Somatostatin in renal physiology and autosomal dominant polycystic kidney disease

REVIEW

A. Lianne Messchendorp[1], Niek F. Casteleijn[2], Esther Meijer[1] and Ron T. Gansevoort[1]; on behalf of the DIPAK Consortium investigators*

[1]Department of Nephrology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands and
[2]Department of Urology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Correspondence and offprint requests to: Ron T. Gansevoort; E-mail: R.T.Gansevoort@umcg.nl

*DIPAK Consortium investigators: Joost P. Drenth, Department of Gastroenterology and Hepatology, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands; Johan W. de Fijter, Department of Nephrology, Leiden University Medical Center, Leiden, The Netherlands; Dorien J.M. Peters, Department of Human Genetics, Leiden University Medical Center, Leiden, The Netherlands; Folkert W. Visser, Department of Nephrology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands;, Jack F. Wetzels, Department of Nephrology, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands; Robert Zietse, Department of Nephrology, Erasmus Medical Center Rotterdam, Rotterdam, The Netherlands

ABSTRACT

Autosomal dominant polycystic kidney disease (ADPKD) is characterized by progressive cyst formation, leading to growth in kidney volume and renal function decline. Although therapies have emerged, there is still an important unmet need for slowing the rate of disease progression in ADPKD. High intracellular levels of adenosine 3′,5′-cyclic monophosphate (cAMP) are involved in cell proliferation and fluid secretion, resulting in cyst formation. Somatostatin (SST), a hormone that is involved in many cell processes, has the ability to inhibit intracellular cAMP production. However, SST itself has limited therapeutic potential since it is rapidly eliminated *in vivo*. Therefore analogues have been synthesized, which have a longer half-life and may be promising agents in the treatment of ADPKD. This review provides an overview of the complex physiological effects of SST, in particular renal, and the potential therapeutic role of SST analogues in ADPKD.

Keywords: ADPKD, cAMP, renal physiology, somatostatin, somatostatin analogues

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disease, with a prevalence of 3–4/10 000 in the general population [1]. ADPKD is characterized by progressive development and growth of numerous renal cysts. This eventually leads to end-stage renal disease in 70% of affected patients at a median age of 58 years. An important extra-renal manifestation is progressive cyst formation in the liver, with a radiological prevalence of 95% by the age of 35–45 years, which leads to symptoms in ∼20% of cases [2, 3]. Symptoms in patients with polycystic liver disease (PLD) arise from the enlarged intra-abdominal volume and include abdominal distension, early satiety, herniations, dyspnoea and pain. In a limited number of affected subjects, liver transplantation is necessary [4].

For a long time there were no therapies to slow the rate of disease progression in ADPKD. In the last two decades, however, novel insight into the pathophysiology of ADPKD has led to the discovery of possible targets for treatment. One of these targets is adenosine 3′,5′-cyclic monophosphate (cAMP), which is elevated in ADPKD due to disrupted intracellular calcium homoeostasis and results in progressive cyst formation in both kidneys [5]. Therapeutic agents that interfere in this pathway can possibly attenuate ADPKD disease progression. The vasopressin V2 receptor antagonist tolvaptan, which down-regulates cAMP, is effective in the treatment of ADPKD [6, 7]. However, the effect of tolvaptan seems limited to renal tubular cells in the distal nephron and collecting duct, which express the V2 receptor. Cysts originating from other nephron segments as well as liver cysts will probably not be affected, although a recent experimental study has suggested that vasopressin V2 receptors are present on biliary cells [8]. However, it has not been shown that tolvaptan affects liver volume in ADPKD. Moreover, aquaretic

side effects limit widespread clinical use of this drug. Therefore there is still an unmet need for new therapies to slow disease progression in ADPKD.

Somatostatin (SST) is a hormone that is involved in many cell processes and directly and indirectly inhibits cAMP production in various tissues, including liver and kidney. SST analogues therefore have a potential role in the treatment of ADPKD for the renal as well as the hepatic phenotype. Studies about SST and its complex signalling pathway mainly date from the 1980s and 1990s. This review provides a summary of the role of SST and SST analogues in physiology, with a focus on the renal effects, and in the pathophysiology of ADPKD. The hepatic effects of SST have recently been reviewed elsewhere [9].

HISTORY OF SST

Somatostatin (SST or SRIF) was first discovered in 1968 by Krulich et al. [10] as a growth hormone–inhibiting factor produced by the hypothalamus. A year later, Hellman and Lernmark [11] found an insulin-inhibiting factor produced by the pancreas. In 1973, Brazeau et al. [12] concluded that these phenomena were caused by the same hormone: SST. After its discovery, subsequent studies revealed that SST is more widely produced throughout the body and induces a broad spectrum of biological effects, but mainly inhibitory.

THE PHYSIOLOGY OF SST

SST

SST is synthesized as part of a large precursor protein, pre-prosomatostatin (preproSST), which is rapidly processed into prosomatostatin (proSST). This prohormone is enzymatically processed mainly at the C-terminal segment to generate two bioactive forms, SST-14 and SST-28 (Figure 1) [13]. ProSST can also be cleaved at other sites, which creates four more cleavage products, but whether these latter cleavage products have a physiological function remains uncertain [14].

Secretion of SST

SST is produced by different cell types. Most SST-producing cells are found throughout the central and peripheral nervous systems, as well as in the pancreas and gastrointestinal tract. SST-producing cells are also found, although in smaller numbers, in other organs, including the kidney. About 65% of the total body SST is derived from the gastrointestinal tract, 25% from the central nervous system, 5% from the pancreas and 5% from the remaining organs [15]. Secretion of SST is either stimulated or inhibited by a broad spectrum of agents, including ions, nutrients, peptides, neurotransmitters, hormones, growth factors and cytokines. Some of these agents exert common effects on SST cells at different locations, whereas others appear to induce tissue selective effects. For example, nutrients, like glucose, stimulate SST secretion by δ-cells of the pancreas but inhibit SST secretion by cells of the hypothalamus [15].

