The Role of the Autonomic Nervous System in Liver Regeneration and Apoptosis – Recent Developments

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Key Words

Liver regeneration · Apoptosis · Autonomic nervous system

Abstract

Hepatocytes have a great replicative capacity and are capable of repopulating the liver. Previous studies have suggested that the autonomic nervous system regulates liver regeneration and apoptosis. Moreover, the central nervous system modulates them through the autonomic nervous system. The lateral hypothalamus (LH) area and the ventromedial hypothalamus (VMH) nucleus have been studied for their role in the integration of neurohumoral information. The LH is part of the parasympathetic system, while the VMH belongs to the sympathetic system. Lesions of the LH reportedly induced an increase in sympathetic nerve activity, while those in the VMH produced facilitation of vagus nerve activity. Moreover, VMH or LH lesions facilitate hepatic regeneration after partial hepatectomy. Furthermore, the hypothalamus mediates hepatic apoptosis through the autonomic nervous system. Although further studies are needed to define the role clearly, the autonomic nervous system is one of the important factors that regulate liver regeneration and apoptosis.

Introduction

The autonomic nervous system influences many of the functions of the body, including those of cardiovascular system, kidneys, liver, pancreas, gastrointestinal tract and glands [1] (fig. 1). Detailed studies of the mechanisms that regulate liver growth and apoptosis have been done in animals subjected to partial hepatectomy or chemical injury [2]. Since the autonomic nervous system directly innervates the hepatic parenchyma and has a role in metabolic control [3], it seems likely that liver regeneration and apoptosis are cooperatively regulated by both humoral factors and the autonomic nervous system. Moreover, it is well known that autonomic abnormalities and neuropathy tend to increase with age [4]. The prevalence and severity of autonomic dysfunction appears to be related to the severity of liver disease and is associated with an increase in mortality [5, 6]. It is also reported that patients with liver cirrhosis have parasympathetic hypofunction and sympathetic hyperfunction [7, 8]. In recent years, there has been increasing interest in the relationships between liver and autonomic nervous system. Here, the author reviews the current status of studies aimed at understanding these relationships.

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Fig. 1. Schematic representation of the autonomic nervous system.

Innervation of the Autonomic Nervous System in the Liver and Sprouting in the Neurons of Regenerated Liver

The hepatic parenchyma has been shown to have parasympathetic and sympathetic innervations [9–11]. However, it is well known that the intrahepatic distribution of nerve fibers is highly species-dependent; also, even within one species, there are notable variations. To reveal the pattern and type of hepatic innervation in different species, Akiyoshi et al. [12] examined the distribution and density of these nerve fibers. These data indicate that there were differences in the patterns of hepatic innervation among rats, golden hamsters, guinea pigs, dogs and humans. The data also show that (1) in rat and hamster livers, hepatic functions may be regulated by both sympathetic and parasympathetic nerves in the portal region; (2) in guinea pig, dog and human livers, they may be regulated by these fibers both in the interlobular region (parasympathetic and sympathetic systems) and in the intraparenchymal region (sympathetic system), and thus, (3) in the guinea pig, dog and human livers, hepatocytes and sinusoidal cells may be innervated by sympathetic nerves. Berthoud et al. [13] investigated the distribution and

structure of vagal rat liver innervation. Vagal afferent fibers produced characteristic terminals at three locations in the liver hilus: (1) fine varicose ending preferentially surrounding, but not entering, the numerous peribiliary glands in the larger intra- and extrahepatic bile ducts; (2) large, cup-shaped terminals in almost all paraganglia, and (3) fine varicose endings in the portal vein adventitia. No fibers and terminals were found in the hepatic parenchyma. Varicose vagal efferent fibers were present within the fascicles of the vagal hepatic branch and fine terminal-like structures in a small fraction of the paraganglia. No efferents were found to terminate in the hepatic parenchyma or on the few neurons embedded in nerves or paraganglia. With regard to the sympathetic nerve, in the liver tissues from rats, guinea pigs and humans, Fukuda et al. [14] also reported that sympathetic nerve fibers were localized around blood vessels in the portal area and around the central vein. Normal guinea pig and human liver showed intralobular sympathetic fibers, while rat liver did not [15]. Moreover, it was reported that livers of the guinea pig, rabbit and cat have dense innervation of sympathetic nerves [15]. In these animals, nerve terminals are distributed not only in the Glisson's sheath but also deep into the parenchyma.

