Volume homeostasis is a common physiological phenomenon for fluid secreting organs, such as exocrine and endocrine glands. It is a manifestation of a finite intraluminal space and an ever changing demand for secretory fluids. Volume homeostasis addresses issues of fluid secretion, storage and clearance for efficient functioning. Here we discuss the evidence gathered over the past 2–3 decades on serotonin’s role as a feedback inhibitor of secretion in the mammary gland, salivary gland, liver, pancreas, lung, thyroid gland and prostate gland. We propose that serotonin action is a common mechanism of regulating intraductal volume homeostasis.

In any organism, a large fraction of the body is composed of fluid. There are various specialized fluids that perform specific functions e.g., milk provides nourishment to the infant, saliva, pancreatic juice and bile aid in digestion, prostate fluid contributes to semen etc. With the presence of these different specialized fluids arises the issues of their compartmentalization and volume regulation in relation to their demand and physical space available in the organ (volume homeostasis).

The majority of these secretory organs (including exocrine and endocrine glands) have the basic tissue architecture of an arborized ductal network that terminates into numerous spherical lobules, alveoli or acini. These ductal and lobuloalveolar structures are lined by epithelial cells that are responsible for production and secretion of the specialized fluids. In addition, the junctions between these epithelial cells (adherence and tight junctions) compartmentalize the ductal and lobuloalveolar structures from the surrounding stroma and thus define the physical space available for fluid secretion. Because of these reasons the ductal and alveolar epithelial cells are paramount for volume homeostasis.

The repertoire of serotonin’s (5-Hydroxytryptamine, 5-HT) actions affect virtually all major organ systems including, cardiovascular, pulmonary, gastrointestinal, genitourinary and the central nervous system. The serotonin system is highly complex; consisting of rate limiting biosynthetic enzymes tryptophan hydroxylase (TPH), 5-HT reuptake transporter (SERT) which internalizes 5-HT, monoamine oxidases (MaO) which metabolise 5-HT and an extensive network of >20 different receptors that are divided into seven classes (5-HT₁–5-HT₇) based on pharmacological properties.

Given the extensive presence and function of 5-HT, here we conduct a highly focused discussion of involvement of 5-HT in volume homeostasis and make the case that this is a common mechanism present across various fluid secreting organs.

**Mammary Gland**

5-HT action on volume homeostasis has been most extensively studied in the mammary gland. The mammary gland is an exocrine gland that is the most recent acquisition on an evolutionary timescale. It is found in all mammals and its main function is nourishing the infant through milk secretion. Unlike most organs, mammary gland development occurs postnatally in association with pregnancy. The mammary gland secretes milk in a cyclical manner in relation to suckling of the infant and stores milk in between bouts of nursing (milk stasis). This necessitates the presence of a reversible feedback inhibitory mechanism to rein in milk secretion in accordance with the volume-space availability of the gland.

A comparative genomic analysis of non-secretory and hyper-secretory mouse mammary glands showed high induction of the 5-HT biosynthetic enzyme, TPH1. 5-HT biosynthesis was detected during lactation and 5-HT was found in the mammary epithelium and in milk. Interestingly, 5-HT biosynthesis was induced by milk stasis (accumulation) during lactation. 5-HT inhibits milk protein secretion in vivo and in explant cultures. Alternatively, 5-HT biosynthesis disruption and 5-HT receptor antagonists significantly enhance secretory features and caused alveolar dilation. This led to the conclusion that 5-HT, in an autocrine-paracrine manner, regulates volume homeostasis within the mouse mammary gland. Similar actions of 5-HT in affecting lactation have been observed in humans and bovine.

Human mammary epithelium expresses multiple 5-HT receptors (5-HT₁A, 5-HT₁B, 5-HT₁D and 5-HT₂). Similar observations have been made in rodents and bovine. Among these, 5-HT₂ expression is conserved across species and hence has been studied most extensively. 5-HT₂ receptor is localized to the

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bouts of nursing (increased pressure). However, upon weaning continued milk stasis breaches the tight junction and induces mammary gland involution.16,17 The impact of 5-HT on milk secretion has been validated in vivo in both bovine and humans via administration of SERT inhibitors (SSRIs) which increase the bioavailability of 5-HT. SSRIs delay the onset of copious milk secretion in primiparous women.6 In bovine, SSRIs suppress milk secretion and accelerate involution (via breach of epithelial tight junctions). 15 Hence 5-HT acts as a critical regulator of milk secretion and milk volume in the mammary glands. Other actions of 5-HT in the mammary gland include regulating mammary epithelial turnover via regulating processes such as cell shedding and apoptosis.18 These effects are likely mediated by other receptors present in the mammary epithelium and will not be discussed in detail in this article.