SST receptors and their activation

SST can act on multiple cellular targets via a family of five receptors: SST receptor (SSTR) 1–5 [15]. The SST receptor
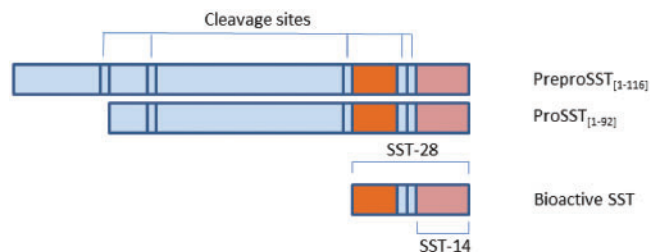
FIGURE 1: SST: its precursors and cleavage products (modified from Patel et al. [13]).

subtypes are more or less of equal size and consist of seven α helical transmembrane domain, G protein-coupled receptor proteins. Typically, more than one receptor subtype is expressed in a single organ. All receptor subtypes have nanomolar affinity for SST-14 and SST-28, but SSTR1–4 have higher selectivity for SST-14, whereas SSTR5 has a higher selectivity for SST-28 [13].

Ligand binding to these receptors generally results in three effects: inhibition of secretion, inhibition of cell proliferation and induction of apoptosis. Ligand binding to any of the five receptor subtypes first results in activation of the inhibitory G-protein (Gi), followed by modulation of multiple second messenger systems including but not limited to receptor coupling to adenylyl cyclase, receptor coupling to K^+ channels, receptor coupling to Ca^{2+} channels, receptor coupling to protein phosphatases, receptor coupling to exocytotic vesicles and receptor coupling to the mitogen-activated protein kinase pathway. Which second messenger is altered is dependent on the tissue-specific distribution of ligands, receptor subtype and tissue localization of the receptors. For instance, SSTR2–5 are coupled to K^+ channels, SSTR1 and -2 are coupled to voltage-dependent Ca^{2+} channels, SSTR2 and -5 are coupled to phospholipase C and SSTR1 is coupled to a Na^+/H^+ exchanger [16]. As a joint effect, all receptor subtypes inhibit adenylyl cyclase and cAMP production.

As SST is produced at sites where the different receptors are expressed, it is suggested that SST elicits its action especially in an autocrine/paracrine manner. However, circulating levels of SST derived from the gastrointestinal tract modulate insulin release, thereby eliciting a true endocrine effect [17, 18]. SST receptor activation therefore involves auto-, para- as well as endocrine mechanisms.

Although the acute administration of SST produces a large number of inhibitory effects, the initial response diminishes with continued exposure to the peptide. The ability of SST receptors to regulate their responsiveness to agonist-specific stimulation typically involves receptor desensitization due to uncoupling of G proteins, as well as receptor internalization and receptor degradation. This process is dependent on receptor subtype, exposure time, ligand concentration and heterologous regulation through other signalling systems [19]. The phenomenon of receptor desensitization is important for treatment with SST (see below).

Metabolism of SST

SST-14 and SST-28 are rapidly metabolized in vivo by cleavage through amino peptidases in blood and tissues. Experiments

with infusion of SST indicate that the liver and kidneys are the main sites of elimination of the molecule (37 and 32.7%, respectively). The remaining 30% of elimination is attributed to the lungs, pancreas and blood, which together results in a metabolic clearance rate of ∼30 mL/kg/min and consequently a very short plasma half-life of 1–3 min *in vivo* [13].

Renal localization of SST-producing cells and SST receptors

As mentioned above, SST-producing cells are also found in the kidney. *In vitro* studies have shown, for instance, that SST is secreted by mesangial cells and proximal tubular cells. Secretion can be stimulated by cAMP and inhibited by epidermal growth factor and hydrocortisone [20, 21]. Since SST is known to be an endogenous inhibitory regulator, it is suggested that this renal-derived SST modulates mesangial and proximal tubular cell growth and function after binding to renal SSTRs.

There have only been a few studies investigating the renal localization of SSTRs. These studies have shown that mainly SSTR1, -2 and -5 are expressed, especially in the distal tubules [22, 23]. However, a more recent study found positive staining for all receptor subtypes throughout the tubular system, except in the collecting duct [24]. Our study group also investigated renal SSTR localization. We observed SSTR2 expression mainly in distal tubules and collecting ducts in mice, which was in agreement with mRNA expression. In humans, we found conflicting data for immunostainings and mRNA expression [25]. Unfortunately, it is difficult to compare human studies since most studies focus on only very small sections of the kidneys and/or different antibodies were used, sometimes with distinct antigen specificity for the SSTRs. It is important to know which SSTR subtypes are expressed across the various segments of the nephron segments for therapy with SST analogues, which will be discussed later. The renal localization of SSTRs therefore warrants further research.

Effect of SST pathway activation in renal physiology

As mentioned above, binding of SST with SSTRs can activate pathways that can modulate renal cell function and growth. Since renal cells both secrete SST and express SST receptors, SST probably modulates renal cell function and growth in an autocrine/paracrine manner. This theory is supported by the fact that although all SSTRs have nanomolar affinity for biologically active SST (SST-14 and SST-28), systemic fasting plasma SST concentrations have a range that is 100- to 1000-fold lower, that is, between 0.008 and 0.02 nM, which is equivalent to 14–32.5 pg/mL [13]. These very low concentrations are assumed to not reach the threshold to activate SSTRs in the kidney. As SST is partly eliminated by the kidney, it should be stated that filtered SST could theoretically reach higher concentrations in (pre)urine and in this way potentially modulate downstream tubular function.