Carobi [16] investigated the possible presence of neural sprouting in the vagal afferent neurons of regenerated rat liver after hepatectomy. This experiment was carried out to see if the increase in hepatic parenchyma could provide an adequate stimulus for the sprouting process. Neural sprouting did not occur in regenerated rat liver after 3 weeks. However, Tadokoro [17] previously demonstrated that the speed of axonal growth was approximately 5 mm/day around the porta hepatis in a rat surgical hepatic degeneration model. Therefore, it may be possible for the regenerating axons sprouting from proximal axonal stumps to reach the hepatic hilus within 3 days after transplantation. Consistent with this, Takahashi et al. [18] reported that liver allografts became extrinsically reinnervated, with the regenerating axons reaching the hepatic hilus 3 days after transplantation in rats and that the process of extrinsic hepatic reinnervation is considered to almost terminate 4 months. Moreover, Philips et al. [19] also reported that the liver can undergo dramatic afferent reinnervation after subdiaphragmatic vagotomy. Furthermore, it was reported that sympathetic fibers were absent from regenerating nodules in a human cirrhotic liver [14].

Autonomic Nervous System and Hepatic Function

Selective hepatic vagotomy does not disrupt the putative feedback loop between body weight and feeding [20]. However, it has been reported that the vagotomy reduces food intake, water intake and body weight after hepatic vagotomy only in 100-gram rats, but not 200- and 280-gram rats [21, 22]. When 100-gram animals with either hepatic branch vagotomies or sham operations were housed at three different room temperatures (12–17, 17–22, 22–27°C), the reduction in weight of vagotomized animals correlated with the lowest room temperature, and food intake was also decreased in direct relation to the temperature [23]. Therefore, the hepatic vagal mechanism modulates food intake in young animals, and such a mechanism may be modulated by the environmental temperature. Moreover, to further characterize the possible effect of hepatic vagotomy on food intake, Langhans et al. [24] offered rats a novel-tasting diet immediately after hepatic branch vagotomy or sham vagotomy and measured food intake as well as diet selection (novel-tasting vs. familiar diet). They found that hepatic branch vagotomy and sham vagotomy had different aversive effects, which led to transient differences in postoperative food

intake when diets with a novel and strong taste were presented during the initial postoperative period. Therefore, information conveyed by the hepatic branch of the vagus can apparently lead to a conditioned feeding response. This is evidence for a more subtle role of the liver in the control of food intake than previously thought.

It is well known that a 90% majority of the fibers in the vagus nerve is afferent [25]. Vagal afferent nerves were reported to contain glucose-sensitive nerve fibers [26], amino acid-sensitive nerve fibers [27], lipid-sensitive nerve fibers [28] or osmosensitive nerve fibers [29]. With regard to efferent nerve fibers, Nijima [30] recorded efferent discharges from nerve filaments dissected from the hepatic branch of the vagus nerve in the rat. It was concluded that changes in the rate of hepatic glycogenesis, which occur in response to changes in blood glucose concentration, were mediated in part by the vagal efferent innervation of the liver.

Corresponding to the different density of innervation among the species, noradrenaline overflow from perfused liver during hepatic nerve stimulation was much higher in the guinea pig than in the rat [31]. Nevertheless, the nerve stimulation elicited an increase in glucose output from rat liver to approximately the same degree as that from guinea pig liver [31]. These observations suggested that in rat liver most of hepatocytes are not activated by direct contact with the sympathetic nerves, but through an indirect mechanism of signal transfer. One of the possible mechanisms is the involvement of intercellular communication via specific channels of gap junction, which exist between adjacent hepatocytes and permit the passage of small molecules and ions [32]. Therefore, to explore the possible role of gap junctions between liver cells in neural regulation of hepatic glucose metabolism, Iwai et al. [33] examined the effects of hepatic nerve stimulation on metabolic and hemodynamic changes in regenerating rat liver. They found that the impaired effects of sympathetic nerve stimulation on glucose metabolism observed in regenerating liver were derived neither from reduced release of noradrenaline nor from depletion of liver glycogen, but rather from transient reduction of gap junction, which assist signal propagation of the nerve action through intercellular communication in rat liver.

