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Research Article

# Pathogenetic Mechanisms for the Development of Secretory Insufficiency in Chronic Pancreatitis of Alcohol Etiology

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## Abstract

Chronic alcoholic pancreatitis. The data on the concentration of acetylcholine and serotonin in the development of pancreatitis are presented. Options for the formation of the disease are proposed. The role of parasympathetic innervation in the process of stimulation of secretory activity is gradually reduced. There is a transition to an autonomous system of regulation. the main stimulant is serotonin. Serotonin reduces its involvement in the inflammation process. Becomes a secretory agent. The new regulatory system is worse than the one that was primordially, but Vagus stimulation fails in conditions of massive fibrosis in the pancreatic tissue. The new system leads to maladaptation of regulatory mechanisms. Against this background, damage to the pancreas and the development of complications continue.

***Keywords:*** *Pancreatitis; Alcohol; Acetylcholine; Serotonin*

## Introduction

Pancreatitis is a chronic progressive disease. with recurrent course. Undoubtedly, the content and ratio of neurotransmitters with various functional properties should reflect the dynamics of the pathological process during periods of remission and exacerbation [1,2,7]. Repeated damage leads to a destructive and fibrotic process. Thus, after each exacerbation, there are residual morphological and functional changes in the form of destruction of the acini, their infiltration, swelling of the vessel walls, development of connective tissue, which aggravates the course of the disease and can cause changes in the mechanisms of regulation of functional activity of the pancreas.

## Aim of the Study

To determine the role of neurotransmitters - acetylcholine and serotonin in the pathogenesis of the formation of functional pancreatic insufficiency in chronic pancreatitis (CP).

## Materials and Methods

This work summarizes the results of a survey of 108 patients with chronic alcoholic etiology (AHP). The control group consisted of 30 people. 30 patients with AHP were examined repeatedly in dynamics. Duration of observation is from 1 to 10 years. To determine acetylcholine, a chemical reaction was used based on a specific reaction for acetylcholine and a number of other substances derived from carboxylic acid. This method is based on the reaction of acetylcholine with hydroxylamine in an alkaline environment. In this case,

hydroxamic acids are formed, which, with salts of ferric iron at pH = 1.2 - 1.5, give a color reaction. The method is widely used to determine acetylcholine and acetylcholine-like substances in the blood and in other biological fluids. Each time, a standard was determined in parallel with the studies. When determining cholinesterase activity, acetylcholine was used as a substrate. In the tissue, the content of serotonin was determined by extracting it into acidified butanol. In the blood, the destruction of the formed elements with perchloric acid was preliminarily carried out, followed by extraction of serotonin into the butanol fraction.

## Results and Discussion

During ACP, 3 variants (stages) of the development of the disease are distinguished (Figure 1). The first stage (A) of the disease is characterized by the presence of persistent or paroxysmal pain lasting from several days to a week, which alternate with remissions of the disease [1,3,4]. At this stage, there are no signs of exocrine and endocrine pancreatic insufficiency, as well as minimal structural changes. The duration of this stage is an average of 5 years. The second stage (B) of the disease is characterized by a decrease in the severity and duration of the pain syndrome due to inflammatory changes in the pancreas. Signs of exocrine and endocrine pancreatic insufficiency appear. Most patients have structural and morphological changes in the pancreas (calcifications, duct changes, fibrosis). The average duration of this stage is about 6 years or more. The third stage (C) of the disease - in the pancreas, the foci of acute and chronic inflammation and total fibrosis of its parenchyma are combined, the islands of acinar cells are "walled up" in the connective tissue (Figure 2-4). Pains are usually stop [1,6].

