their intralobular location. Therefore, it is believed that in rodent models of hepatitis treated with neural modulation, KCs and hepatocytes may be in contact with neurotransmitters released by periportal innervation. It is proposed that the diffusion of norepinephrine or substance P (SP) along the sinusoids into the lobes may be efficient enough to modulate KC function toward an inflammatory profile and hepatocyte apoptosis (Figure 2). However, this usually occurs in the lobes [78].

The discovery that the immunosuppressive effect is truly caused by α-adrenergic stimulation is supported by the inhibition of the T cell response with the α-blocker, phentolamine. Additionally, it was discovered that the relevant receptor belongs to the α2-subtype employing selective subtype agonists [79]. When β-receptors were concomitantly blocked with propranolol, long-term *in vivo* treatment with noradrenaline or adrenaline resulted in a substantial decrease of the *in vitro* reactivity of peripheral blood T cells [80].

A study demonstrated that HSCs express important enzymes for catecholamine biosynthesis and generate NE and other catecholamines. Furthermore, when normal HSCs are cultured with α- or β-adrenoceptor antagonists, increasing HSC numbers are considerably suppressed, indicating that HSCs use catecholamines to autoregulate their proliferation. Studies using inhibitors indicate that kinases that support cell survival and proliferation must be activated for NE to exert its trophic effects. The activation of comparable signalling