Activation of SST receptors causes inhibition of the release of aldosterone and renin [26, 27]. Multiple studies have suggested that SST is also involved in renal water handling and can inhibit the proliferation of renal cells [28, 29]. Furthermore, SST causes glomerular vasoconstriction, resulting in decreased renal blood flow and consequently a reduction of the glomerular filtration rate (GFR) [30]. These physiological processes are probably all, or at least partly, a result of the ability of SST to inhibit renal cAMP production [31, 32]. Interestingly, one of the pivotal detrimental factors in the pathophysiology of ADPKD are elevated levels of cAMP. Theoretically, SST and related agonists therefore have the potential to induce a therapeutic effect in ADPKD.

SST IN THE PATHOPHYSIOLOGY OF ADPKD

ADPKD is predominantly caused by a mutation in the *PKD1* gene, in 80% of cases, or in the *PKD2* gene, in 10% of cases. In rare cases, other mutations are found, which have recently been identified [33, 34]. In the remainder of cases, the mutation that underlies the disease is not known. *PKD1* encodes for the protein polycystin-1 and *PKD2* for the protein polycystin-2 [35]. These proteins form the so-called polycystin complex that is localized at the base of the primary cilium, which acts as a mechanosensor detecting flow in the renal tubules. When this sensor is stimulated, calcium influx occurs from pre-urine into the cytoplasm of renal tubular epithelial cells and from intracellular stores. In ADPKD, the polycystin complex is dysfunctional and consequently calcium cannot enter the cells nor can calcium be released from intracellular stores. Low intracellular calcium leads to high activity of adenylyl cyclase and reduced activity of calcium-sensitive cAMP-degrading enzyme (phosphodiesterase), which both lead to high intracellular cAMP levels. In turn, these high intracellular cAMP levels lead to aberrant renal tubular epithelial cell proliferation and chloride-driven fluid excretion in the kidney, the two key components of the process of cyst formation and growth in ADPKD [36] (Figure 2). In PLD, increased cholangiocyte proliferation and fluid secretion are the key features, which are stimulated by cholangiocyte cAMP [37].

As described, SST can lead via all its receptor subtypes to direct inhibition of adenylyl cyclase and cAMP production. Furthermore, some SSTR subtypes can be coupled to various phospholipase C isoforms, leading to increased Ca^{2+} levels, which is an indirect mechanism by which SST can lead to lower intracellular cAMP (Figure 2). Therefore SST has the potential to slow disease progression in ADPKD. As described previously, endogenous SST reaches very low plasma concentrations, unable to trigger SST receptors. We have observed that SST concentrations are similar in ADPKD patients compared with healthy controls (A.L. Messchendorp *et al.*, unpublished data). For this reason, SST needs to be administered to be of therapeutic use. However, administration of endogenous SST is of limited therapeutic potential since it is rapidly eliminated *in vivo*. Therefore analogues have been synthesized in which the biochemical stability of the peptide has been increased by incorporation of modified amino acids, which typically show selectivity for one or some of the SST receptor subtypes.

SST ANALOGUES

Based on differences in ring chemistry, size and position of bridging units, various analogues with different affinities for the SSTR subtypes exist. The most important and clinically used

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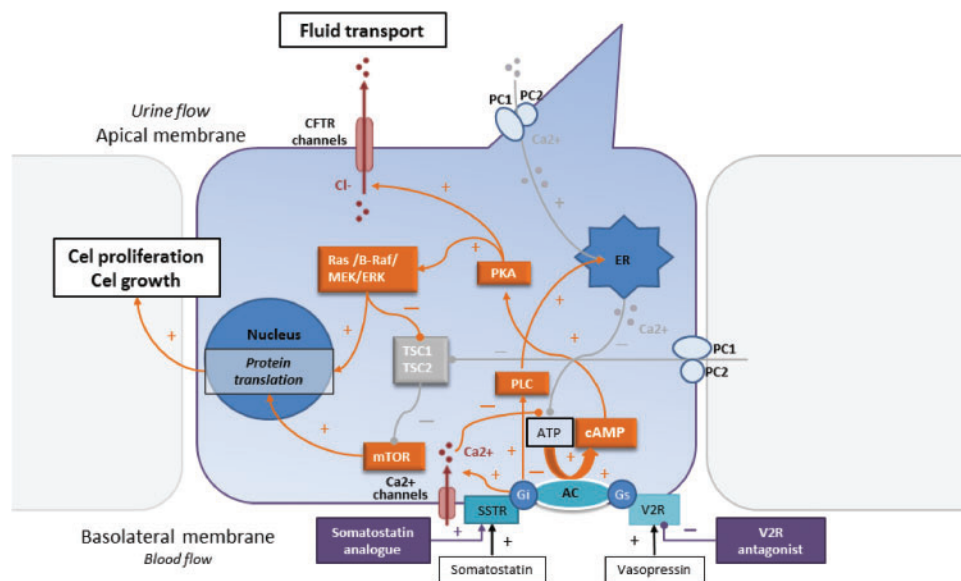
FIGURE 2: Schematic representation of the pathophysiological processes that drive cyst formation and growth in renal tubular epithelial cells of the collecting duct in ADPKD and the mechanism of action of vasopressin V2 receptor antagonists and SST analogues. In ADPKD, the polycystin complex (formed by the proteins PC1 and PC2 on the apical membrane) is dysfunctional, which leads to diminished calcium influx or diminished release of calcium from intracellular stores. Low intracellular calcium levels in turn stimulate activation of adenylate cyclase (AC), which converts adenosine triphosphate into cAMP. cAMP is an important player in several pathways that could possibly lead to cyst expansion. cAMP increases cell proliferation via protein kinase A and activation of the Ras/Raf/ERK pathway. Furthermore, cAMP activates apical-positioned chloride channels (CFTR channels), leading to fluid secretion into the cyst lumen. cAMP production can be inhibited by blocking the vasopressin V2 receptor (V2R), which is coupled to G stimulatory (Gs) proteins that can activate AC. Activation of the SST receptor (SSTR) can inhibit cAMP production in a direct and indirect way. AC can be directly inhibited by the receptor-coupled G inhibitory (Gi) proteins. Activation of these Gi proteins can also activate calcium channels and stimulate intracellular release of calcium via phospholipase C, which can restore intracellular calcium stores. This leads indirectly to inhibition of cAMP production. Orange and grey lines indicate that the pathway is activated or inactivated, respectively.