Insulin is regarded to be one of the hepatotrophic factors [34], because it exerts direct effects on organelles, stimulates DNA and protein synthesis [35], and its secretion is known to be regulated through the hepatic vagus branch [36]. However, during starvation, the plasma insulin level was reported to decrease after partial hepatectomy in subdiaphragmatic vagotomized rats and hepatic

Table 1. Comparisons of the effects of subdiaphragmatic vagotomy and hepatic vagotomy compared with sham vagotomy after partial hepatectomy

	Subdiaphragmatic vagotomy	Hepatic vagotomy
Restoration of liver weight	↓	→
Increase in the DNA of regenerating liver	↓	→
Increase in the protein content of regenerating liver	↓	→
Rate of hepatic DNA synthesis	↓, delay	→, delay
Plasma insulin level during starvation	→	→
Daily food intake after partial hepatectomy	↓	→
Body weight increase after partial hepatectomy	↓	→

↓ = Suppress; → = no effect.

vagotomized rats, as in sham-operated rats [37]. Meanwhile, Trabelsi et al. [38] evaluated the effect of a selective hepatic vagotomy on the insulin response in rats fasted for 24 h when blood glucose levels were or were not maintained by a constant glucose infusion. It was concluded that the decline in plasma glucose concentration during fasting did not totally explain the insulinopenic response to fasting and that the liver, though the mediation of the hepatic vagus nerve, did not seem to contribute to insulinopenia in 24-hour fasted rats. Moreover, it is well known that, in response to insulin, one of hormones, hepatic insulin-sensitizing substance (HISS) is released from the liver to stimulate glucose uptake in skeletal muscle but not liver or gut. Consistent with this, Lautt et al. [39] recently reported that the interruption of the hepatic parasympathetic nerves by surgical denervation or atropine blocked the release of HISS.

With regard to hepatic enzymes, the hepatic and renal scores, total protein, glutamic pyruvic transaminase (GPT), lactate dehydrogenase, total bilirubin, total cholesterol, blood urea nitrogen and creatinine indicated no significant differences between the hepatic vagotomized and sham vagotomized rats. Moreover, because hepatic branch vagotomy had no effect on the concentration of albumin, one of the proteins specially produced in the liver, the vagus nerve must have no role in protein production in the remaining liver. Meanwhile, it was reported that the value of alkaline phosphatase (ALP) in hepatic vagotomized rats was significantly lower than in controls [40]. Reilly et al. [41] observed histologically that cholinergic nerves innervate bile ducts running along the hepatic vasculature. Moreover, electrical stimulation of vagus nerve induced an increase in intracholedochal pressure, suggesting a direct relationship between the vagus nerve and bile secretion [42]. In general, the serum level of ALP in liver diseases is elevated by bile stasis. Therefore, the

elevated activity of ALP could be interpreted as resulting from the bile stasis caused by increased intracholedochal pressure due to vagal stimulation. However, more detailed studies on the exact relationship between the vagus nerve and bile secretion are needed.