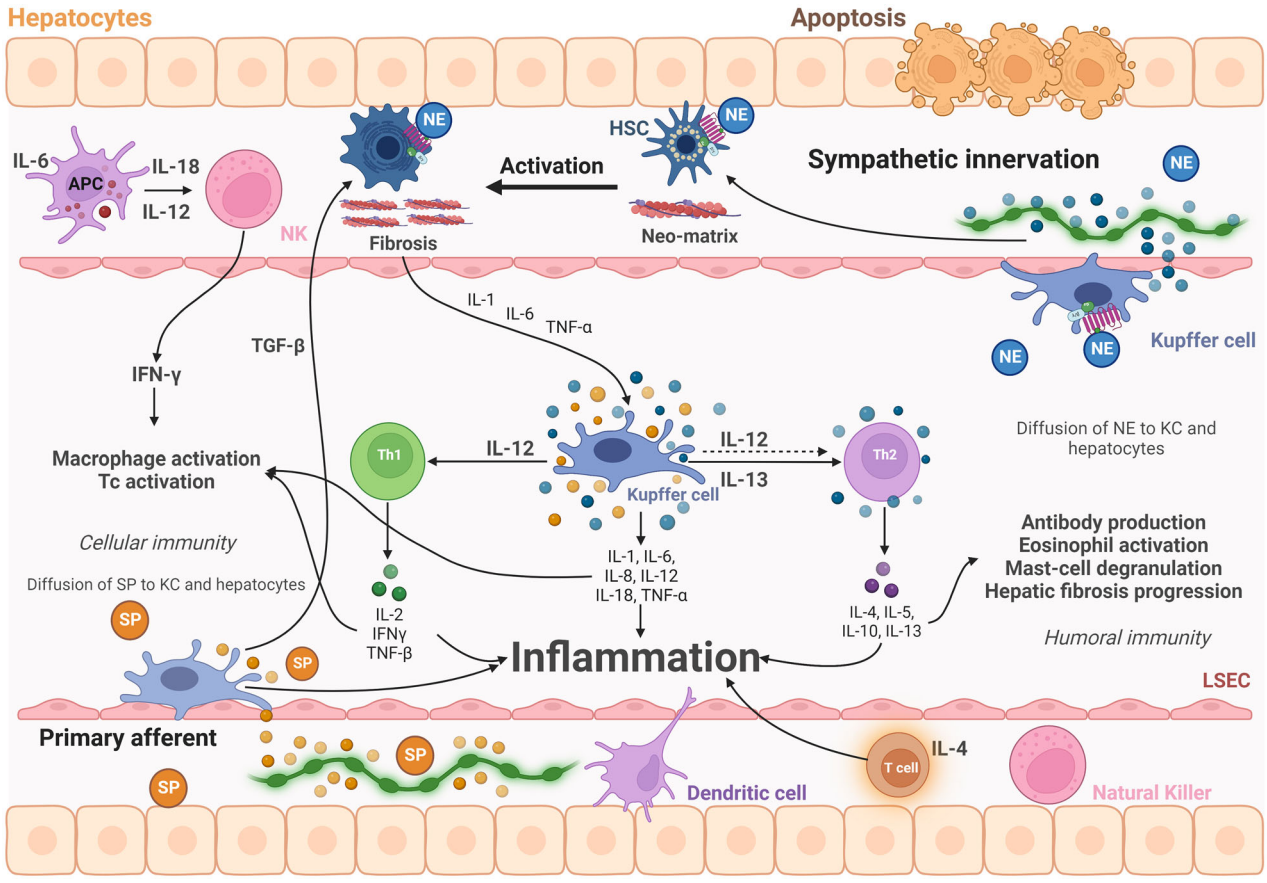


Figure 2. Modulation by neurotransmitters, neuropeptides and adrenoreceptors of cells and cytokines of the immune response during the development of liver fibrosis. KCs and hepatocytes are distant from these nerve fibres; however, diffusion of norepinephrine along sinusoids may be efficient enough to modulate KCs and activate apoptosis in hepatocytes.

pathways by leptin, another substance that stimulates HSC development, makes this study intriguing [81].

The functional expression of α/β-adrenoceptors and neuropeptide Y receptors (NPY), which are increased in the livers of individuals with cirrhotic NAFLD, is demonstrated in a study of activated human primary hepatic stellate cells (hHSC). hHSC produce and release NE/EPI in culture, which is necessary for healthy basal growth and survival. Exogenous NE/EPI and NPY stimulated hHSC proliferation in a dose-dependent *via* p38 MAP, PI3K, and MEK signalling. Without the involvement of the pro-fibrogenic cytokines leptin, IL-4, and IL-13, or the antifibrotic cytokine IL-10, NE, and EPI, but not NPY-enhanced expression of collagen-1α2 *via* TGF-β [82].

Proliferation of hepatic stellate cells by norepinephrine

HSCs express 1-adrenoceptors [83], but it is unclear if they also express α-adrenoceptors or which subtypes are expressed. Primary HSCs were found to express the β-adrenoceptors, α-1B, α-1 D, β1, and β2 by RT-PCR analysis. Western blot analysis was used to identify a comparable expression profile. Inhibitor studies provide further evidence that HSCs are both a reservoir and a direct cellular target of NE. They also suggest that the trophic activities of NE require the activation of kinases that enhance cell survival and proliferation [84].

It has recently been demonstrated that hepatocellular carcinoma (HCC) cells, the liver cell line L02, and HSCs (LX2 cells, p-HSC) express adrenergic receptors (ADRs). The mRNA expression of 1 A-ADR was significantly elevated compared to the various expressions of α1B, α1D, β1, β2, and β3-ADR in HSCs. Western blot analysis further supported the pronounced upregulation. HSCs were stimulated by NE administration, which also improved cell proliferation and raised mRNA and protein expression of COL1A1 and α-SMA, two key indicators of HSC activity.

However, the HCC cells did not proliferate more rapidly when exposed to NE at the same concentrations as +HSCs. More significantly, both nonselective and selective α1-ADR antagonists (prazosin and 5-methylurapidi) effectively suppressed NE-dependent

HSC activation as demonstrated by decreased expression of α-SMA and Collagen 1 α1, decreased cell proliferation, and enhanced cell death in LX2 cells. Based on these results, NE, a stress hormone, increases HSC activation by activating α1A-ADR signalling [85].