Table 1. SST analogues and their characteristics

SST analogue	Manufacturer	Receptor affinity [38]	Registered indications	Administration route	Half-life	Dosing regimen
Octreotide (SMS 201-995, Sandostatin)	Novartis Pharmaceuticals	SSTR2 > SSTR3, -5	Acromegaly, Gastro-entero-pancreatic endocrine tumours, Advanced neuroendocrine tumours, TSH-secreting pituitary adenomas, Prevention of complications after pancreatic surgery, Acute oesophageal variceal bleeding	IR, Subcutaneous, Intravenous, LAR, Intramuscular	IR, Subcutaneous 100 min LAR steady state for 3–4 weeks	IR, Subcutaneous 2–3× per day, Intravenous continuous, LAR 1× per 4 weeks
Lanreotide (BIM 23014, Somatuline)	Ipsen Ltd.	SSTR2 > SSTR3, -5	Acromegaly, Gastro-entero-pancreatic-neuroendocrine tumours, Thyrotropic adenomas	ATG, Subcutaneous, SR, Intramuscular	ATG 23–30 days, SR 5 days	ATG 1× per 4 weeks, SR 1× per 7–14 days
Pasireotide (SOM-230, Signifor)	Novartis Pharmaceuticals	SSTR1, -2, -3, -5	Acromegaly, Cushing's disease	IR, Subcutaneous, LAR, Intramuscular	IR, 12 h, LAR, 16 days	IR, 2× per day, LAR, 1× per 4 weeks

IR, immediate-release; LAR, long-acting release; ATG, autogel; SR, slow-release. The information in this table is derived from https://www.medicines.org.uk/emc/. Year of last update 2016 for octreotide and lanreotide; 2017 for pasireotide; Year of access 2018.

SST analogues are octreotide, lanreotide and pasireotide. There is ample clinical experience with these drugs, as these drugs have been used for many years in neuroendocrine disorders like acromegaly to inhibit growth hormone secretion, but also to treat neuroendocrine tumours by inhibiting serotonin secretion. Different SST analogues, administration routes (intravenous, subcutaneous, intramuscular) and dosing regimens are used for the various indications (Table 1).

Table 2. Most common adverse effects of SST analogues

System	Adverse effect
Gastrointestinal	Diarrhoea[++], abdominal pain[++], nausea[++], constipation[++], flatulence[++], dyspepsia[+], vomiting[+], abdominal bloating[+], steatorrhoea[+], loose stools[++], discoloration of faeces[+]
Hepatobiliary	Cholelithiasis[++], cholecystitis[+], biliary sludge[+], hyperbilirubinaemia[+], acute pancreatitis[−−]
Glucoregulation	Hyperglycaemia[+], diabetes mellitus[+]
Cardiac	Bradycardia[+], tachycardia[−−], prolonged QT intervals[−]

[++]very often, >10%; [+]often, 1–10%; [−]sometimes, 0.1–1%; [−−]rarely, 0.01–0.1%.

Adverse effects of SST analogues

SST analogues, in general, elicit similar adverse effects, because they mostly interact with the same receptors. Most of the receptors are found in the gastrointestinal tract and consequently adverse effects are predominantly related to this tract. Pasireotide, however, seems to lead to hyperglycaemia and ECG abnormalities more often than the other SST analogues [39]. Interestingly, most of these adverse effects become milder or disappear after longer duration of the treatment. This may be caused by receptor desensitization, as described earlier. The most common adverse effects are summarized in Table 2.

Besides these adverse effects, there may also be ADPKD-specific adverse effects. In a recent randomized study [40], it became apparent that the use of SST analogues was associated with the development of hepatic cyst infection in patients with ADPKD. In the Developing Interventions to halt Progression of Autosomal dominant polycyctic Kidney disease (DIPAK) 1 trial, which included patients with later-stage ADPKD, 9 hepatic cyst infection events in 8 subjects were noted in the 153 subjects that received lanreotide during 2.5 years of treatment and none in the 152 subjects of the control group. A literature review revealed that hepatic cyst infections also occurred in other studies with SST analogues in patients with ADPKD or PLD. Most of these complications were seen with lanreotide, but hepatic cyst infections have also been observed with other SST analogues [41]. The exact mechanism of hepatic cyst infections with SST analogues is unknown, but it has been suggested that a reduction in bile flow may play a role. Also, a history of hepatic cyst infections seems relevant. After a protocol amendment excluding patients with a history of hepatic cyst infections, the incidence of this complication decreased significantly in the aforementioned trial.

STUDIES WITH SST ANALOGUES IN ADPKD

Several preclinical and clinical studies have been conducted that studied the efficacy of SST analogues to inhibit cAMP production, hepatic and kidney cyst growth and renal function decline. It is remarkable that the first clinical study was performed before any preclinical data were available. The rationale for the first clinical study by Ruggenenti *et al.* [42] was based on an observation in a single ADPKD patient that received octreotide for acromegaly. In this specific patient, a potential beneficial effect of SST was considered because kidney function and kidney volume remained stable during treatment with octreotide. As there was extensive experience with SST analogues in the treatment of neuroendocrine disorders, a Phase III study with an SST analogue as treatment for ADPKD was started immediately, not awaiting pre-clinical data.