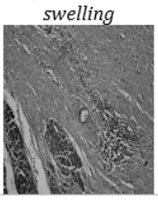
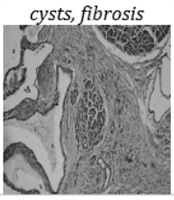
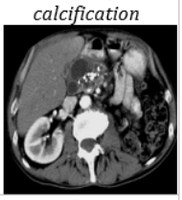
| ***Control*** | | ***Chronic pancreatic of alcohol etiology*** | | |
|---|---|---|---|---|
| | | ***Option A*** | ***Option B*** | ***Option C*** |
| *The number of patients examined* | *(n = 15)* | *(n = 17)* | *(n = 21)* | *(n = 28)* |
| *Structural and morphological changes* | *0* | *Inflammation, swelling*  | *Inflammation, swelling, cysts, fibrosis*  | *Fibrosis, cysts, calcification*  |
| *Disease duration* | *0* | *< 5 years* | *< 10 years* | *> 10 years* |
| *Pain syndrome, graduation on a 10-point scale of years* | *0* | *6-8* | *5* | *2* |
| *Elastase in feces (E-1)* | *200 - 500 mcg/g* | *<= 200 mcg/g* | *<=150 mcg/g* | *< 100 mcg/g* |
| *5-HT, % increase after eating* | *121* | *111* | *154* | *240* |
| *Ach, % increase after eating* | *125* | *104* | *89* | *78* |

