Title: Metabolic effects of Secretin

Author names: Revathi Sekar[a], Billy K.C. Chow[a]

Affiliations: [a]School of Biological Sciences; The University of Hong Kong, Pokfulam, Hong Kong

Corresponding author: **Prof. Billy K. C. Chow**, School of Biological Sciences, The University of Hong Kong, Pokfulam Road, Hong Kong. E-mail: bkcc@hku.hk Phone: 852-22990850. Fax: 852-25599114

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Abstract

Secretin (Sct), traditionally a gastrointestinal hormone backed by a century long research, is now beginning to be recognized also as a neuroactive peptide. Substantiation by recent evidence on the functional role of Sct in various regions of the brain, especially on its potential neurosecretion from the posterior pituitary, has revealed Sct's physiological actions in regulating water homeostasis. Recent advances in understanding the functional roles of central and peripheral Sct has been made possible by the development of Sct and Sct receptor (SctR) knockout animal models which have led to novel approaches in research on the physiology of this brain-gut peptide. While research on the role of Sct in appetite regulation and fatty acid metabolism has been initiated recently, its role in glucose homeostasis is unclear. This review focuses mainly on the metabolic role of Sct by discussing data from the last century and recent discoveries, with emphasis on the need for revisiting and elucidating the role of Sct in metabolism and energy homeostasis.

Keywords: Secretin (Sct); metabolic role; food intake; glucose homeostasis; fatty acid metabolism; energy homeostasis.

1. Introduction

In a fascinating experiment by Bayliss and Starling in 1902, a loop of jejunum was enervated in an anaesthetized dog such that it was connected to rest of the body only by blood vessels, and

when acid was infused into the lumen of the isolated jejunum, pancreatic secretion was still found to occur [7]. This result differed from the existing idea then, that pancreatic secretion was controlled only by neural vagus stimulation. A chemical substance travelling through blood to cause this secretion was proposed and the first ever hormone secretin (Sct) was discovered marking the establishment of the field of Endocrinology. With such great historic importance and being the longest known hormone, Sct has been researched for a century and a decade now during which it has been purified, structurally determined, and its receptor identified, cloned and characterized [19]. Sct is best known for its action in the exocrine pancreas, stimulating secretion of bicarbonate, water, and electrolytes from pancreatic ductal epithelial cells. It is also associated with bile release from the liver, and gastric pepsin release and gastric acid inhibition from the stomach [54]. Recent evidence has established Sct as a neuropeptide while its metabolic role will be reviewed here in this article.

2. Secretin and feeding

2.1 Early studies

Early evidences that Sct is released after ingestion of a meal had come in the late 1970s and early 1980s. Pelletier *et al.* found that Sct is released intermittently after a liquid meal in humans and they proposed that this increase would be sufficient for potentiating bicarbonate release [84]. A study in 1979 in dogs also reported that plasma immuno reactive Sct levels are significantly increased after a meat meal [49]. Following this, several other studies have also confirmed the rise of plasma Sct concentrations after ingestion [26, 43, 56, 70]. At around the same time, studies were also conducted on effects of Sct in suppressing feeding. Glick *et al.* in 1971 [40] reported the

effects of CCK and Sct in feeding behavior and concluded that neither of the peptide had any effect. Two years later, there was another study reporting that, among these two peptides, only CCK was able to reduce food intake in rats [39]. Since then, there were contradictory reports regarding the role of Sct in satiety showing that Sct had no effect on feeding behavior in rat [64] and sheep [25], while Grovum [42] suggested that intravenous infusion of Sct could reduce appetite in fasted sheep. With these contrasting evidences had come a long halt in studies on role of Sct in appetite control, while CCK, studied along with Sct in most of these initial reports, is now one of the most researched peptides for its role in the inhibition of food intake.