Autonomic Nervous System and Liver Regeneration

Vagus Nerve

In animal models, the weight of the regenerating liver is restored to approximately 80% of the preoperative weight 72 h after partial hepatectomy [43]. Restoration of the liver weight is reported to be significantly impaired in subdiaphragmatic vagotomized rats (table 1) [37]. This impairment is associated with a reduction in food intake, because there was no difference in the liver weights between the control rats and the pair-fed subdiaphragmatic vagotomized rats [44]. Subdiaphragmatic vagotomy also causes considerably more loss of body weight than sham vagotomy. The increase in DNA and protein content of the regenerating liver is also suppressed by subdiaphragmatic vagotomy. Moreover, subdiaphragmatic vagotomy delays and suppresses the rate of hepatic DNA synthesis after partial hepatectomy. Consistent with this, the increase in activity of hepatic aspartate transcarbamoylase and thymidine kinase, the key enzymes in synthesis of pyrimidine nucleotides via the de novo and salvage pathways, respectively, during liver regeneration, is significantly suppressed and retarded in subdiaphragmatic vagotomized rats. The onset of DNA synthesis triggered by partial hepatectomy is also delayed by the subdiaphragmatic vagotomy.

Hepatic vagotomy delays but does not suppress the increase in the rate of hepatic DNA synthesis and the

activity of thymidine kinase after partial hepatectomy (table 1) [45]. The time-course of liver DNA content restoration after partial hepatectomy is not affected by hepatic vagotomy. Hepatic vagotomy does not affect daily food intake or body weight increase after partial hepatectomy. The difference between subdiaphragmatic vagotomy and hepatic vagotomy depends on the fact that the vagus nerve innervates not only the liver but also many organs [46], and subdiaphragmatic vagotomy, not hepatic vagotomy, reduces food intake and massively delays gastric emptying [44, 47].

Pietroletti et al. [48] examined the relationship of the autonomic nervous system and dual blood supply for an optimal regenerative response in liver remnants after liver resection. They found that the autonomic nerve supply of the portal triad plays at least an important permissive role in liver regeneration. Therefore, there may be the possibilities that the hepatic vagus nerve affects hepatocytes through free radical injury that might be induced by ischemia from vagally induced changes in vascular tone. However, in rats subjected to portacaval transposition in order to increase the liver blood flow, tritiated thymidine was incorporated into liver DNA much as it was in the control rats [49]. Moreover, in examination of acute changes, sectioning of the hepatic branch of splanchnic or vagus nerve did not change the blood flow in the hepatic artery or the portal vein [40]. Alteration in blood supply to the liver associated with nerve sectioning play an insignificant role in liver regeneration. Therefore, the vagus nerve may stimulate liver regeneration directly and specially, although elucidation of its mechanism awaits further studies.

Sympathetic Nerve

Hepatic branch sympathectomy proved to have no influence on liver regeneration [40]. Moreover, Kato and Shimazu [37] reported that bilateral major splanchnicectomy at the subdiaphragmatic level produced no effect on liver regeneration. However, it has been suggested that adrenergic agents regulate liver regeneration [50]. Cruise et al. [51] also reported that noradrenaline stimulated DNA synthesis by cultured rat hepatocytes through α_1 -adrenergic receptors. Moreover, Iwai and Shimazu [52] used slightly injured, galactosamine-treated, isolated rat liver and found that the activation of hepatic sympathetic nerves and circulating catecholamines exaggerates acute liver damage through an action on liver cells, which depends on the influx of extracellular Ca^{2+} . In 1960, Calvert and Brody [53] proposed that carbon tetrachloride (CCl_4) exerted its necrotic effect not by acting on the liver

parenchyma directly, but by causing a persistent sympathetic discharge resulting in diminished hepatic blood flow and cellular hypoxia. However, recently, CCl_4 is generally proposed to induce cellular injury through its metabolites that are generated by a cytochrome P-450-dependent step [54]. Hsu [55] examined effects of the sympathetic nervous system on liver injury induced experimentally by CCl_4 in spontaneously hypertensive rats (SHR) and normotensive Wistar-Kyoto rats (WKY). It was found that the SHR had an elevated catecholamine content in the adrenal gland without any treatment, and fluorescence histochemistry also revealed dense adrenergic innervations in the liver. Moreover, the SHR showed greater sensitivity to CCl_4 stimulation in the sympathetic nervous system than the WKY, resulting in decreased hepatic blood flow in the acute stage and depleted catecholamine in the adrenal gland and lowered blood pressure in the chronic stage. Plasma GPT activity was increased in both strains but more significantly in the SHR than in the WKY. Histological examination of the liver in the SHR showed established cirrhosis, whereas only bridging fibrosis was seen in the WKY. Therefore, the pathogenesis of the liver damage increased by CCl_4 in the SHR is attributable to the enhanced response of the sympathetic nervous system that releases massive amounts of catecholamine which then leads to vasoconstriction and metabolic changes that promote liver damage.