Pre-clinical studies

Only six experimental studies have been published that investigated the effects of SST analogues in experimental PKD. The results of these studies are summarized in Table 3 [43–48]. The first study, published in 2007 by Masyuk *et al.* [43], showed in an *in* vitro model of cystogenesis that octreotide inhibited cAMP levels by 35%. *In vivo* kidney and hepatic cyst growth, fibrosis and mitotic indices were reduced in the polycystic kidney (PCK) rat by 20–60%. After that landmark study, Spirli *et al.* [44] described in 2012 that the combination of octreotide and sorafenib (an inhibitor of tyrosine protein kinases and Raf kinases), but not octreotide alone, was effective in reducing the cystic area and proliferation in polycystin-2-defective mice. In 2013, Tietz Bogert *et al.* [45] developed a hepatic cyst model with zebrafish embryos. Hepatic cystogenesis was inhibited when these embryos were exposed to the SST analogue pasireotide. In the same year, Masyuk *et al.* [46] found that octreotide and pasireotide reduced intracellular cAMP levels and cell proliferation, affecting cell cycle distribution, decreasing the growth of cultured cysts *in vitro* and inhibiting hepatorenal cystogenesis *in vivo* in PCK rats and in *PKD2(WS25/-)* mice (a model for ADPKD). In that study, pasireotide in the applied dose was more potent than octreotide. In 2015, Hopp *et al.* [47] found in a hypomorphic *PKD1* model that treatment with tolvaptan and pasireotide alone markedly reduced renal cyst progression and that the combination showed an additive effect. Furthermore, combination treatment significantly reduced cystic and fibrotic volume and decreased cAMP to wild-type levels. They also showed that hepatic hypertrophy could be corrected with pasireotide. Lastly, Kugita *et al.* [48] recently investigated the efficacy of treatment with pasireotide and octreotide in PCK rats. They showed that pasireotide and the combination of pasireotide with octreotide lowered kidney and liver weight, cystic volume and renal cAMP levels. Treatment with octreotide alone did not have an effect. In combination, these preclinical studies suggest that SST analogues can inhibit both renal and hepatic cystogenesis and therefore may inhibit ADPKD progression. These studies also point to possible differences in efficacy between SST analogues.

Clinical studies

At the moment, seven clinical studies have been completed with SST analogues in ADPKD patients. The results of these studies are summarized in Table 4 [42, 49–54]. These studies have uniformly shown that SST analogues can slow the growth in total liver volume. These studies also confirm the hypothesis that SST analogues have a beneficial effect on the renal cystic phenotype. Growth in total kidney volume (TKV) in subjects using SST analogues was less than in subjects using placebo in

Table 3. Summary of experimental studies performed with SST analogues in PKD/PLD models

References	SST analogue	Experimental design	Outcome Renal phenotype	Liver phenotype
Masyuk *et al.* [43]	Octreotide	*In vitro: N* = 15 PCK bile ducts grown in 3-dimensional culture with Oct or vehicle *In vivo: N* = 60 PCK rats treated with Oct or vehicle 4–16 weeks	*In vitro:* NA *In vivo:* 19–39% reduction in kidney weight, renal cystic volume and renal fibrosis	*In vitro:* 35% reduction in cAMP levels 44% reduction in cyst growth *In vivo:* 32–39% reduction in cAMP levels 20–60% reduction in cyst growth, fibrosis and mitotic indices
Spirli *et al.* [44]	Octreotide (and sorafenib)	*In vivo: N* = 32 Pkd2cKO mice treated with vehicle, sorafenib, Oct or sorafenib/Oct 8 weeks	*In vivo:* NA	*In vivo:* Sorafenib/Oct: Reduction in liver cyst volume, proliferation (Ki67), liver weight and increased apoptosis (CC3)
Tietz Bogert *et al.* [45]	Pasireotide	*In vivo: N* = 800 Zebrafish injected with morpholinos *sec63, prkcsh* and *pkd1a* (PLD model) or control buffer and treated with pasireotide, VK3 or 4-PBA	*In vivo:* NA	*In vivo:* Reduction of hepatic cystogenesis
Masyuk *et al.* [46]	Octreotide and pasireotide	*In vitro:* Cholangiocytes from control and PCK rats, healthy humans and ADPKD patients, normally cultured or in Oct or pasireotide	*In vitro:* NA	*In vitro:* Reduction of cAMP levels, cell proliferation (Oct 9.6–18.4%/pasireotide 18.6–33.7%) and hepatic cyst expansion (Oct 1.6–2.3x/ pasireotide 2.2–4.7x)
		In vivo: N = 27 PCK rats and *N* = 14 Pkd2^{ws25/-} mice treated with Oct, pasireotide or vehicle 6 weeks	*In vivo:* Reduction of kidney weight (Oct 16%/pasireotide 20%), cystic volume (Oct 19%/pasireotide 30%), fibrotic volume (Oct 18%/ pasireotide 25%)	*In vivo:* Reduction of liver weight (Oct 9%/pasireotide 16%), cystic areas (Oct 24%/pasireotide 36%), fibrotic areas (Oct 10%/ pasireotide 19%)
Hopp *et al.* [47]	Pasireotide (and tolvaptan)	*In vivo: N* = 81 Pkd1(RC/RC) mice receiving no treatment, tolvaptan, pasireotide or tolvaptan/pasireotide 5 months	*In vivo:* Reduction in kidney weight, cystic volume, fibrotic volume and cAMP level with tolvaptan/pasireotide >tolvaptan or pasireotide	*In vivo:* Reduction of hepatocyte hypertrophy by pasireotide
Kugita *et al.* [48]	Octreotide and pasireotide	*In vivo: N* = 24 PCK rats treated with vehicle, Oct, pasireotide or Oct/pasireotide 12 weeks	*In vivo:* Reduction of kidney weight, cystic volume, proliferation (Ki67) and cAMP levels in pasireotide or Oct/ pasireotide	*In vivo:* NA