2.2 Secretin a neuropeptide

In 1981, Charlton *et al.* [17] and O'Donohue *et al.* [79] found Sct immuno-reactivities in various regions of rat and pig brains by radio immuno-assay and high-pressure liquid chromatography. This was followed by another report in 1984 [92] showing that Sct-like immuno-reactivities are specifically high in rat hypothalamus and pituitary. Simultaneously, Propst *et al.* demonstrated cAMP production by Sct in neuroblastoma–glioma hybrid cells [86] and the same phenomenon was also shown to occur in cultured mouse brain cells [107], rat brain slices [37], hypothalamic and hippocampal regions [48], and in rat superior cervical ganglion (SCG) [46]. A study by Yung *et al.* [114] in 2001 showed that Sct is localized in somatodendritic area of Purkinje cells of cerebellar cortex and that it functions as a retrograde messenger to facilitate GABA transmission from basket cells to Purkinje neurons. This sealed any doubts in the neuroactive role of Sct. Fuelled by its proposed therapeutic advantage in autism, Sct was then further found

to be localized in cerebral cortex, amygdaloidal complex, hippocampus, hypothalamus, brain stem, and its possible neuroactive roles in these regions were also discussed [53, 57, 99, 110]. It was also found that peripheral Sct induced an increase in the Fos-positive neurons in many brain regions like amygdala (CeA), area postrema (AP), nucleus tractus solitarius (NTS), locus coeruleus (LC), Barrington's nucleus (Bar), parabrachial nucleus (PBel), and arcuate nucleus (Arc) which is the centre for regulating feeding behavior. This increase in the Fos expression was completely abolished by subdiaphragmatic vagotomy indicating that peripheral Sct might communicate to the brain through the vagal pathway [113]. Incidentally, Sct was also shown to activate the vagal afferent neurons through its receptor [62], proving that a communication pathway between the gut and the brain by Sct exists. In the brainstem, Sct and SctR mRNA were shown to be expressed in AP and NTS [99]. Along with increasing c-Fos expression, Sct could also activate tyrosine hydroxylase in NTS and depolarize NTS neurons [113]. Sct was also shown to be endogenously released from the hypothalamic explants when depolarized. This K^+-induced release was suggested to be associated with voltage-gated sodium and calcium channels [22]. This growing and compelling evidence on the involvement of Sct in key regions of feeding centers, including Arc, has led to recent research on the central and peripheral actions of Sct in modulating food intake [18].

2.3 Secretin inhibits food intake

Cheng *et al*. [18] have shown that peripheral and central administration of Sct reduces food intake in fasted mice and this effect was specific to its receptor as the SctR knockout mice did not express the anorectic effect. SctR belonging to the glucagon receptor family or the class II

family of G protein-coupled receptors has a strong affinity for Sct and lower affinity for vasoactive intestinal peptide (VIP) [34, 47]. Since VIP binds to SctR at pharmacological doses, the possibility of cross talk of these peptides on the anorectic role of Sct is minimal. Besides, VIP has no reported effects on food intake in mice [73] while Sct's anorectic effect has been shown clearly to be specific to its receptor with the use of SctR-knockout mice [18]. Sct reduced food intake at 0.15 nmol (150 pmol) and 1 nmol by intracerebroventricular (i.c.v) injections and at 5 nmol (about 0.5 mg/kg) by intraperitoneal (i.p) injections, while leptin reduced food intake at 3 pmol and 60 pmol by i.c.v [71] and 0.12 mg/kg by i.p [6]. CCK-8 exhibits its anorectic properties at 0.03 nmolby i.c.v and 1 nmol by i.p [45]. Although higher concentrations of Sct has been used, it has been ensured that the dosage used is not pharmacological by monitoring plasma Sct levels 2, 4 and 6 hours after injection.

By immuno-histochemical and *insitu* hybridization staining techniques, it was shown that Sct and its receptor are expressed in hypothalamic Arc and para ventricular nucleus (PVN). It was also shown that Fos-positive cells in these brain regions are dramatically increased after i.p or i.c.v injection of Sct. Furthermore, peripheral and central Sct also caused a significant increase in proopiomelanocortin (POMC) mRNA and decrease in the agouti-related protein (AgRP) transcript levels in Arc as assessed by laser captured microdissection (LCM)-coupled to quantitative real-time PCR. POMC neurons in the Arc were shown to be colocalized with both the SctR and Fos-positive neurons in response to i.p and i.c.v Sct. Thus, it was proposed that Sct activates POMC neurons to bring about its anorectic effect. Indication for the involvement of melanocortin system was demonstrated by the increased transcript levels of melanocortin-4 receptor (Mc4R) in PVN after i.p and i.c.v Sct, and also by the attenuation of both peripheral and central Sct-induced anorexia after administration of SHU9119, a Mc4r antagonist, in the PVN.