Neuroimmunomodulation by adrenoblockers in liver cirrhosis

Advances in the treatments for liver cirrhosis with α and β adrenoblockers

In a mouse model of progenitor cell activation, recent studies demonstrate that inhibition of the sympathetic nervous system, either through α1-adrenergic antagonism with prazosin or chemical sympathectomy with 6-hydroxy dopamine, promotes progenitor cell activation and lessens liver damage [86]. Similar studies on chronically CCL_4-intoxicated mice revealed that 6-hydroxydopamine and the sympathetic neurotransmitter prazosin prevented fibrosis [85]. Stellate cells may produce and respond to norepinephrine, as demonstrated by other investigators [87]. Recently, acute galactosamine intoxication and acute and chronic CCL_4 intoxication were investigated. Authors demonstrated that prazosin considerably increased the number of progenitor cells (identified by OV-6) and dramatically decreased the number of hepatic stellate cells (identified by GFAP, desmin, and α-SMA) in acute and chronic rat models. The prazosin-treated animals had less fibrosis than the control animals, supporting the findings. Isolated progenitor and stellate cells both express α-adrenergic receptors. Prazosin is a well-tolerated medication that offers intriguing possibilities for upcoming therapy approaches [85].

In conclusion, the liver has a cell compartment composed of progenitor and hepatic stellate cells with neuroendocrine characteristics. There is growing proof that this cell compartment is influenced by the sympathetic and parasympathetic nervous systems [88]. In hamster models of fibrosis and cirrhosis, it has been concluded that the alpha-adrenoblockers doxazosin and carvedilol reduce type-I collagen by reducing the expression of TGF-β due to receptor blockade. In a similar model, tissue regeneration was also observed [89].

In a hamster liver cirrhosis model, treatment with doxazosin or carvedilol improved histology due to a decrease in collagen fibres in the parenchyma. Carvedilol increased the expression of the cell proliferation markers, α-FP, Ki-67, and c-Myc; however, doxazosin did not show changes in their expression, so these adrenoblockers are proposed as treatment in the regression of chronic heart diseases. Unfortunately, the drugs showed minimal alterations in hepatocyte morphology [90].

Curcumin, an antioxidant and anti-inflammatory compound, has been shown to reverse liver cirrhosis. Investigations in the potential modulation of Nrf-2 and NF-κB in hamster models of carbon tetrachloride (CCl_4)-induced cirrhosis showed that the toxicity produced by the metabolism of these antagonists decreases. Therapy with carvedilol and the addition of doxazosin to curcumin raised the Nrf-2/NF-κB mRNA ratio and its protein expression in inflammatory liver cells, presumably as an additional hepatoprotective mechanism [91].

According to authors, carvedilol's antioxidant and anti-inflammatory properties can lessen hepatocyte damage, stop hepatic stellate cell activation, and reduce collagen production. The results of a histological investigation confirmed the antifibrotic action of carvedilol by demonstrating how co-treatment with carvedilol reduced the histopathological changes caused by CCl_4 [92]. After CCl_4 intoxication, fibrotic lesions were confirmed by Masson's trichrome stain, while carvedilol-treated CCl_4-intoxicated rats simultaneously showed similar normal levels of TGF-β1, hydroxyproline, and minimal collagen deposition. Serum albumin and total protein measurements were used to demonstrate the hepatic synthesis capability and the antifibrotic effects of carvedilol. It was reported that both experienced significant depletion from persistent CCl_4 intoxication, but intoxicated rats treated with concomitant carvedilol showed a return to normal levels [92].