Oct, octreotide; NA, not applicable.

most studies. However, results with respect to the rate of decline in kidney function are equivocal. From the seven clinical studies, there were a number that showed a beneficial effect on the rates of growth in total kidney and liver volume, but also a greater decline in estimated GFR (eGFR) with SST analogues than with placebo [42, 53]. However, these studies were all underpowered and of too short a duration to allow firm conclusions on the renoprotective effect of SST analogues. Later, the A Long-Acting somatostatin on DIsease progression in Nephropathy due to autosomal dominant polycystic kidney disease (ALADIN) study was published, which included more subjects ($n = 79$) and was of longer duration (3 years) [52]. For the pre-specified efficacy outcomes [absolute change in TKV at Year 3 and slope of measured GFR (mGFR) from Years 0 to 3], no significant benefit of treatment with octreotide was observed [52]. That no beneficial effect of SST analogues was observed on

the rate of kidney function decline in these studies may have several explanations. First, the effect of SST analogues on the rate of decline in kidney function is difficult to assess, because these drugs induce a biphasic effect on GFR. Shortly after the start of treatment, an alleged haemodynamic, reversible decrease in GFR is observed. Theoretically, a slower decline in the rate of annual GFR loss occurs thereafter that reflects the structural beneficial effect that is obtained with the SST analogue. Such a biphasic effect on eGFR has been observed with tolvaptan in ADPKD [6, 55] and with angiotensin-converting enzyme inhibitors in other renal diseases. As well, the clinical studies with SST analogues in ADPKD, which were of short duration in general, show a greater decline in eGFR with SST analogues than with placebo. When studying a drug with a biphasic effect on GFR, its chronic structural renoprotective effect should be investigated by studying the change in kidney function on

Table 4. Summary of studies performed with SST analogues in ADPKD

References	SST analogue	Trial design	Effect versus control on GFR = kidney function	TKV	TLV
Ruggenenti et al. [42]	Octreotide	$N = 14$ ADPKD Cross-over 6 months	Not significant Pla: −0.2 versus Oct: −5.5 mL/min/1.73 m² NS	Significant benefit Pla: +6.6 versus Oct: +3.6% P < 0.05	Significant benefit Pla: +1.2 versus Oct: −4.4% P < 0.05
van Keimpema et al., 2009 [49]	Lanreotide	$N = 54$ PLD/ADPKD RCT 6 months	Not stated	Benefit Pla: +3.5 versus Lan: −1.5% P = 0.08	Significant benefit Pla: +1.6 versus Lan: −2.9% P < 0.01
Chrispijn et al., 2012 [50]	Lanreotide	$N = 41$ PLD/ADPKD Open label FU of Keimpema, 2009 12 months	No control group Not stated	No control group Benefit Lan: −1% NS	No control group Significant benefit Lan: −4% P < 0.05
Hogan et al., 2012 [51]	Octreotide	$N = 42$ PLD/ADPKD RCT 12 months	Not significant Pla: −7.2 versus Oct: −5.1% NS	Significant benefit Pla: +8.61 versus Oct: +0.25% P < 0.05	Significant benefit Pla: +0.92 versus Oct: −4.95% P < 0.05
Caroli et al. [52]	Octreotide	$N = 79$ ADPKD RCT 3 years	Primary analysis (slope Years 0–3) Pla: −4.95 versus Oct: −3.85 mL/min/1.73 m²/year NS Post hoc analysis (slope Years 1–3) Significant benefit Pla: −4.32 versus Oct: −2.28 mL/min/1.73 m²/year P < 0.05	Primary analysis (absolute change at Year 3) Pla: +454 versus Oct: +220 mL P = 0.25 Post hoc analysis (slope Years 0–3) Significant benefit Pla: +152 versus Oct: +77 mL/year P < 0.05	Significant benefit (Pisani, 2016) Pla: +6.1 versus Oct: −7.8% P < 0.05
Gevers et al. [53]	Lanreotide	$N = 43$ ADPKD Uncontrolled 6 months	No control group Lan: −3.5% P < 0.001	No control group Lan: −1.7% P < 0.01	No control group Lan: −3.1% P < 0.001
Meijer et al., 2018 [54]	Lanreotide	$N = 305$ ADPKD Open-label RCT 2.5 years	Not significant Co: −3.46 versus Lan: −3.53 mL/min/1.73 m²/year NS	Benefit Co: 5.56 versus Lan: 4.15% P = 0.02	Overall Co: 2.9 vs. Lan: −0.9%, P = 0.001 Subgroup with liver volume > 2L Co: 3.92 vs. Lan: −1.99%, P < 0.001
Van Aerts et al., in press					

Pla, placebo; Oct, octreotide; Lan, lanreotide; co, control; NS, not significant TLV, total liver volume.