Peripheral Sct was shown to inhibit food intake without causing conditioned taste aversion indicating a direct effect of Sct on satiety control [18]. However, whether central Sct also possesses the same characteristics must be studied, since the conditioned taste aversion caused by hormones like glucagon like peptide-1 (GLP-1) is different with respect to the site of injection in brain, indicating distinct receptor population could mediate different functions [111]. In teleosts, Sct gene has not been found, while other members of same peptide family including glucagon like peptide (GLP) and glucagon, as well as other peptides such as alpha-MSH and CCK have also been found to exhibit anorectic actions [109]. The mechanism for Sct-induced anorexia needs to be investigated further, while it is quite clear that both central and peripheral Sct utilizes a common melanocortin pathway to exert their effects. It is well known that Sct is stimulated from the duodenal S cells after a meal and it is highly plausible that this increase in plasma Sct at the periphery communicates with the brain to inhibit food intake. But the recent evidence on endogenous release of Sct in hypothalamus [22] implies that a role for central Sct cannot be ruled out. Mode of communication to the brain by peripheral Sct is likely to be vagal-dependant as Sct and its receptor are localized in the vagal afferent neurons, and central Fos expression by peripheral Sct is attenuated after vagotomy. A similar reduced anorectic action of peripheral Sct was also observed after vagotomy indicating the involvement of vagal route [116]. Although Sct has been shown to cross the blood-brain barrier [5], the possibility of this route for peripheral Sct to exert its anorectic effect is unlikely since attenuated effects were observed after vagotomy as mentioned. On the other hand, we found that i.c.v-Sct was able to inhibit food intake even after vagotomy [116], clearly suggesting a central action of Sct in controlling food intake. These data pave the way for Sct to be included in the research on an integrated pathway of nutrient and fluid balance. Circumventricularorgans (CVO) in the brain, especially the

subfornical organ (SFO), are being proposed for integration of ingestion behavior [38, 108]. SFO in the past is known to be the key centre for modulating drinking behavior, but it is now beginning to be proposed as a feeding centre as well [95]. Studies of ghrelin and amylin (orexigenic and anorectic peptide, respectively) have shown that they stimulate different subpopulation of neurons in the SFO, suggesting that SFO might be the center to influence hypothalamic regulation of feeding [87]. Sct and its receptor are shown to be expressed in SFO and Sct also stimulates cFos expression in SFO neurons [21]. Central Sct is recently known to play an indispensible role in mediating ANGII-stimulated water homeostatic responses in the brain [58] and now with this new evidence on its anorectic effect, Sct could as well be involved in an integrated pathway modulating ingestion behavior.

3. Secretin and Fatty acid metabolism

Evidences for stimulation of lipolysis by Sct could be dated back to 1969 [91] when Daniel Rudman and Alejandro E. Del Rio reported that synthetic porcine Sct peptide fragment could stimulate lipolysis in isolated fat cells from rats. In 1970, two separate reports by Rodbell *et al.* and Butcher *et al.* confirmed that Sct stimulates lipolysis and that Sct increases the adenylcyclase and cAMP levels in rat fat cells [13, 90]. Since then, there were inconsistent evidences. Sct was shown to be unable to activate lipolysis in chicken and mouse fat cells [24, 36]. Another report by Ng TB in 1990 [75] showed that Sct could lead to lipolysis in adipose cells of several mammalian species including rat, mouse, hamster, guinea pig and rabbit, and that Sct was able to suppress basal- and insulin-stimulated lipogenesis. Other reports suggested that Sct could not

