Int J Physiol Pathophysiol Pharmacol 2017;9(5):153-156
www.ijppp.org /ISSN:1944-8171/IJPPP0067563

Original Article

Protective roles of hepatic GABA signaling in liver injury

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Received October 19, 2017; Accepted October 26, 2017; Epub November 1, 2017; Published November 15, 2017

Abstract: In addition to functioning as a neurotransmitter, γ-aminobutyric acid (GABA) generates signals, via its type A or type B receptors ($GABA_A$Rs or $GABA_B$Rs), in various types of cells. Studies, including ours, show that $GABA_A$R-mediated auto- and paracrine GABAergic signaling occurs in rodent hepatocytes and cholangiocytes, protecting the liver against toxic injuries. This short article briefly introduces the GABA signaling system in rodent livers and discusses potential mechanisms by which the hepatic GABA signaling protects the liver function.

Keywords: GABA, hepatocyte, cholangiocyte, proliferation, apotosis

Gamma-aminobutyric acid (GABA) is the primary inhibitory neurotransmitter in the adult central nervous system (CNS) [1] and it is produced from glutamic acid by decarboxylation through the catalytic activity of glutamic acid decarboxylase (GAD) [2]. GABA generates biological signaling through activation of its ionotropic type A or metabotropic type B receptors ($GABA_A$Rs or $GABA_B$Rs). To date, 19 $GABA_A$R subunits (α1-6, β1-3, γ1-3, δ, ε, π, θ, and ρ) have been identified in mammals. $GABA_A$Rs are pentameric Cl^- channels with various subunit combinations [3]. In neurons of the adult CNS, $GABA_A$Rs primarily mediate Cl^- influx causing membrane hyperpolarization and hence inhibition [4]. In the embryonic brain, however, $GABA_A$Rs mediate Cl^- efflux inducing membrane depolarization and Ca^{2+} entry through voltage gated Ca^{2+} channels thus regulating the proliferation, migration, and differentiation of neuroprogenitors [5-7].

$GABA_A$R-mediated signaling also exists in non-neuronal cells of visceral organs [8-10] and their physiological and pathophysiological roles have been investigated. For example, our studies have demonstrated that GABAergic signaling mechanisms are present in epithelial cells of the lung [7, 8, 11] and the intestines [12], involving in allergic responses. Minuk and colleagues identified sodium-independent but bicuculline-sensitive $GABA_A$Rs in hepatocytes [13] and they proposed that alterations in hepatic GABAergic signaling may contribute to the pathogenesis of hepatocellular carcinoma [14]. In addition, another group reported that GABA protects hepatocytes against ethanol cytotoxicity through unknown mechanism(s) [15]. Notably, $GABA_A$R-mediated signaling also occurs in the intrahepatic biliary epithelium, where GABA may stimulate small cholangiocyte differentiation into large cholangiocytes [16, 17].

Most recently we studied the role of hepatic GABAergic signaling system in liver functions under normal conditions and in disease models of liver injury [18, 19]. Specially, we found that auto- and/or paracrine GABAergic signaling systems exist in rat hepatocytes and cholangiocytes as evidenced by the expression of both $GABA_A$R subunits and GAD [18]. It is known that acute D-galactosamine (GalN) [18] or excessive ethanol [20] exposure causes apoptotic injuries in the liver. Interestingly, the expression of GABA synthesizing enzyme GAD and $GABA_A$R subunits is up-regulated in the rodent livers following administration of GalN

[18] or excessive ethanol [19]. Moreover, pretreating the rodents with GABA or the $GABA_AR$ agonist muscimol, but not the $GABA_BR$ agonist baclofen, greatly protects hepatocytes from the "toxin"-induced apoptosis and reserves the liver function [18, 19]. These results indicate that GABAergic signaling in hepatocytes functions to protect the cells against toxic injures, as shown in pancreatic β-cells [21, 22].

Administration of GalN induces formation of pseudo-bile ductules and islet-like structures by cholangiocytes in the portal and periportal areas in the rat liver [18]. Our immunohistochemical assays show that a $GABA_AR$ signaling mechanism also exists in cholangiocytes of the GalN-induced pseudo-bile ductules. Notably, systemic administration of the $GABA_AR$ agonist muscimol fundamentally inhibits the pseudo-duct formation in GalN-treated rats [18]. This finding supports the notion that intrahepatic GABAergic signaling restrains liver cell proliferation [23]. We propose that $GABA_AR$ signaling in cholangiocytes confines the overexpansion of pseudo-bile ductules and prevents biliary flow obstruction, hence protecting hepatocytes from bilirubin toxicity.

What is the mechanism by which $GABA_AR$ signaling restrains the cellular phenotypic transformation and proliferation? A recent study in the Lu laboratory [24] may provide a hint for answering this question. Specifically, the Lu laboratory found that following administration of the pancreatic β-cell toxin streptozotocin (STZ) to mice, some pancreatic β-cells containing extremely low level of immunoreactivity to insulin start expressing aldehyde dehydrogenase 1 family member A3 (ALDH1a3), a marker of mesenchymal progenitor cells [25]. This result suggests that an epithelial-mesenchymal transition (EMT)-like phenotypic transformation occurs in some of the STZ-injured pancreatic β-cells. Remarkably, pretreating the mice with GABA essentially prevents the STZ-induced expression of ALDH1a3 and significantly reserves the mass of β-cells that display normal immunoreactivity of insulin [24]. It is known that adult pancreatic α-cells have the potential to transform into β-cells [26] and that $GABA_AR$ signaling inhibits cell proliferation but fosters cell differentiation [5]. Indeed, a recent study reported that long-term treatment of GABA greatly increases the mass of pancreatic β-cells in mice by fostering the transformation of pancreatic α-cells to β-cells [27]. Together, available data suggest that $GABA_AR$ signaling facilitates cell differentiation to developed phenotypes but restricts EMT-like transformations of differentiated cells.

Cholangiocyte proliferation leads to "ductular reaction", a major characteristic of liver pathological conditions [28-30]. On the other hand, cholangiocyte proliferation may contribute to liver regeneration. These proliferating progenitor cells in rodent livers are often referred to as "oval cells" that are derived from epithelial cells of the canals of Hering in the periportal region [31]. In relation to this notion, $GABA_AR$ signaling facilitates the α-to-β cell genesis [27] by increasing the duct epithelium originated genesis of new α-like cells and then β-like cells [32]. Therefore, the role of GABA signaling in regulating oval cell proliferation at the canals of Hering and in liver regeneration should be explored in future studies.

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