Evaluation of the Role of Free Serotonin Level in Pathogenesis of Esophageal and Fundal Varices

Thesis submitted for partial fulfillment of Master Degree in Tropical Medicine

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2013

Acknowledgements

*Firstly, I am extremely grateful and thankful to **Allah** who gave me the ability and the power to finish this work.*

*I appreciate the supervision of **Ass. Prof.\ Nadia Abdel Aaty,** Assistant Professor of Tropical Medicine, Ain Shams University, for who spared no time or effort providing me with constructive guidance which was a paramount axis in the initiation and progression of this work.*

*My sincere thanks and gratitude to **Ass. Prof.\ Amal Tohamy,** Lecturer of Tropical Medicine, Faculty of Medicine, Ain Shams University, during the research period.*

*My sincere thanks to **Doctor \ Hossam El Deen Salem,** Lecturer of Tropical Medicine, Faculty of Medicine, Ain Shams University, for his supervision and participation in this work.*

*My deepest thanks to **Doctor\ Wesam El Sayed,** Clinical Pathologist, for her help in practical part of this work.*

Also, I wish to thank everybody who helped me throughout this research. Finally, great thanks to my family who supported me during this work. Special dedication for the soul of my father, God forgives him.

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2013

List of Contents

List of Abbreviations

5-HT	5-hydroxytriptamin (serotonin)
AKT	protein kinase
CCl_4	carbon tetrachloride
cGMP	cyclic guanosine monophosphate
CTGF	connective tissue growth factor
DDC	D-amino acid decarboxylase
ECM	Extracellular matrix
eNOS	endothelial NO synthase
ET	endothelin
FHVP	free hepatic vein pressure
GAVE	*gastric antral vascular ectasia*
GOV	gastroesophageal varices
GRK	G protein-coupled receptor kinase
HBV	Hepatitis B Virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C Virus
HSCs	Hepatic stellate cells
HVPG	hepatic vein pressure gradient

IGF	insulin-like growth factor
IGV1	isolated gastric varices
INR	International randomization ratio
MAO	monoamine oxidase
MDCT	multidetector row CT
MRE	magnetic resonance elastography
NAFLD	Non-alcoholic fattyliver disease
NASH	Non-alcoholic steatohepatitis
NGF	nerve growth factor
NO	Nitric oxide
PBC	Primary biliary cirrhosis
PDGF	platelet-derived growth factor
PHG	portal hypertensive gastropathy
PHx	partial hepatectomy
PT	prothrombin time
SECs	Sinusoidal endothelial cells
SERT	serotonin transporter
SMA	smooth muscle actin
TGF	transforming growth factor

TIPS	transjugular intrahepatic portosystemic shunt
TNF	tumor necrosis factor
TPH	tryptophan hydroxylase
VEGF	Vascular endothelial growth factor
WHVP	wedged hepatic venous pressure

List of Tables

List of Figures

Introduction

Esophageal varices are a major concern in patients with cirrhosis. These varices have a high propensity to bleed because of the fragility of the engorged blood vessels ***(Cichoz-Lach et al., 2008)***. The prevalence of varices in patients with cirrhosis is approximately 60-80% and the risk of bleeding is 25-35%. The incidence of esophageal varices increases by nearly 5% per year, and the rate of progression from small to large varices is approximately 5 to 10 % per year ***(Amico and* Morabito*, 2004).***

Esophageal variceal bleeding is one of the most dreaded complications of cirrhosis because of its high mortality. Each episode of bleeding has a 30%–50% mortality risk. Furthermore, after the initial episode of bleeding the incidence of rebleeding is up to 70% and frequently occurs within 6 weeks of the initial hemorrhage ***(Sharma and* Rakela*, 2005)***.

The normal hepatic venous pressure gradient (HVPG) is typically 5–10 mmHg. The risk of developing esophageal varices increases when the HVPG reaches a minimum pressure of 10–12 mmHg ***(Toubia and* Sanyal*, 2008)***. Portal hypertension, as measured by the HVPG, occurs through complex physiological

responses resulting in both mechanical and dynamic blockages in the liver ***(Dib et al., 2006)***.

Increased intrahepatic resistance and hyperdynamic circulatory alterations with expansion of collateral circulation play a central role in the pathogenesis of portal hypertension. Portal hypertension is also characterized by changes in vascular structure, termed vascular remodeling, which is an adaptive response of the vessel wall that occurs in response to chronic changes in the environment such as shear stress. Angiogenesis, the formation of new blood vessels, also occurs with portal hypertension related in particular to the expansion of portosystemic collateral circulation. ***(Kim et al., 2010)***

The circulatory component involved in portal hypertension is dynamic blockage. This process occurs as a result of inappropriate vasoconstriction and vasodilatation within the portal system ***(Dib et al., 2006).***

The hepatic stellate cell membrane contains numerous receptors whose expression is increased with the extent of liver damage; to which different vasoconstrictors are bound; one of them is serotonin ***(Oben et al., 2004).***

Serotonin or 5-hydroxytryptamine (5-HT) is known to regulate several key aspects of liver biology and these functions include hepatic blood flow, innervation and wound healing ***(Ruddell et al., 2008)***. Serotonin is mostly metabolized into 5-hydroxyindoleacetic acid by monoamine oxidase in hepatic and lung endothelial cells ***(Culafic et al., 2007)***. Vasoconstriction is a classic response to administration of serotonin. ***(Fanburg and* Lee*, 1997).***

Beside its role as a neurotransmitter in the central nervous system, serotonin appears to be a central physiologic mediator of many gastrointestinal (GI) functions and a mediator of the brain-gut connection ***(Lesurtel et al., 2008)***.

Altered concentrations of circulating serotonin have been implicated in several pathologic conditions including hypertension, primary pulmonary hypertension, liver cirrhosis, and psychiatric disorders ***(Humbert et al., 2002)***.

The acute and chronic hepatic insufficiency gives rise to serotonin system changes, contributing to the development of hepatic encephalopathy, portal hypertension, and hyperdynamic circulation ***(Borcsiczky et al., 1996).***

After application of serotonin inhibitors, portal pressure is decreased in patients with liver cirrhosis, confirming the importance of serotonin in the pathogenesis of portal hypertension. ***(Li et al., 2006 & Culafic et al., 2007)***

Recenltly it was reported that plasma serotonin levels are significantly higher in patients with cirrhosis than in the controls and represent the degree of liver insufficiency. In addition, platelet poor plasma serotonin estimation is a better marker for liver insufficiency than platelet serotonin content ***(Culafic et al., 2007)***.

Moreover, increased level of free plasma serotonin was hypothised to contribute to variceal development ***(Rudić et al., 2010)***

In this study the role of free serotonin concentration in plasma on the development of esophageal and fundal varices was evaluated.

Aim of the Work

This study aims to:

Determine the effect of free serotonin concentration in plasma on the pathogenesis of esophageal and fundal varices in cirrhotic patient.