**Salivary Glands**

The salivary glands are exocrine glands with classic ductal and acinar structure and produce saliva whose main function is to keep food moist while eating. In mammals like humans they also secrete digestive enzymes such as amylases.19 Immunohistochemical analysis of rat submaxillary salivary glands showed the presence of 5-HT in the epithelial cells of excretory ducts and acini.20 The same cells that were positive for 5-HT were also found to contain serotonin (5-HT). These actions of 5-HT in the salivary glands resemble those in the mammary glands, suggesting a conserved role of 5-HT in glandular tissue function.
were also found to contain 5-HT4b and 5-HT7a (Gs coupled stimu-
crine regulation by 5-HT. In addition, the rat submaxillary glands
angiocyte secretion that contributes towards bile. 30 Analogously,
inhibits the proliferation of cholangiocytes and it inhibits the chol-
the biliary tree; it
has two distinct effects on the biliary tree; it
increased upon blockage of bile duct (Bile duct ligaton-BDL). 30
The increased 5-HT has two distinct effects on the biliary tree; it
bile synthesis, hormone production, decomposition of red blood cells
and bile secretion for digestion and emulsification of lipids. 27
The biliary tree consists of arborized bile ducts lined by cholangiocytes which are epithelial cells that contribute to bile secretion. 28 Cholangiocytes are normally mitotically dormant, but proliferate in response to blockage of bile duct (and subsequent bile accumulation and increased pressure). 29
In rats, cholangiocytes synthesize and secrete 5-HT which is
increased upon blockage of bile duct (Bile duct ligation-BDL). 30
The increased 5-HT has two distinct effects on the biliary tree; it
the barrier function in an effort to contain bile intraluminally.
5-HT has been shown to affect mammary epithelial tight junc-
tion permeability. 8,14 (Fig. 1), however such action of 5-HT in
liver has not been explored.

Pancreas

The pancreas consists of two secretory systems, endocrine (insulin secreting β cells) and exocrine (digestive enzyme secreting epitel-
scence 33. In terms of negative feedback, a direct autocrine-paracrine
inhibition of exocrine secretion has been documented with 5-HT
identified as one of the highly potent local inhibitors. 34 Other local
to control the basal fluid secretion of pancreatic juice.35 Solitary serotonin producing
cells are dispersed across the acinar and ductal epithelium of the exocrine pancreas. 36 Isolated guinea pig pancreatic exocrine
duct explants have been found to respond to 5-HT. 35 Exogenous 5-HT decreased the HCO3− dependent basal fluid secretion of the explants. This inhibitory action of 5-HT was observed even in presence of stimulatory signals like secretin or Acetylcholine (ACh). Interestingly, 5-HT acted specifically through the baso-
larateral side as apical application of 5-HT had no effect. This effect of 5-HT was mediated by 5-HT3 receptor. 5-HT3 is a
and bicarbonate secretion even in presence of the stimulant secretin.
In addition to the autocrine signaling to inhibit bile secretion, 5-HT also stimulating the stromal cells in a paracrine manner to
produce TGFB1. 31 Increased TGFB1 counters the autocrine
inhibition of bile secretion and proliferation in cholangiocytes by
suppressing 5-HT synthesis.

Interestingly, similar to mammary gland, cholestasis induces changes in the tight junction protein distribution. 32 This affects

Liver

The liver is the largest internal organ and the largest gland in the human body. The highly specialized tissues of liver perform vari-
ous vital functions like detoxification, glycogen storage, protein

Pancreatic duct cells secrete HCO3− ions to control the basal fluid secretion of pancreatic juice. 33 Solitary serotonin producing
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and cyclically (digestive and post-digestive periods); a stimulatory
input that initiates secretion and a negative feedback input that
inhibits secretions when not required. Pancreatic exocrine stimula-
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cytoplasmic process along the basement membrane making direct contact with several neighboring epithelial cells as well as epithelial-mesenchymal interaction with subbasement membrane mesenchyme. Mechanical stretch induces TPH1 and 5-HT release by NECs. Blocking NEC mechanoreceptors attenuates the release of 5-HT. Mechanical stretch in turn stimulates proliferation of lung epithelial cells and induction of extracellular matrix (ECM) and differentiation of alveolar cells.

Complementing the above study, cultured guinea pig lungs from late gestation fetuses show a 5-HT dose-dependent decrease in the rate of fluid secretion, and activated reabsorption of fluid in the lung. This phenomenon is critical for the transition of the lungs during childbirth. Furthermore, 5-HT receptor antagonism blocks these effects. Taken altogether, serotonin is induced by stretch, and causes fluid clearance in the late gestation developing lung thus, functioning as a regulator of volume homeostasis in the developing lung.

**Thyroid**

The thyroid gland is one of the largest endocrine gland and controls energy metabolism, growth and function of many other organ systems of the body. It performs these functions by release of two hormones, triiodothyronin (T3) and thyroxine (T4). Unlike the exocrine glands discussed earlier in this article, the thyroid mainly consists of spherically structures called thyroid follicles made of thyroid epithelial cells. These follicular cells synthesize the thyroid hormones. The centers of these follicles are filled with colloid, which is a proteinaceous depot of thyroid hormone precursors. In addition to follicular cells, specific cells nestled between the follicles called parafollicular cells are also present. 5-HT has been localized to both follicular and parafollicular cells. Interestingly, 5-HT is also present in the colloid in the follicular lumen and its concentration in the colloid is greater than the follicular cells. This suggests secretion of 5-HT by the follicular cells. However, localization of SERT only in the follicular cells has led to the hypothesis that 5-HT is synthesized by parafollicular cells and acts in a paracrine manner on the follicular cells. Hence, the source of 5-HT synthesis still remains unclear.