With regards to liver regeneration after partial hepatectomy, to determine if the sympathetic nerve has a role in liver regeneration after partial hepatectomy, Iwai et al. [56] measured the alterations of tissue noradrenaline content and its turnover in rats. Fractional turnover rate of noradrenaline was reduced transiently in regenerating liver 24–48 h after partial hepatectomy and returned to normal 8–9 days after the operation; therefore, sympathetic nerve activity of the liver was suppressed at the early stage of regeneration. However, Knopp et al. [57] reported that 20 min after partial hepatectomy, the plasma noradrenaline level increased, but after 1 h, it decreased to the basal level in both partial hepatectomized rats and sham-operated rats and remained unchanged 4 and 24 h later. Moreover, the plasma levels of adrenaline and corticosterone also rapidly increased 20 min after partial hepatectomy or sham operation [57]. The first peak of catecholamine and corticosterone levels resulted from an unspecific stressor associated with the surgery. Then at 4 h, the plasma level of adrenaline was higher than in sham-operated rats, but after 24 h, the adrenaline level returned to basal values [57]. The prolonged elevation of adrenaline found after

partial hepatectomy seems to be specific for liver regeneration.

Ohtake [58] examined the role of the abdominal sympathetic nervous system in regulating portal venous flow in anesthetized rats using an ultrasonic volume flowmeter. Results showed that sympathetic nerve regulated portal venous flow directly. Neither proper hepatic arterial occlusion nor partial hepatectomy affected the response. In the partially hepatectomized animals, stimulation of the hepatic branch did not decrease the splenic flow but decreased the superior mesenteric venous flow and induced a similar response in portal venous flow even when the superior mesenteric venous flow was interrupted. This fact may be related to the possibility that changes in the portal venous flow by the sympathetic nervous system may affect liver regeneration. However, Ohtake et al. [40] also reported that sectioning of sympathetic nerves, which results in increased blood flow in the liver, did not affect liver regeneration.

With regards to immunology, it is well known that thymic atrophy is always induced 24 h after partial hepatectomy as a stress-associated response. Consistent with this, Minagawa et al. [59] proposed the possibility that sympathetic nerve stimulation is quite important for the induction of the specific pattern of the immune system seen after partial hepatectomy. Sympathetic nerve stimulation after partial hepatectomy results in subsequent activation of natural killer cells, and these natural killer cells might be associated with immunologic surveillance during hepatocyte regeneration.

It is also well known that gentle organ manipulation rapidly causes disturbances in the activation of Kupffer cells [60]. Consistent with this, Schemmer et al. [60] recently reported that both the autonomic nervous system and gut-derived endotoxin were involved in this matter.

Autonomic Nervous System and Liver Apoptosis

The liver can precisely regulate its growth and mass. Apoptosis is a type of cell death that serves to eliminate excessive or unwanted cells during the remodeling process in liver regeneration, as well as in embryonic development and wound healing [61]. Surgical resection of hepatic lobes or hepatocytes loss caused by viral or chemical injury triggers hepatocyte replication, while enlarged liver mass is corrected by apoptosis. As has been mentioned, noradrenaline markedly enhances the stimulation of hepatic proliferation [51]. However, it was reported that

noradrenaline prevented Fas-induced hepatocyte apoptosis via a β_2 -adrenergic receptor [62]. These findings led us to speculate that the autonomic nervous system may play a role as a stimulator of cell growth through inhibiting apoptosis in the regenerating liver. Moreover, although it was well known that CCl_4 hepatotoxicity was more severe in SHR showing sympathetic hyperactivity than in WKY with normal sympathetic hyperactivity [55], Hamasaki et al. [63] reported that both acute and chronic CCl_4 -induced liver damage was enhanced in SHR as compared with WKY. The proliferating cell nuclear antigen (PCNA) labeling index, indicating the number of regenerating hepatocytes, paralleled the severity of liver damage. In contrast, the number of TdT-dUTP nick-end labeling (TUNEL)-positive cells did not correspond to the severity of liver damage. Therefore, Hamasaki et al. [63] suggested that noradrenaline suppressed apoptosis in hepatocytes but did not suppress liver damage.