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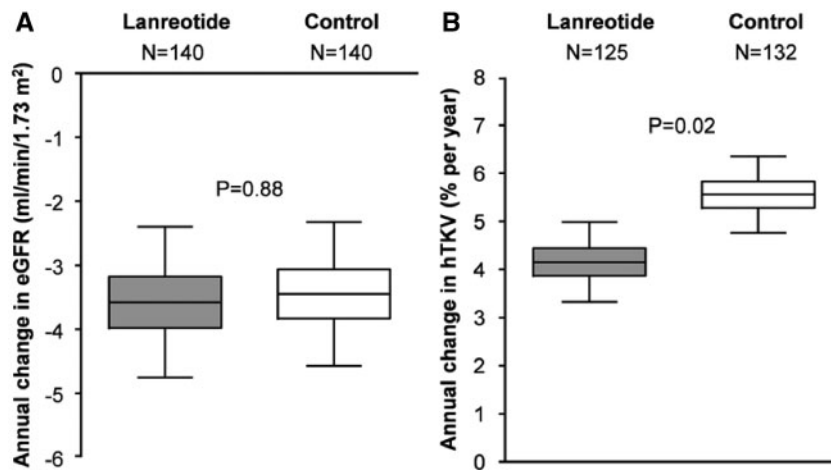
FIGURE 3: Effect of the SST analogue lanreotide 120 mg subcutaneously once every 4 weeks compared with control treatment in a 2.5-year prospective trial in patients with ADPKD. (**A**) The change in eGFR 16 weeks after the last dose of lanreotide (measured at a post-treatment visit) compared with the baseline pre-treatment value [lanreotide −3.58 versus control −3.45, difference −0.13 (95% CI −1.76–1.50) mL/min/ 1.73 m^2/year, P = 0.88]. (**B**) The change in height-adjusted TKV (hTKV) measured at the same time points [lanreotide 4.15 versus control 5.56, difference −1.33%/year (95% CI −2.41 to −0.24), P = 0.02]. Boxplots show predicted mean and 25 and 75th percentiles and the lower and upper ends of the error bars show predicted 2.5 and 97.5th percentiles, respectively, as derived from mixed model analyses (from reference Meijer *et al.*, *JAMA* in press).

treatment in a trial of longer duration. A *post hoc* analysis of the ALADIN study indeed suggested that octreotide had a beneficial effect on the slope in mGFR decline on treatment (Years 1–3). Unfortunately, there were differences in baseline characteristics between the two study groups in this trial that favoured the octreotide group. Given these reasons, a definitive conclusion on the renoprotective effect of SST analogues could still not be reached. A larger, open-label randomized controlled trial (RCT) was performed by our study group, investigating the effects of 2.5 years of treatment with the SST analogue lanreotide in 305 ADPKD patients with an eGFR or 30–60 mL/min/ 1.73 m^2 the DIPAK 1 study [54]. Given the aforementioned experience, change in kidney function on treatment was chosen as the primary outcome. This study confirmed that lanreotide significantly reduced liver and kidney cyst growth. However, no attenuation of eGFR slope was observed. The rate of eGFR loss on treatment, the primary endpoint of the study, was −3.53 with lanreotide versus −3.46 mL/min/1.73 m^2/year in the control group. The difference between both groups was only −0.08 [confidence interval (95% CI) −0.71–0.56] mL/min/1.73 m^2/ year and not significant (P = 0.81). When the secondary endpoint, annual rate of eGFR loss, was calculated using only the pre- versus post-treatment eGFR values, no effect of lanreotide was observed (Figure 3, left panel). A prespecified subgroup analysis did not provide evidence that lanreotide improved the primary outcome in any of the subgroups studied. For TKV, however, the results were beneficial. The rate of change in height adjusted TKV (hTKV) between the pre- and post-treatment visit was significantly lower in the lanreotide group: 4.15%/year (95% CI 3.33–4.99) versus 5.56 (95% CI 4.76–6.36) in the control group [difference −1.33%/year (95% CI −2.41 to −0.24), P = 0.02], corresponding with a 24% reduction in hTKV growth rate (Figure 3, right panel). The benefit of lanreotide on hTKV growth was observed in all subgroups tested. The change in hTKV was also assessed using data from the magnetic

resonance imaging (MRI) at the end of the treatment period instead of the MRI at the post-treatment visit. In that case, the difference between both groups in the hTKV growth rate was stronger [−2.14%/year (95% CI −3.14 to −1.12, P < 0.001), indicating that after stopping lanreotide treatment, some rebound occurs, but a beneficial effect on kidney volume is maintained even after stopping treatment. Currently there is one clinical study ongoing with SST analogues in ADPKD patients and two studies that are finalized but not yet published (Table 5) [56–58].

IS THERE A PLACE FOR SST ANALOGUES IN ADPKD?

The DIPAK 1 study provides convincing evidence that lanreotide does not slow the rate of renal function decline in later-stage ADPKD. Can we, therefore, state that there is no role for SST analogues in the treatment of the renal phenotype of ADPKD? This may not necessarily be true since lanreotide did show an effect on growth in TKV and liver volume. This is surprising because it is a paradigm in nephrology that effects on TKV can be used as a surrogate marker for effects on kidney function. The question arises whether the divergent treatment effects on GFR and TKV are explained by trial design or are they drug specific?

In this respect, an important difference in trial design between the DIPAK 1 and ALADIN studies was that the ALADIN study had mGFR as the outcome (plasma clearance of the exogenous filtration marker iohexol), whereas the DIPAK 1 study used GFR estimated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine formula. As is generally known, creatinine is not only filtrated by the glomerulus, but also partially secreted by renal tubular cells. This is accounted for in the CKD-EPI formula [59]. Because ADPKD is a disease characterized by an increase in renal tubular cell

Table 5. Summary of ongoing or finalized but as yet unpublished studies with SST analogues in ADPKD [56–58]

Institute	SST analogue	Trial design	Inclusion criteria	Clinical endpoint	ClinicalTrials.gov identifier
Mayo Clinic, Rochester, MN, USA	Pasireotide 60 mg s.c., 1×/28 days	$N = 48$ RCT 12 months	PLD >4000 mL Age >18 years eGFR >30 mL/min/1.73 m^2	Change in TLV	NCT 01670110
Mario Negri Institute, Milan, Italy	Octreotide 40 mg s.c., 1×/28 days	$N = 100$ RCT 36 months	ADPKD Age >18 years eGFR 15–40 mL/min/1.73 m^2	Change in mGFR Change in TKV	NCT 01377246
Necker Hospital, Paris, France	Lanreotide 120 mg s.c., 1×/28 days	$N = 180$ RCT 36 months	ADPKD Age >18 years eGFR 30–89 mL/min/1.73 m^2	Change in mGFR	NCT02127437

s.c., subcutaneous.