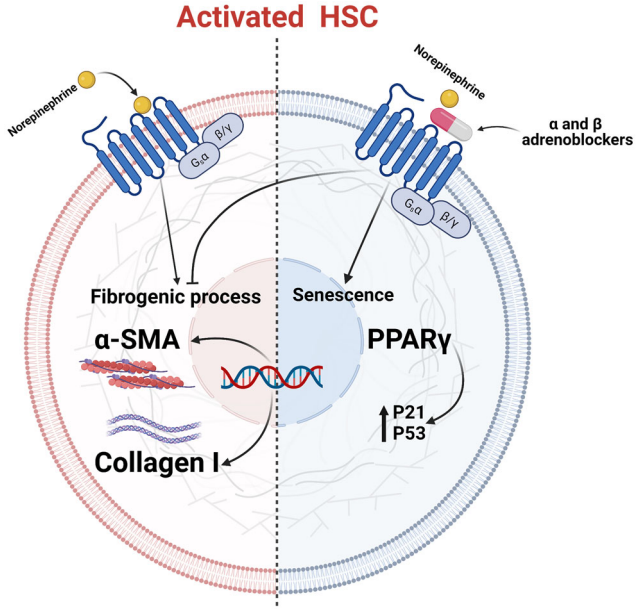
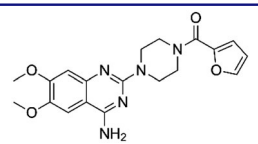
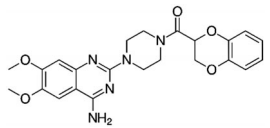
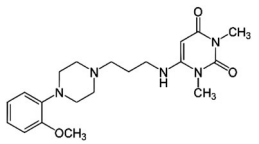
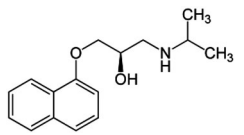
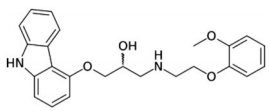
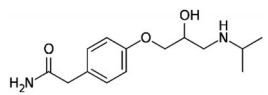


Figure 3. PPAR-γ expression is elevated in quiescent HSC and is overexpressed in active cells once they enter senescence due to adrenergic receptor blockade.

Table 1. α and β adrenoblockers used in preclinical studies for chronic liver diseases.

Adrenergic Antagonists	Chemical structure	Adrenergic receptor target	Target cell or tissue to control hepatic fibrosis	Research Status	Reference
Prazosin		Alpha 1 non-selective	Hepatic Stellar Cell	Preclinical study	Dubuisson et al. [98] Sancho-Bru et al. [81] Sigala et al. [99] Svegliati-Baroni et al. [100] Oben et al. [101] Oben et al. [81] Lin et al. [85]
Doxazosin		Alpha 1 non-selective	Hepatic Stellar Cell	Preclinical study	Muñoz-Ortega et al. [89] Cervantes-García et al. [102] Serna-Salas et al. [90, 93] Macias-Pérez et al. [91] Xiu et al. [103]
5-Methylurapidil		Alpha 1 selective to subtype A	Hepatic Stellar Cell	LX-2 cell line *in vitro* study	Lin et al. [85]
Propranolol		Non-selective beta subtypes beta 1 and 2	Hepatic Stellar Cell and Portal Circulation	Preclinical study for portal hypertension	Ding et al. [104] Mende et al. [105] Strack et al. [106] D'Amico et al. [107] Abdel-Kawy et al. [108] McKee et al. [83] Oben et al. [87] Oben et al. [109] Schepke et al. [110] Hobolth et al. [111] Aguilar-Olivos et al. [112] Suna et al. [113] Chun-Chen et al. [114]
Carvedilol		Alpha 1 non-selective and beta non-selective subtypes beta 1 and 2	Hepatic Stellar Cell and Portal Circulation	Preclinical study for portal hypertension	Hamdy et al. [92] Muñoz-Ortega et al. [89] El-Demerdash et al. [115] Meng et al. [116] Serna-Salas et al. [90] Wu et al. [117] Ling et al. [118] Bosch [119] Aguilar-Olivos et al. [112] Hobolth et al. [111] Abdel-Kawy et al. [108]
Atenolol		Selective beta subtype Beta 1	Portal Circulation	Preclinical study for portal hypertension	Mikheeva et al. [120]