Chronic co-treatment of rats with L-tryptophan (a 5-HT precursor that increases 5-HT production) and a SERT inhibitor (increases 5-HT availability) reduced serum levels of thyroid hormone. Alternatively, chemical inhibition of 5-HT synthesis (DL-p-chlorophenylalanine) or administration of broad spectrum 5-HT receptor antagonist increases serum levels of thyroid hormone. These observations indicate that 5-HT regulates thyroid hormone secretion likely in an autocrine-paracrine manner. However, in this case an indirect effect of 5-HT via influence on neural—pituitary axis cannot be ruled out.

**Prostate**

The prostate gland is an exocrine organ in males that secretes and stores a slightly acidic fluid that contributes towards the final semen. Prostate structure is typical of an exocrine gland with a ductal architecture ending into acini that secrete the fluid. In the prostate, distinct 5-HT producing cells have been found and are referred to as the neuroendocrine (NE) cells. The scientific community studying the prostate gland has delved into intensive study of NE cell’s involvement in prostate cancer, however there are only a few studies addressing the structure and function of NE cells in normal prostate physiology.

The serotonin producing cells are widely distributed in the prostate epithelium, but are more abundant in the major ducts and irregularly distributed in the acini. Analogous to the lung, there are at least two different subpopulations of 5-HT producing cells. One subpopulation (mainly in the peripheral zone) responds to the factors present at birth and at puberty and are suggested to play a role in prostatic growth and differentiation. These will not be discussed in detail in this article. The second subpopulation mainly resides in prostatic duct system, and are not influenced by the same factors but are postulated to be involved in homeostatic regulation of the secretory process of the gland. The morphology of these cells is similar to those found in lung epithelium, where these cells extend dendrite-like processes underneath and between adjacent epithelial cells. Based purely on the morphological similarity and physiological comparison with other organs it is postulated that these 5-HT producing cells directly regulate the secretion of adjacent epithelial cells in a paracrine manner. Along similar lines as that of lung, the prostate 5-HT secreting cells may also be induced to secrete 5-HT by a stretch-activated mechanism. These hypotheses remain to be experimentally validated.

**Conclusions**

Based on the literature discussed here, it is evident that 5-HT plays a central role in volume homeostasis of various fluid-secreting organs (including endocrine and exocrine). There appears to be a common pattern of 5-HT system in these secretory organs where 5-HT is secreted upon fluid accumulation and/or increased intraluminal pressure (Fig. 1). However, it is important to note that in organs like salivary glands, the wide spread localization of 5-HT may be a manifestation of 5-HT uptake via SERT and only a few subset of cells may actually be synthesizing 5-HT. 5-HT mainly acts as a feedback inhibitor of fluid secretion. Although 5-HT receptor expression in the organs varies widely (Table 1), they are mainly found to be located on the basolateral side of the epithelial cells (Fig. 1). Additionally, 5-HT regulation of volume homeostasis in these secretory organs is conserved across multiple species and classes.

All this evidence points to the hypothesis that 5-HT regulation of secretion and volume homeostasis is a very basic and evolutionarily ancient phenomenon that has been adapted and used to suit the needs of various organ systems as they evolved. The abundant repertoire of 5-HT receptors may be a manifestation of this divergent evolution. This hypothesis is supported by the findings that on an evolutionary timeline 5-HT is a very old molecule with function in both plant and animal kingdom. Also, 5-HT is linked to ion transport and fluid secretion right from establishment of body axis and first epithelial differentiation to intestinal fluid and ion transport.
Table 1. Serotonin receptor expression in ductal organs

| Organ/Tissue | Receptor | Function | References |
|--------------|----------|----------|------------|
| Mammary Gland | 5HT₁ | Tight junction regulation | 53 |
| Epithelial cells (immortal and primary) | 5HT₁, 5HT₆, 5HT₇ | Unknown | 8, 14 |
| Isolated epithelial cells | 5HT₁, 5HT₆, 5HT₇ | Suppression milk gene expression | 9 |
| Bovine epithelium | 5HT₁, 5HT₆, 5HT₇ | Inhibit fluid secretion | 10 |
| Salivary Glands | 5-HT₁₅, 5-HT₁₈, 5HT₁₉ | Inhibit fluid secretion | 21 |
| Liver | 5HT₁ | Inhibit HCO₃⁻ secretion | 30 |
| Pancreas | SHT₁ | Inhibit fluid secretion | 33 |
| Isolated interlobular ducts | 5HT₁ | Oxygen sensing | 38, 39 |
| Lungs | Neuroepithelial bodies | 5HT₁ | 40 |
| Neuroepithelial cells | ? | Inhibit secretion and induce fluid resorption | |
| Thyroid | Follicular cells | 5-HT₁ and 5-HT₇ | Biphasic action on growth and inhibition of hormone secretion | 42 |
| Prostate | Human prostate homogenate | 5HT₁, 5HT₆, 5HT₁₀ | Growth promoting in cancers | 43 |

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