World Journal of Gastrointestinal Pathophysiology

Online Submissions: http://www.wjgnet.com/2150-5330office
wjgp@wjgnet.com
doi:10.4291/wjgp.v2.i3.57

World J Gastrointest Pathophysiol 2011 June 15; 2(3): 57-60
ISSN 2150-5330 (online)

Parimal Chowdhury's work on smoking related pancreatic disorders

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Author contributions: Chowdhury P contributed solely to this manuscript.
Supported by the Earlier Grants from NIH and a Grant through University of Arkansas for Medical Sciences
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Received: December 14, 2010 Revised: May 18, 2011
Accepted: May 25, 2011
Published online: June 15, 2011

Figure 1 Parimal Chowdhury (left), PhD, Professor, University of Arkansas for Medical Sciences Department of Physiology and Biophysics, 4301 W Markham Street, Little Rock, AR 72205, United States.

Abstract

Cigarette smoking is a known risk factor for the development of numerous diseases. The role of nicotine in the induction of pancreatic inflammation and pancreatic cancer as a result of cigarette smoking has been recognized and reported in the literature. The mechanism by which nicotine induces such pathologies is as yet unknown. An understanding of the proliferative potential of nicotine in primary and tumor cells of the pancreas will allow us to develop measures that will ultimately lead to intervention, prevention and treatment of these diseases. Studies show that nicotine can increase the cell numbers of certain cancer cell lines, suggesting that exposure to nicotine can lead to the disruption of the dynamic balance between cell death and proliferation, which is required for normal functioning of cells. We hypothesize that nicotine induces oxidative stress in pancreatic acinar cells and thus contributes to this disruption. We have used the AR-42J cell line in our study because of its stability as an immortal tumor cell line and its known physiological similarity to primary acinar cells. Our studies show that mitogen activated protein kinase signaling is induced by nicotine in AR42J cells, causing an increase in lipid peroxidation and a subsequent decrease in cell function. Our data suggest that exposure to nicotine induces oxidative stress, leading to cell injury and compromised function, thus implicating cigarette smoking as a plausible mechanism.

Key words: Nicotine; AR42J cell; Effect on mechanisms; Lipid peroxidation; MAPK signaling; Cell function

Peer reviewers: Zoltan Rakonczay, MD, PhD, University of Szeged, PO Box 427, Szeged 6701, Hungary; Wai-Keung Chow, MD, Division of Gastroenterology, China Medical University Hospital, No.2 Yu-Der Rd., Taichung 400, Taiwan, China; Marco Del Chiaro, Dr., Gastrointestinal Surgery, Karolinska University Hospital, Stockholm SE-141 86, Sweden

Chowdhury P. Parimal Chowdhury's work on smoking related pancreatic disorders. *World J Gastrointest Pathophysiol* 2011; 2(3): 57-60 Available from: URL: http://www.wjgnet.com/2150-5330/full/v2/i3/57.htm DOI: http://dx.doi.org/10.4291/wjgp.v2.i3.57

INTRODUCTION AND EDUCATIONAL EXPERIENCE

Dr. Parimal Chowdhury PhD. (Figure 1) is currently working as Professor of Physiology & Biophysics and Associate Professor of Pharmacology & Toxicology at the University of Arkansas for Medical Sciences (UAMS), Little Rock, Arkansas. He also has a joint appointment as Adjunct Professor in the Department of Applied Science at the University of Arkansas at Little Rock (UALR). Before joining the UAMS in 1980, Dr. Chowdhury worked as Assistant Professor at the University of Medicine & Dentistry of New Jersey, New Jersey Medical School, Newark, New Jersey. He graduated with B.Sc. and M.Sc. from Dacca University. Later, Dr Chowdhury moved to Canada and earned his Ph.D. degree in Immunochemistry/Physiology in 1970 from the prestigious McGill University, Montreal, Canada.

Dr. Chowdhury's research is focused on the study of how nicotine, a major component in cigarette smoking, induces patho-physiological changes in the exocrine pancreas. Applying physiological, biochemical, ultra structural and molecular techniques, his group focuses on the implications of associated studies that explain the development of pancreatitis in rats caused by nicotine which lead to pancreatic carcinogenesis. Dr. Chowdhury is also concentrating on developing an animal model of simulated weightlessness following induced microgravity, and to study the physiological responses of various tissues to hind limb suspension with the ultimate aim of developing a countermeasure for space travel-related sickness. Dr. Chowdhury' s research projects have been supported in part by funds from the NIH, the Arkansas Space Grant Consortium, and other agencies.