The hepatic density of β_2 -adrenoreceptors of C57BL/6 mice is low but that of recently described transgenic F28 mice is much higher [64]. F28 mice are naturally protected against hamster anti-mouse Fas antigen monoclonal antibody, Jo2; F28 mice were resistant to Jo2-induced liver apoptosis and death. The β -adrenoreceptor antagonist propranolol sensitized the F28 livers to Jo2. In normal mice, clenbuterol, a β_2 -adrenoreceptor-specific agonist, considerably reduced Jo2-induced liver apoptosis and death; salbutamol, another β_2 -adrenoreceptor-selective agonist, also reduced Jo2-induced apoptosis and retarded death but with less efficacy than clenbuterol; and propranolol blocked the protective effect of clenbuterol. These indicate that the expression level of functional β_2 -adrenoreceptors modulates Fas-regulated liver apoptosis and that this apoptosis can be inhibited in vivo by giving β_2 -adrenergic receptor agonists [62].

Central Nervous System and Liver Regeneration and Apoptosis

The hypothalamus has a vital role in the integration of neurohumoral information [65], and it possesses autonomic centers connected to viscera via the autonomic nervous system. The lateral hypothalamus (LH) and the ventromedial hypothalamus (VMH) nucleus have been studied for their role in the integration of neurohumoral information [66]. Both are considered to act reciprocally in several regulatory functions: feeding behavior, autonomic regulation and metabolic regulation [65]. The LH is part of the parasympathetic system, and the VMH

belongs to the sympathetic system [67, 68] (fig. 2). Lesions in the LH reportedly induced an increase in sympathetic nerve activity, while those in the VMH produced facilitation of vagus nerve activity [23, 69]. As described above, both the sympathetic and parasympathetic nervous system are important modulators of liver regulators [45, 50, 70]. Iwai and Shimazu [71] studied the effects of hypothalamic stimulation on experimental liver injury induced by CCl₄ or dimethylnitrosamine in rats by measuring plasma GPT activity as an index of acute liver injury. Electrical stimulation of the VMH in CCl₄-treated rats caused a marked increase in plasma GPT activity, accompanied by a significant decrease in GPT activity in the liver, although CCl₄ treatment alone had no significant effect on plasma GPT activity. A similar effect of VMH stimulation on plasma GPT activity was observed in rats treated with dimethylnitrosamine, another hepatotoxic chemical. No such exaggerated effect of VMH stimulation on plasma GPT activity was observed after stimulation of the LH. Surgical sympathetic denervation of the liver greatly suppressed the increase in plasma GPT activity after CCl₄ injection and VMH stimulation. Measurement of regional blood flow indicated that VMH stimulation did not produce a significant change in blood flow to the liver. Therefore, VMH was involved in the progress of chemically-induced liver injury through activation of the sympathetic hepatic nerves, possibly by affecting liver metabolism rather than blood flow to the liver. Moreover, Kiba et al. [72–74] previously reported that vagal activity produced by VMH lesions produced an increase in cell proliferation of the liver. It was also reported that VMH lesions facilitated hepatic regeneration after partial hepatectomy [75]. Although, as mentioned above, previous studies also indicated a reciprocity in the regeneration of autonomic function between the VMH and LH [69], Kiba et al. [76] reported that LH lesions facilitated hepatic regeneration. The LH has been shown to project directly and strongly to the dorsal motor nucleus of the vagus nerve in the medulla oblongata [65] (fig. 2), and is part of the parasympathetic nervous system [67]. Iwai and Shimazu [56] measured the changes in hepatic noradrenergic content and its turnover after partial hepatectomy to determine whether the sympathetic nerve has a role in liver regeneration; they found that sympathetic nerve activity of the liver was suppressed early (24–48 h) after partial hepatectomy. In contrast, an increase in sympathetic firing rate occurred 24 h after LH lesioning [77]. Therefore, it was suggested that LH lesions may prevent the suppression of sympathetic nerve activity soon after partial hepatectomy, thereby facilitating hepatic DNA synthesis.