stimulate *in-vitro* glycerol release in isolated human adipose cells [10] . It was also reported that Sct could not stimulate free fatty acid release from healthy humans *in vivo* [89]. With these contradictory reports, the role of Sct in adipocyte metabolism had not been addressed until a very recent research by Miegueu *et al*. [68]. In their studies, Miegueu *et al.* had not only evaluated the potential of Sct in stimulating lipolysis, but also found that it could stimulate fatty acid and glucose uptake in both 3T3 L1 adipocytes and isolated rat adipocytes *in vitro*. Lipolysis, which was measured by the amount of glycerol released, had increased in the presence of Sct, while non-esterified fatty acid (NEFA) accumulation declined in the media with Sct-treated 3T3 L1 cells. When tested for uptake of fatty acid, Sct was shown to significantly stimulate fatty acid uptake and also expression of genes related to lipid uptake and storage, including fatty acid binding protein 4 (FABP4), diglyceride acyltransferase-1(DGAT-1), cluster of differentiation 36 (CD36) and caveolin 3 (Cav3). Long-term incubation with Sct resulted in augmentation of the triglyceride storage mass indicating increased lipid storage. Glucose uptake was also increased significantly in the presence of Sct along with the gene expression of glucose transporter type 4 (GLUT4). Sct caused an increase in mitochondrial activity, thymidine incorporation and CCAAT/enhancer-binding protein-beta(C/EBP-β) expression. SctR's expression was also higher during differentiation, indicating that Sct could function to stimulate proliferation and differentiation of the cultured adipose cells. But the key finding by Miegueu *et al.* is that Sct, while stimulates lipolysis, simultaneously increases lipid uptake thereby enhancing substrate cycling [68]. VIP , the peptide that interacts with SctR with low affinity, has also been shown to stimulate lipolysis but its lipolytic effects are mediated specifically by the VPAC2-R subtype [2]. VIP have been shown to stimulate lipolysis at concentrations from 0.1 nM to 100 nM in isolated rat adipocyte while Sct could also stimulate spontaneous lipolysis at 0.1 nM in isolated rat

adipocyte *in vitro* [68]. This indicates that Sct is closely related to the regulation of highly controlled adipose metabolism which remains to be tested *in vivo*.

Metabolic role of Sct in starvation has long been suggested since 1975. Many studies in human subjects have been conducted and it has been found that circulating plasma Sct levels rose significantly in fasted subjects [44, 67, 81, 96]. While data from humans were consistent, in dogs they were contradictory [66, 93]. This rise in plasma Sct was postulated to be related to its lipolytic property which remains to be proven as the role of Sct in lipolysis *in vivo* has to be clarified. The idea that gastric acid, which stimulates Sct for bicarbonate secretion, could stimulate this increase in Sct levels during starvation was negated by the findings that cimetidine, a gastric acid inhibitor, could not suppress the increase in plasma Sct level and it was concluded that factors other than HCl are involved [9, 102]. It was also postulated that increase in plasma Sct levels after exercise could be due to its lipolytic properties as well [8]. But the lack of strong *in-vivo* evidence in the role of Sct in lipolysis has prevented any definitive conclusions in its metabolic role in fasting.

Several studies have reported that Sct is released in response to duodenal fatty acid infusion [69, 88] and the length of the fatty acid chain could modulate this response [112]. It was also shown that sodium oleate could directly stimulate Sct-producing S cells *in vitro* [16]. Although this release of Sct is postulated to be associated with pancreatic secretion [94], bicarbonate release [26] and more recently anorectic signals [18], further research should be done to clarify the relationship of fat and Sct release. Furthermore, SctR expression was shown to be upregulated in the human omental adipose tissue of obese individuals [41]. Miegueu *et al.* reported that there is

a strong positive correlation between SctR expression in human omental adipose tissue and body mass index, insulin and Apolipoprotein B [68], suggesting a potential role for Sct and its receptor in the development of obesity which is worth studying.