Dr. Chowdhury has authored/co-authored over 117 peer-reviewed research publications including book chapters, and editorials in high-impact journals such as *AJP, Ann Clin Lab Sci, Gastroenterology, J Pancreatol, JBC, J Biomed Optics, J Cell Physiol, J Clin Immunoassays, J Lab Clin Med, JPET, J Surg Res, Pancreas, Exp Biol and Med, Science*, *World J Gastroenterol* as well as many others. He has had over 260 scientific research abstracts published, from presentations at various local, national and international conferences. He serves on the Editorial Board of the *World Journal Gastroenterology and the World Journal of Gastrointestinal Pathophysiology*, and is a reviewer for numerous peer-reviewed journals.

Dr. Chowdhury has traveled extensively worldwide, and has delivered lectures as visiting scientist/professor. He is an active member of various national/international societies and has served on many committees. He served as President of the International Society for the Prevention of Tobacco Induced Diseases (ISPTID), an international scientific society (2006-2008), and also as President of the Association of Scientists of Indian Origin in America (ASIOA), a scientific society in the USA (2006-2008). He is also a member of the Central Arkansas Chapter of the Society of Sigma XI and represents Arkansas at the national meeting each year. He has been a recipient of many competitive awards and honors throughout his career. Dr. Chowdhury has supervised and/ordirected many students for their thesis and/or dissertation projects.

ACADEMIC STRATEGY AND GOALS

Cigarette smoking is a risk factor for many diseases[1-5], including alcoholic and chronic pancreatitis, and has been suggested as the single most important factor for the induction of pancreatic diseases[6,7]. Nicotine, a major component of the particulate fraction of cigarette smoke, is ingested via smoking of cigarettes or the use of other forms of tobacco. It is a known addictive agent, a drug which can be abused, and a procarcinogen. In animal studies, nitrosamines and N-nitroso-nornicotine, chemicals found in tobacco smoke, appear to be carcinogenic in the pancreas. Studies show that nicotine can increase the cell numbers of certain cancer cell lines[8-10]. It is our belief that pathophysiological changes in the pancreas in smokers, leading to the development of pancreatitis, are caused primarily by nicotine from the cigarette smoking.

Studies from our laboratory have shown that rats exposed to nicotine via oral and aerosol routes develop changes in pancreatic function and histology that are consistent with the onset of pancreatitis. Further studies are designed to critically evaluate the effects of nicotine in the development of pancreatitis in rats.

We hypothesize that rats exposed to nicotine will develop pancreatitis and that the pathological injury in the pancreas induced by nicotine is caused by alterations in cellular, subcellular and/or genetic mechanisms.

Over the years Dr. Chowdhury's research group has developed an animal model of pancreatic injury by nicotine in rats, who have been exposed to it through either via inhalation or ingestion. Subsequent molecular analysis has led to a hypothesis of identification of predisposed pancreatitis development by nicotine, leading to pancreatic oncogenesis. Dr. Chowdhury's group has approached the nicotine-induced effect further through mitogen-activated signaling pathways involving transcription factors. The current research strategy addresses the oxidative effect by nicotine at cellular level, leading to injury and compromised pancreatic function. We have used the AR42J cell line in our study because of its stability as an immortal tumor cell line and its known similarity in physiological characteristics to primary acinar cells[11].

ACADEMIC ACHIEVEMENTS

The following few selected contributions highlight Dr. Chowdhury's activities in the field of nicotine induced pancreatic injury and dysfunction.