Reported research [93] demonstrated that the α1-adrenoblocker doxazosin decreased the fibrogenic activity of activated HSCs, which is connected to the induction of cellular senescence *via* α1 AR antagonism, suggesting that α1-AR is a potential treatment for liver fibrosis. The adrenoblocker downregulated collagen 1 and ACTA2 and increased the expression of PPAR-γ in the presence and absence of TGF-β, confirming that doxazosin delays stellate cell activation (Figure 3). The peroxisome proliferators control the activation of the nuclear hormone receptor superfamily that includes the PPARs. PPAR-γ is activated following ligand binding and joins with retinoids X receptor (RXR) to form a heterodimer. High levels of PPAR-γ expression are found in HSCs that are quiescent and inhibited during liver cirrhosis. According to studies, activating PPAR-γ inhibits HSC activation and decreases collagen deposition during liver injury [94].

Curcumin inhibited TGF-β signalling by increasing the expression of PPAR-γ, which in turn blocked connective tissue growth factor and pro-collagen I from being expressed in activated HSCs in a dose-dependent manner [95]. Thiazolidinedione (TZD), a PPAR-γ agonist, keeps HSCs quiescence in an *in vivo* model of hepatic fibrosis by controlling adipogenicity transcription factors, which also prevents HSCs from becoming activated shown by α-SMA immunostaining and producing collagen I with Sirius Red staining [96]. However, GW570 nonthiozolidinedione PPAR agonist inhibited collagen I α1 and α-SMA mRNA and protein expression on isolated stellate cells in *in vivo* model of hepatic fibrosis because physical interaction between PPAR-γ and JunD in stellate cells suppresses AP-1 activity, which prevents their activation [97].

A sustained senescence-associated secretory phenotype can negatively affect tissues and organs because the proinflammatory profile of senescent cells can increase epithelial cell proliferation and tumorigenesis, even though senescence induction is a promising therapeutic strategy to reverse hepatic fibrogenesis [86].

Studies demonstrate the use of α and β adrenoblockers in *in vitro* and *in vivo* preclinical treatments for different chronic liver diseases, such as fibrosis and cirrhosis, that generally target liver stellate cells (Table 1).

Conclusions and future directions

Possible treatments for hepatic fibrosis and cirrhosis might depend on neurotransmitter and hepatic nervous