***Figure 1:*** *Options for the course of chronic pancreatitis.*

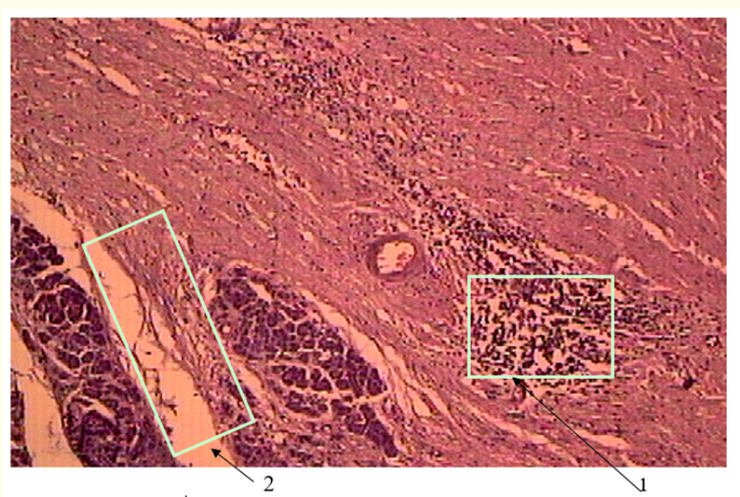



***Figure 2:*** *Chronic inflammation (1) and swelling of the tissue (2) of the pancreas. G&E x120.*

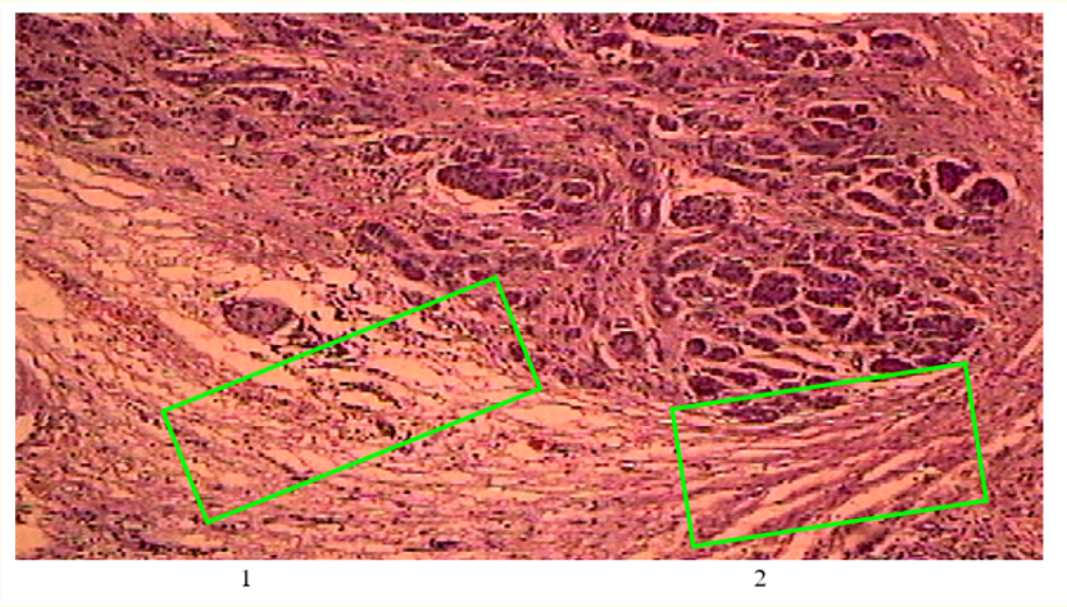



***Figure 3:*** *Severe sclerosis (1) and chronic inflammation (2) of the pancreas. G&E x120.*

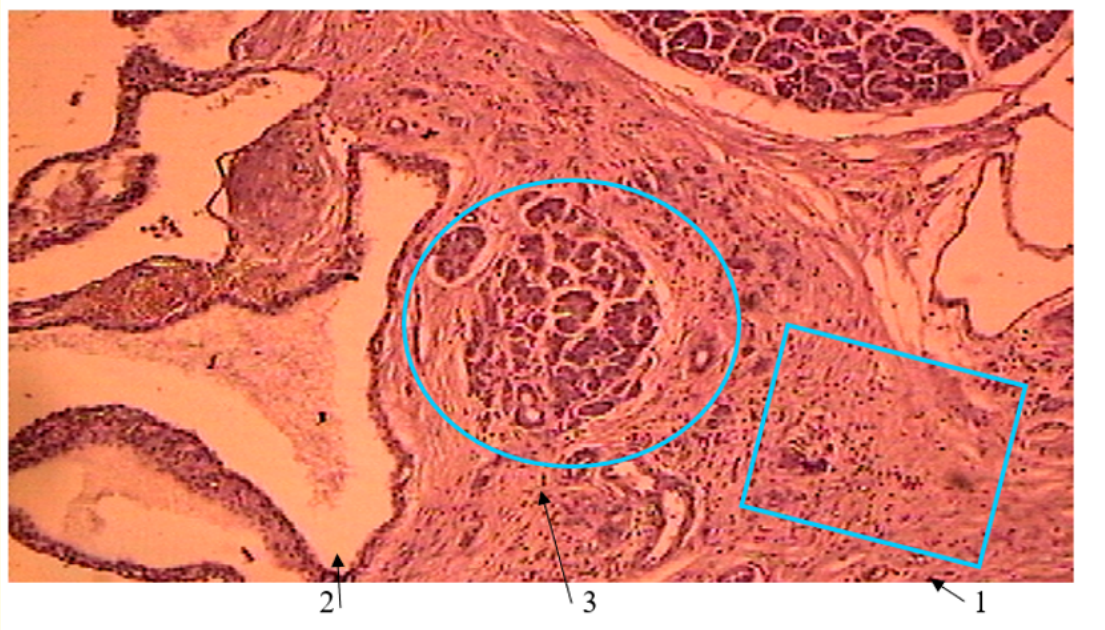



***Figure 4:*** *Severe sclerosis (1), cysts (2). Pancreatic "walled" areas (3). G&E x120.*

Content of 5-HT before and after meals is higher than in the control (Figure 5), Figure 5 and 6 demonstrate different options CP. Changes in the ratio of neurotransmitters and hormones in CP are adaptive in nature (maintaining the secretory activity of the pancreas). This is clearly demonstrated by the nature of changes in the 5-HT content in the blood before and after a standard breakfast (Figure 5 and 6). So, demonstrate, that we have process adaptation - compensation and decompensation.