Lipolysis and lipogenesis are related to lipid-associated and metabolic disorders including obesity, diabetes, hyperlipidemia [55]. Recent studies suggest the involvement of lipases belonging to the lipolytic pathway in tumor proliferation or cancer-associated cachexia [115] reinforcing the potential therapeutic importance of lipolysis. Although the above listed scarce findings suggest a connection between Sct with fatty acid metabolism, in fact, the role of Sct in it is still unclear. The pathway responsible for the lipolytic actions of Sct remains unidentified and there is no *in vivo* evidence for Sct's role in lipolysis yet. As Sct is shown to stimulate both lipolysis and fatty acid uptake *in vitro*, it would be interesting to study the modulation of lipid homeostasis by Sct *in vivo.* Recent advances indicate the involvement of a central regulation in mediating peripheral lipid metabolism, associating leptin, ghrelin, GLP-1, neuropeptide Y (NPY) and melanocortin system [76, 77].Thus with evolving research in lipid metabolism and escalating evidences on its potential importance in human disorders, there is a need for a detailed research on the effects of Sct in fatty acid metabolism, especially in *in-vivo* studies.

4. Secretin and Insulin/Glucose homeostasis

Just four years from its discovery, Sct was studied on its therapeutic effect on diabetic patients in 1906. The study was initiated by Moore [72] based on the prior knowledge that pancreas malfunction was related to diabetes and on the proposal that Sct could stimulate pancreatic

secretion. He found that Sct reduced hyperglycemia in diabetic humans, and his work was followed by various other studies which failed to reproduce a similar effect [4, 23, 35, 63].They discredited the proposal stating that the strict carbohydrate-free diet followed in Moore's study, rather than Sct treatment, could have brought about the reduction of glucose levels.

Drupe in 1964 showed that intravenous injections of glucose given along with Sct resulted in a significant reduction in the half-time of glucose disappearance [28], and this study triggered more research on the insulinotropic effects of Sct. It was shown again by the same research group [30] that Sct administration caused an increase in insulin concentration in the portal and peripheral blood in humans. Subsequent studies were done in dogs and humans to confirm the release of insulin after Sct administration [11, 105]. The next research question was naturally whether Sct that is endogenously released at physiological range would have this insulinotropic effect. Studies conducted in patients with histamine-fast [65] and with intra-duodenal acid infusion in humans and dogs [78] showed a negative response, while those with either a duodenal infusion of HCl or betazole-induced release of gastric acid did increase the insulin levels [20, 29]. Evidences then started coming up showing that the effect of Sct on insulin release was glucose-dependant [61, 106]. This insulin release by Sct was shown to be from a single pool of the peptide due to the fact that insulin responses progressively decreased when Sct was administered in identical pulses [60, 61].

Plasma Sct levels were found to be raised in fasting type II diabetes subjects [103] and intravenous injections of crude Sct reduced the glucose levels in these patients [85]. Sct

stimulated exocrine secretion of the pancreas have been shown to be reduced in streptozotocin(STZ)-induced diabetic rats [80] while Sct-induced amylase secretion was impaired in men with type I diabetes [97]. Studies were being conducted on Sct-induced insulin responses in normal, obese and diabetic subjects, in which obese subjects showed higher response and diabetic subjects had no difference with normal subjects [31, 32]. In 1978, a contradictory report which concluded that intravenous injection of Sct, in doses that mimicked the level of endogenous Sct in response to intra-duodenal acid, did not have any effect on glucose-stimulated insulin release [33]. Since then, there were several inconsistent reports. Sct was shown to specifically augment glucose-stimulated insulin release as it did not change the insulin responses to arginine, isoproterenol, tolbutamide and glucagon [59]. In mouse pancreatic islets cells, Sct potentiated *in-vitro* glucose-stimulated insulin release [51] and the N-terminal region of the peptide was shown to be important for this effect [50]. In rats, Sct stimulates insulin secretion without increasing the blood flow to the islets [14], but simultaneously, several reports negate such insulinotropic effects. In isolated perfused rat pancreas, irrespective of the glucose concentrations in the perfusate, Sct failed to stimulate insulin release [83]. Many studies in humans and dogs suggested that Sct either had no effect or the effect was pharmacological and not physiological [12, 33, 52, 98]. One of the reasons for the discrepancy in these findings might be the accuracy in monitoring Sct levels, which in turn might have affected the conclusions of the studies. However, the apparent absence or extreme low density of SctRs on islets suggests that the physiological and pharmacological effects of Sct, if present, may either be through an indirect pathway or may be mediated by another receptor of secretin family that has a lower affinity for the peptide [104]. Peptides like GIP and GLP-1 have a potent direct action exhibiting their incretin effect through specific receptors on islet beta cells [3]. Secretin receptor knockout