Tissue distribution of [^{3}H]-nicotine in rats

We have determined that the pancreas is a target organ for nicotine accumulation. Distribution of [^{3}H]-nicotine in rats, after a bolus injection of nicotine, or a continuous infusion of nicotine, has revealed that the accumulation of nicotine was highest in the kidneys, regardless of the route of administration. Retention of nicotine by constant

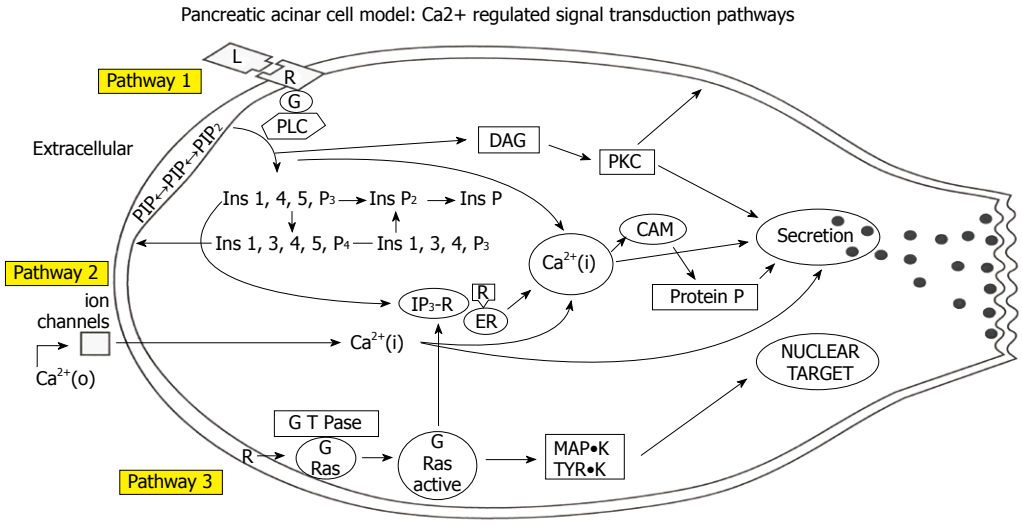

Figure 2 Pancreatic acinar cell model. A pancreatic acinar cell model showing the multiple signal transduction pathways is proposed that will replicate signal transduction pathways of a normal acinar cell described previously by other investigators[14-16]. Known agonists and antagonists acting directly on acinar cell surface receptors (pathway 1), ion channels (pathway 2), and intracellular receptors (pathway 3) are utilized to delineate the mechanism.

infusion was significantly higher in most organs, including the pancreas (6.4% ± 0.5% [^{3}H]-nicotine/g tissue), compared to retention resulting from the bolus injection (5.2% ± 0.4% [^{3}H]-nicotine/g tissue). These results indicate that the length of time of exposure to nicotine can be associated with the amount of nicotine that is stored in the organs of rat.[12]

Induction of pancreatic acinar pathology via the inhalation of nicotine

Rats exposed to aerosolized nicotine *via* inhalation induced onset, progression, and sequential development of lesions in the pancreas. Experimental groups were exposed to saline or nicotine for 15, 30, 45, and 60 min, twice a day, for 21 d. Results showed that pathological pancreatic lesions remained confined to the exocrine pancreas. The effects on pancreatic histology and plasma levels of nicotine were shown to be related to the time of exposure.[13]

Mechanism of action of nicotine on the exocrine pancreas

The mechanism by which nicotine induces pancreatic pathology is unknown. However, studies from our laboratory strongly indicate the involvement of the exocrine pancreas rather than the endocrine pancreas as a potential target for injury. A pancreatic acinar cell model X that will replicate signal transduction pathways of a normal acinar cell described previously by other investigators[14-16] is proposed in Figure 2. Known agonists and antagonists acting directly on acinar cell surface receptors, ion channels, and intracellular receptors will be utilized to delineate the mechanism. A schematic diagram showing the multiple signal transduction pathways is also shown in Figure 2 (pathways 1, 2, 3). Using this model, we plan to examine each of these distinct transduction pathways in a systematic manner.

CONCLUSION

The successful completion of these studies will provide an animal model for the study of this disease and should provide important information that could aid health care providers in establishing methods for the control, diagnosis, and treatment of pancreatitis.

ACKNOWLEDGMENTS

I am grateful to the past and present members of my laboratory for their contribution to our studies. I express my deepest gratitude to my colleagues in and around the world, in particular, Professor Phillip L. Rayford (deceased) for his support throughout the continuity of these studies.

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S- Editor Zhang HN **L- Editor** Herholdt A **E- Editor** Zhang L