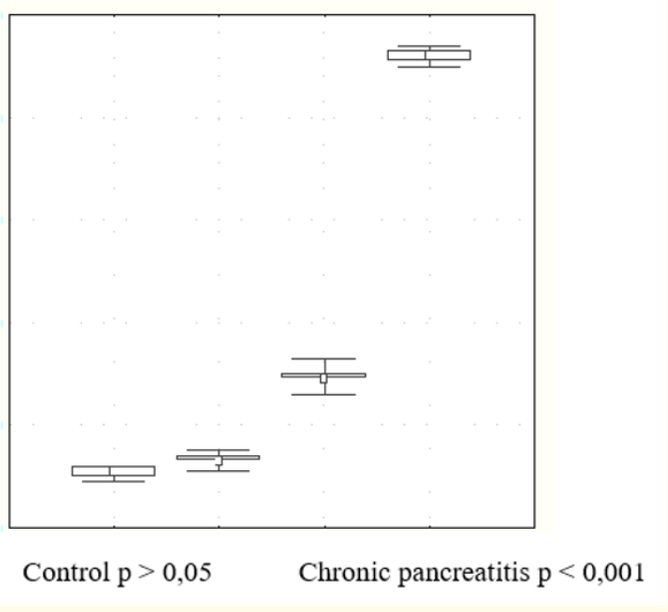



***Figure 5:*** *Content of 5-HT before and after meals.*

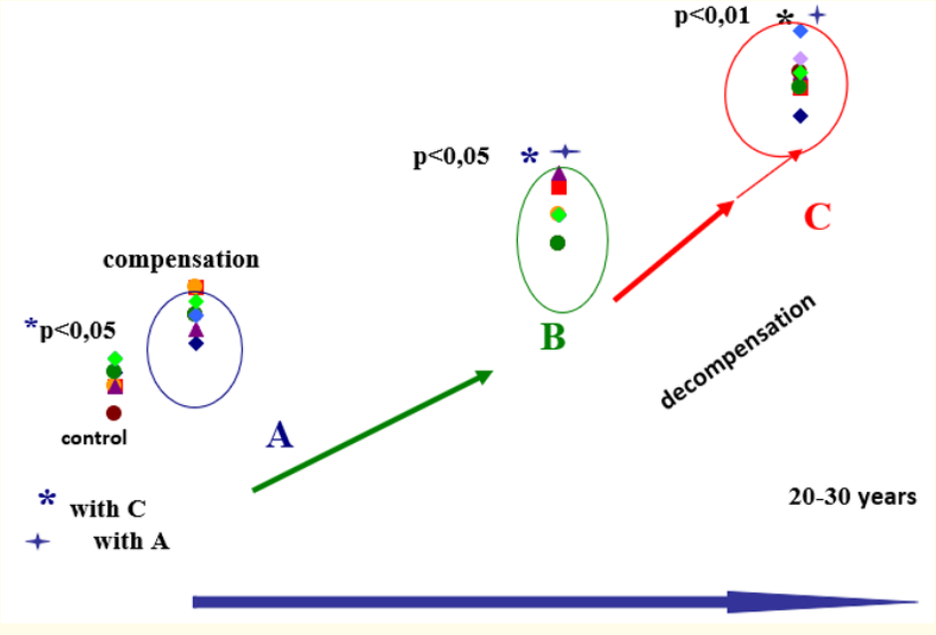



***Figure 6:*** *HT before meals.*

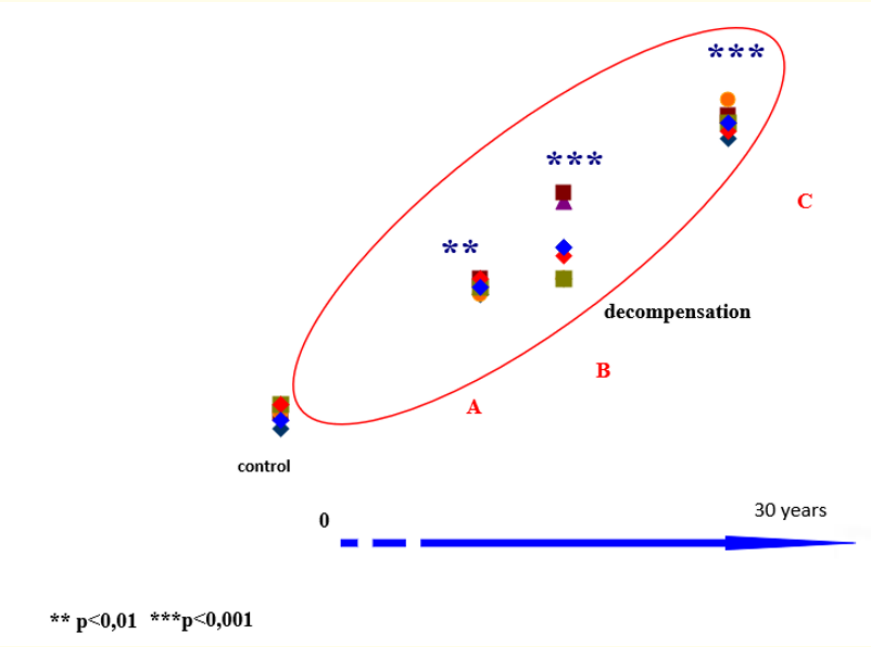



***Figure 7:*** *5-HT content after meal.*

On an empty stomach, the concentration of 5-HT is higher than in the control. This increase has significant differences. However, the level of serotonin in this case is close to the upper 5-HT values in the control ($p < 0.05$) - Option A. After a standard food load, the 5-HT level increases significantly, $p < 0.01$. Options B and C on an empty stomach differed from the control level $p < 0.01$ and after a food load, a high content of 5-HT in the blood was noted ($p < 0.01$ and $p < 0.001$). Food load is a test that demonstrates that with significant structural changes in pancreatic tissue decompensation of regulatory mechanisms occurs. The regulation of the secretory activity of the pancreas is carried out due to 5-NT in patients with CP. A healthy main stimulant is Ah. Mutual duplication of the effects of stimulation or inhibition of the gastroduodenal zone contributes to the synchronism, sequence, integration and self-control of the activities of its organs. At the same time, in addition to the internal relationships in the gastroduodenal system, there is a hierarchy of control mechanisms, due to which, when the local regulatory system is disrupted, higher levels of control and control that mobilize neurohormonal correction mechanisms are automatically activated. The disturbing effect leads to a complex of reactions, the purpose of which is to adapt the body to changing conditions, to prevent or smooth out a possible shift in the internal environment. For chronic pancreatitis, repeated exacerbations of the inflammatory process and progressive fibrosis are characteristic. The processes of fibrogenesis lead to the replacement of pancreatic secreting cells with connective tissue. Functional and structural changes as a result of the inflammatory process in the pancreas change the neurohormonal regulation of its secretory function. The use of food load (regular breakfast in stationary conditions) made it possible to identify changes in the content of biologically active substances that regulate the secretory response to food intake. In healthy individuals, there is a tendency to increase in serum acetylcholine and serotonin. In patients, there is a decrease in acetylcholine compared with the initial level and an increase in serotonin. An imbalance between acetylcholine and serotonin was revealed. This indicates a violation of the traditional "scheme" of regulatory relationships and suggests that in this case the role of the parasympathetic department of the autonomic nervous system is reduced. Patients form new functional regulatory mechanisms that reliably manifest themselves after a food load. A gradual increase in the content of connective tissue in the pancreas reduces its functional activity and requires an increase