model animals could be employed for better understanding of Sct's effect on islet beta cells. Central control of insulin secretion could be viewed as an indirect pathway, e.g., leptin and NPY modulates insulin secretion mainly through receptors in the hypothalamus [74] and NTS [27], respectively. Sensing of glucose by brain regions [101] including the hypothalamus, has recently been shown to trigger insulin release [15, 82] establishing a brain-endocrine pancreatic axis. There is strong evidence for vagal stimulation of beta cell secretion [100]. Such effects are brought about at least in part by acetylcholine on beta cells, although a role for VIP, PACAP and GHRH is also likely [100]. With increasing awareness in the direct and indirect mechanisms of insulin secretion and with improved techniques such as glucose clamps, a role of Sct in insulin and glucose homeostasis warrants a revisit and further research.

6. Conclusion

Recent evidences on pleiotropic actions of Sct, especially on its role as a neuropeptide, have led to a revision of the plausible physiological functions of this important peptide. A lot of data on the metabolic role of Sct from the 60s, 70s and 80s, although contradictory, have been overlooked and followup studies have not been performed thoroughly. In light of this, it is noteworthy that Sct's level in circulation have been shown to increase in both energy rich (postprandial) and energy deficient (starvation) states and hence Sct should be investigated to clearly elucidate its role in metabolism and energy homeostasis. With recent studies marking a rebirth of this research, and with markedly improved techniques and current understanding on the actions of Sct in brain, along with development of unique resources such as Sct and SctR

knockout animal models, future works in this area will hopefully shed mechanistic insights into understanding how this unique hormone exerts its metabolic actions via central and/or peripheral pathways. Metabolic disorders including obesity and diabetes are growing in epidemic proportions, hence, demand for therapeutics and research on understanding the molecular mechanisms underlying these disorders are on the rise. Further research pertinent to the metabolic role of Sct could unveil possible relationships of Sct with some metabolic disorders for future discovery of therapeutic options for these diseases.