Fig. 2. Relationships between hepatic autonomic nervous system and central nervous system. DMV = nucleus dorsalis nervi vagi; LH = lateral hypothalamus; NA = nucleus ambiguus; VMH = ventromedial hypothalamus.

Central neuropeptides play important roles in many instances of physiological and pathophysiological regulation mediated through the autonomic nervous system. In regard to the hepatobiliary system, several neuropeptides act in the brain to regulate bile secretion, hepatic blood flow, and hepatic proliferation. Stressors and sympathetic nerve activation are reported to exacerbate experimental liver injury [55, 78, 79]. Some stressors are known to stimulate corticotropin-releasing factor (CRF) synthesis in the central nervous system and induce activation of sympathetic nerves in animal models [80–82]. Yokohama et al. [83] examined the effect of intracisternal CRF on CCl₄-induced acute liver injury in rats. Intracisternal injection of CRF dose-dependently enhanced elevation of the serum GPT level induced by CCl₄. Elevation of serum GPT, ALP and total bilirubin levels by CCl₄ were also enhanced by intracisternal CRF injection. It was found that CRF acted in the brain to exacerbate acute liver injury through the sympathetic-noradrenergic pathways. Moreover, Yoneda et al. [84] studied the effect of thyrotropin-releasing hormone (TRH) on hepatic DNA synthesis in rats. TRH is distributed throughout the central nervous system and acts as a neurotransmitter to regulate gastric functions through the vagus nerve. It was found that TRH acted in the central nervous system to stimulate hepatic DNA synthesis through vagal and cholinergic mechanisms and that TRH might be the chemical messenger involved in brain regulation of hepatic proliferation.

Fig. 3. Schema of hepatic autonomic nervous system and liver disease.

γ -Aminobutyric acid (GABA) is a potent inhibitory neurotransmitter with growth-regulatory properties. In fulminant hepatic failure, a condition in which hepatic regeneration may be impaired, systemic serum GABA concentrations are markedly elevated. Minuk et al. [85] determined whether increased amounts of circulating GABA interfere with hepatic regenerative activity. Their results indicated that elevated serum GABA concentrations interfered with the hypertrophic component of hepatic regeneration following partial hepatectomy in rats. Recently, Biju et al. [86] reported that GABAergic activity served to maintain hepatocytes in a quiescent state. Moreover, Biju et al. [86] investigated GABAergic alterations in the hypothalamus and plasma noradrenaline levels during compensatory hyperplasia after partial hepatectomy, lead nitrate-induced direct hyperplasia, and N-nitro-

sodiethylamine-induced neoplasia in liver. The results indicated that liver cell proliferation influences hypothalamic GABAergic neurotransmission, and these changes regulate hepatic proliferation through sympathetic stimulation.

With regards to liver apoptosis, Kiba et al. [87] recently examined whether the Fas (APO-1/CD95)/Fas ligand system mediates apoptosis in rats with VMH lesions. The results indicated that vagal firing after VMH lesioning may stimulate Fas/Fas ligand system-mediated apoptosis through the cholinergic system in the rat liver. However, Fujimoto et al. [88] showed that intestinal mucosal apoptosis decreased in the VMH-lesioned rat. Therefore, further investigations may be required to determine the mechanisms by which VMH lesions modulate apoptosis.

Conclusions

Current literature indicates that the autonomic nervous system regulates liver regeneration and apoptosis. Moreover, the central nervous system modulates them through the autonomic nervous system. Recently, there has been increasing interest in the relationship between liver disease and autonomic nervous system (fig. 3). In regard to this matter, future studies should outline a more complete mechanism.

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