in secretion stimulators (neurotransmitters). The high content of serotonin during CP after a food load can enhance afferent nociceptive flows, and the action of acetylcholine is manifested in a decrease in the threshold of activation of nociceptors, which may be one of the causes of pain after eating in patients with CP. Violation of relationships in the "axes" of regulation requires the inclusion of compensatory mechanisms to ensure the digestive conveyor. On the other hand, adaptation to impaired secretion regulation mechanisms leads to a state of decompensation. Each of the stages of development of pancreatic pathology requires correction in CP therapy, and for this it is necessary to have objective data that will highlight the options for the course of the disease. The quantitative value and ratio of stimulants plays an important role in the development of a full-fledged pancreatic juice, both in volume and in chemical composition, which is important for the "conveyor". The stimulating effect of the Vagus nerve on pancreatic secretion is via acetylcholine, which stimulates the release of duodenal CCK and secretin [1]. Thus, with CP of various etiologies, the level and ratio of neurotransmitters changes. High levels of serotonin and acetylcholine are detected in the blood. An increase in the concentration of stimulants of pancreatic secretory activity is aimed at increasing the secretion of pancreatic enzymes, but as a result of the fact that the secreted pancreatic tissue is replaced by connective tissue, the desired effect does not occur. Depending on the severity of destructive changes in the pancreas in patients with AP, a different degree of exocrine insufficiency was revealed, which may be due to the level of the content of neurotransmitters involved in the stimulating effect of pancreatic secretory activity [1,3-7].

## Conclusion

1. Morphological preparations of the pancreas demonstrate that in one patient with chronic pancreatitis of alcoholic etiology, there may be phenomena of both acute and chronic inflammation and significant fibrosis.

2. Serotonin is only a stimulant of secretion. A new axis of stimulation of secretion is created, worse than natural.

3. The control of the inflammatory reaction in the pancreas is carried out by IFg and IL-1b, which support the inflammatory reaction. This creates the conditions for the formation of a chronic progressive disease and exacerbation.

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