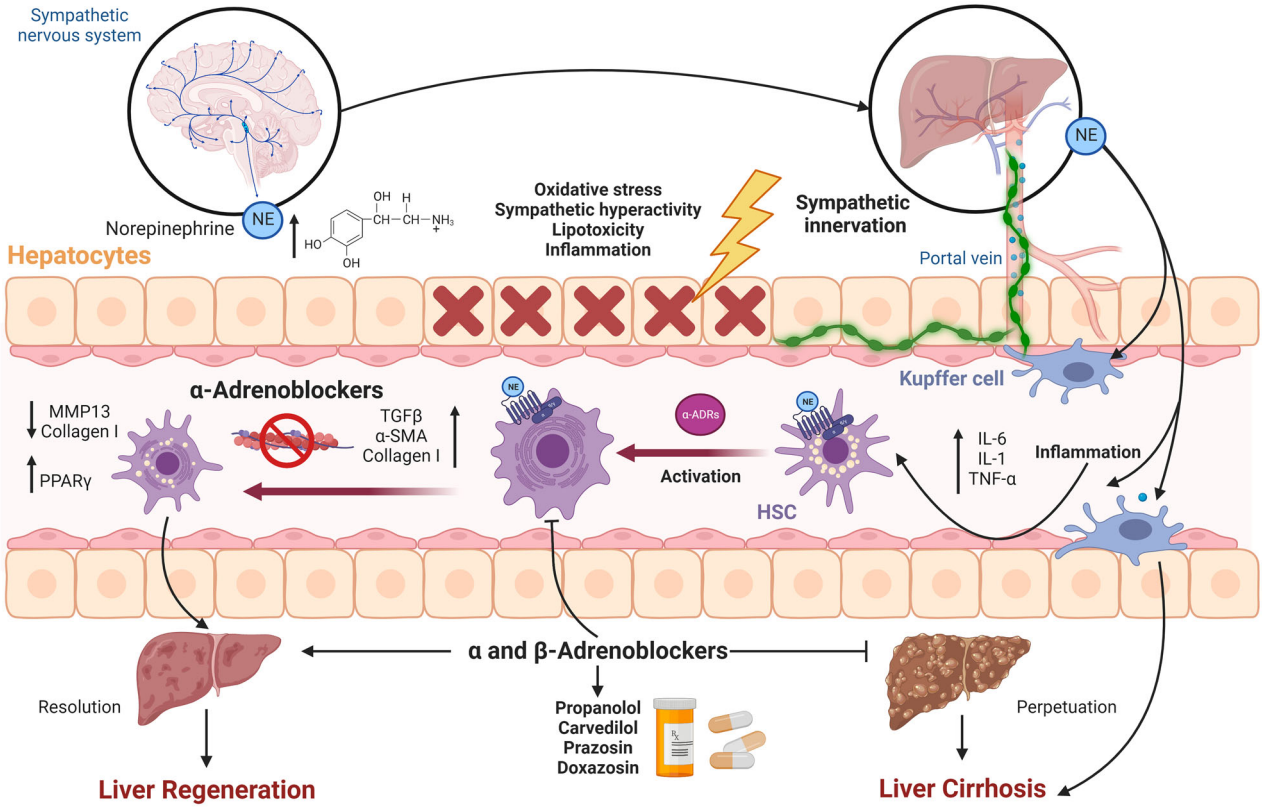


Figure 4. The sympathetic nervous system and the immune system communicate through adrenergic neurotransmitters and cytokines, promoting the activation of HSC and, therefore, fibrosis; however, alpha adrenoblockers can be used as treatments for hepatic cirrhosis.

system regulation. By enhancing HSC activation and proliferation along with increasing cytokine signaling, SNS stimulation aids in promoting hepatic fibrosis. Culturing normal HSCs with α or β adrenoceptor antagonists demonstrated that HSCs express essential enzymes for catecholamine biosynthesis and produce NE and other catecholamines. HSCs use these compounds to autoregulate their growth. By targeting the interruption of catecholamine signaling in hepatic stellate cells, a prospective therapeutic strategy to control the fibrogenic response to liver injury may be proposed by understanding the mechanisms that mediate the profibrogenic activities of catecholamines in the liver. Figure 4 illustrates strategies to reduce hepatic stellate cell activation and, thus, fibrosis based on experimentation with α and β adrenoblockers.

Author contributions

MYMP, MHMO, and JVJ designed the study. MYMP, MHMO, and MdJL wrote the original draft and designed the schematic figures. MYMP, MHMO, MdJL, JVJ, RmdOL, and OSC edited the figure legends and revised the manuscript. JVJ, MdJL, RmdOL, and MHMO performed the final revisions and approved the final version of the article after feedback from all other authors and reviewers. All authors contributed to the study design, critically reviewed the first draft, approved the final version, and agreed to be accountable for the work.

Acknowledgment

MYMP was a recipient of a scholarship from CONACYT.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This work was supported by the Consejo Nacional de Ciencia y Tecnología (CONACYT) Grant 241312, A1-S-21375, and 907029. Consejo Nacional de Ciencia y Tecnología: Grant 241312, A1-S-21375, and 907029. Universidad Autónoma de Aguascalientes PIBB-19-11n and Programa de Apoyo a la Investigación Científica y Tecnológica UANL [PAICyT; 199-CS-2022].

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Data availability statement

The data supporting the findings of this study are available on request from the corresponding author (MHMO).

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