mass, it may be that the GFR estimation equations perform less well in patients with this disease. Indeed, one study concluded that in ADPKD, equations used to estimate GFR may be less reliable and may fail to detect changes in GFR over time [60]. Two other reports, however, showed that equations to estimate GFR perform as well in ADPKD as in non-ADPKD CKD patients [61, 62]. More importantly, when alternative measures for kidney functions were used in the DIPAK 1 study, such as GFR estimated with plasma cystatin C, 24-h urinary creatinine clearance or serum urea, similar results were obtained. These latter data indicate that the results of the DIPAK 1 study are robust.

A second option related to trial design of the DIPAK 1 study, which may explain why lanreotide did not preserve kidney function, could be that patients were studied with later-stage ADPKD. It could be that in later-stage ADPKD, SST receptors are expressed less because of fibrosis formation, as has been shown for the vasopressin V2 receptor in animal experiments, [63] or that patients reached a point of 'no return' beyond which other disease processes have become important and cannot be improved by an SST analogue [64]. However, subgroup analysis of the DIPAK 1 study showed no differences in treatment effect between CKD Stages 3a and 3b, but in earlier disease the situation may be different.

The third option related to trial design could be that the dosage of lanreotide was suboptimal in the DIPAK 1 study. This is less likely because a dosage of lanreotide was used that has been shown to be effective in neuroendocrine disorders. However, it may be that the expression of SSTRs in the kidney is too low for SST analogues to be effective. As far as know, only one study, performed by our study group, has investigated SSTR expression specifically in ADPKD. We observed in two conditional *Pkd1* models that SSTR2 expression levels are reduced during kidney cyst growth. In addition, we saw a significant decrease in SSTR2 expression in epithelia of dilated tubules and cystic epithelia in mice with end-stage PKD compared with wild-type mice. Data of human biopsies, however, are ambiguous [25]. Importantly, in the DIPAK 1 study, there was a beneficial effect of lanreotide on TKV growth. This suggests that SSTRs are expressed in the human ADPKD kidney.

The question then emerges whether the results of the DIPAK 1 study are specific for lanreotide or class related? Octreotide, for example, investigated in the ALADIN study, has slightly more affinity for SSTR2 and SSTR3 and slightly less affinity for SSTR5 as compared with lanreotide [39]. Whether this results in a difference in clinical efficacy in ADPKD is doubtful, because octreotide has been shown to be equally effective in the treatment of acromegaly compared with lanreotide, and both drugs elicit similar adverse effects [65]. Pasireotide, on the other hand, has more marked differences in receptor affinity compared with lanreotide, which more likely could result in a different treatment effect in ADPKD [66]. Also, pasireotide has been shown to be effective in the treatment of Cushing's disease in contrast to octreotide [67], to be more effective in the treatment of acromegaly compared with octreotide [68] and to be more effective than octreotide in two experimental models for ADPKD [46, 48]. More severe hyperglycaemic side effects and frequent ECG abnormalities [39], however, are expected to limit the widespread clinical use of pasireotide for ADPKD, a disease for which lifelong treatment is needed.

Taking the above discussion into account, it may also be argued that treatment effects on GFR and TKV are unrelated (see also Figure 3). That is remarkable, because it is a paradigm that in ADPKD, TKV is related to GFR and can be used as a surrogate outcome, especially in trials in early stages of the disease. However, it could also be that lanreotide has an intrinsic nephrotoxic effect that offsets any potential benefit that could be obtained via its effect on hTKV. However, such a nephrotoxic effect is not known from the literature in non-ADPKD patients. Other potential explanations could be that the effect on TKV growth was not large enough to translate into a functional benefit in the duration of the clinical trial, that it takes more time before a benefit on TKV translates into a benefit on the rate of GFR loss or that patients were included with later-stage ADPKD, in whom growth in TKV may have a less dominant role in causing eGFR loss than in earlier-stage disease.

For now, we may conclude that there is no role for SST analogues to preserve kidney function in ADPKD, unless future data prove differently. However, the available evidence shows that SST analogues do have a beneficial effect on the growth of TKV and liver volume. ADPKD patients with a high intra-abdominal volume and related symptoms may therefore be the target group for treatment with these agents, to prevent or postpone the need for liver transplantation. Because of the possible higher incidence of hepatic cyst infections with SST analogues, it seems wise to exclude patients with a history of hepatic cyst infection from such treatment.

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CONCLUSIONS

Among the pivotal detrimental factors in the pathophysiology of ADPKD are elevated cAMP levels. Although therapies to slow the rate of disease progression in ADPKD have emerged, there is still an important unmet need for new therapies. In this review, we show that SST analogues are theoretically promising as therapeutic agents since these drugs inhibit cAMP production. Both preclinical and preliminary clinical studies suggest beneficial effects of SST analogues in the treatment of ADPKD. However, a recent large-scale RCT showed no beneficial effect of lanreotide on the rate of kidney function decline in patients with later-stage ADPKD despite a beneficial effect on kidney growth. Results of ongoing trials should be awaited before definitive conclusions can be drawn with respect to renoprotection, because results may be different with other SST analogues or in patients with earlier-stage disease. For now, treatment of ADPKD patients with these agents should be limited to patients with a high intra-abdominal volume and related symptoms.

CONFLICT OF INTEREST STATEMENT

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