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611

612 **Figure caption:**

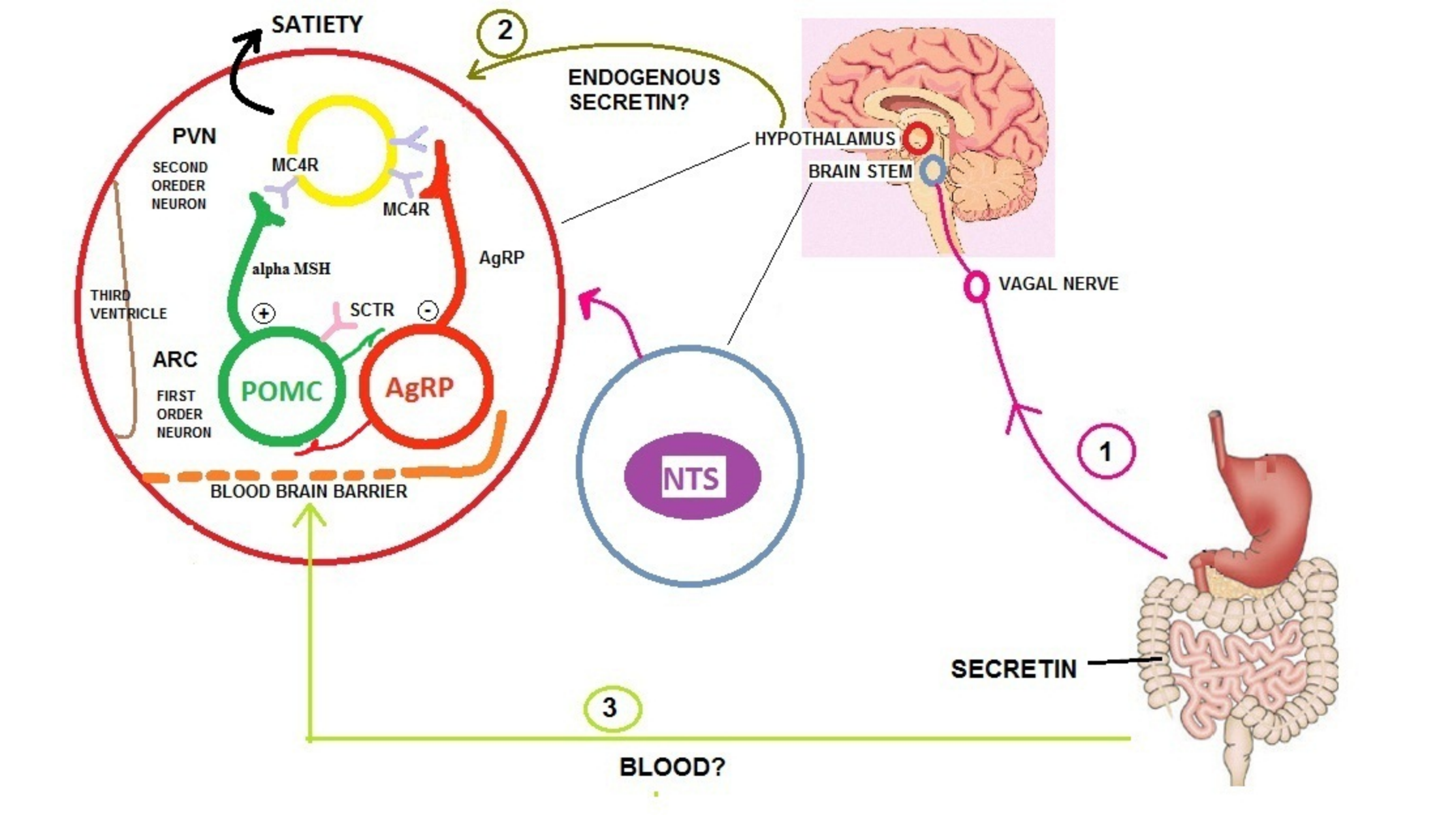
613 **Fig. 1.Working model summarizing the anorectic effect of secretin (Sct)**

614 Sct is released from the S cells of the duodenum in response to gastric acid and digested products
615 of fat or protein entering the duodenum. Gut derived Sct could exert its anorectic effect by the
616 central melanocortin system through either one or combination of the three different routes. **1** (
617 →) Sct released from the gut interacts with the SctR in the vagal afferents and
618 transmits signals through the vagus to reach the NTS in the brainstem which in turn signals to the
619 hypothalamus. **2** (→) Sct released endogenously from the hypothalamus could directly

act on its receptors in the Arc. **3** (⟶) Sct released from the gut into the circulation could pass through the blood brain barrier and activate the Arc neurons. On reaching the Arc, Sct activates the POMC neurons and inhibits the AgRP neurons. POMC is then cleaved into α-MSH and it activates the MC4R in the PVN which signals downstream to reduce intake of food.

Fig. 2.Schematic representation of role of secretin (Sct) in lipid metabolism known

Sct stimulates lipolysis in isolated rat adipocytes, releasing glycerol from the adipose cell through the activation of adeneyl cyclase and cAMP. Sct stimulates esterification of free fatty acid (FFA) resulting in their uptake and also stimulates glucose uptake thus bringing about triglyceride accumulation in isolated cells. '?' in the picture represents the information that are currently unknown and that have not been researched yet. Clearly very little is known on the regulation of lipid metabolism by Sct indicating the necessity for more research on the topic.


SATIETY
2
ENDOGENOUS SECRETIN?
PVN
SECOND OREDER NEURON
MC4R
MC4R
AgRP
alpha MSH
THIRD VENTRICLE
SCTR
ARC
POMC
AgRP
FIRST ORDER NEURON
BLOOD BRAIN BARRIER
HYPOTHALAMUS
BRAIN STEM
VAGAL NERVE
NTS
1
SECRETIN
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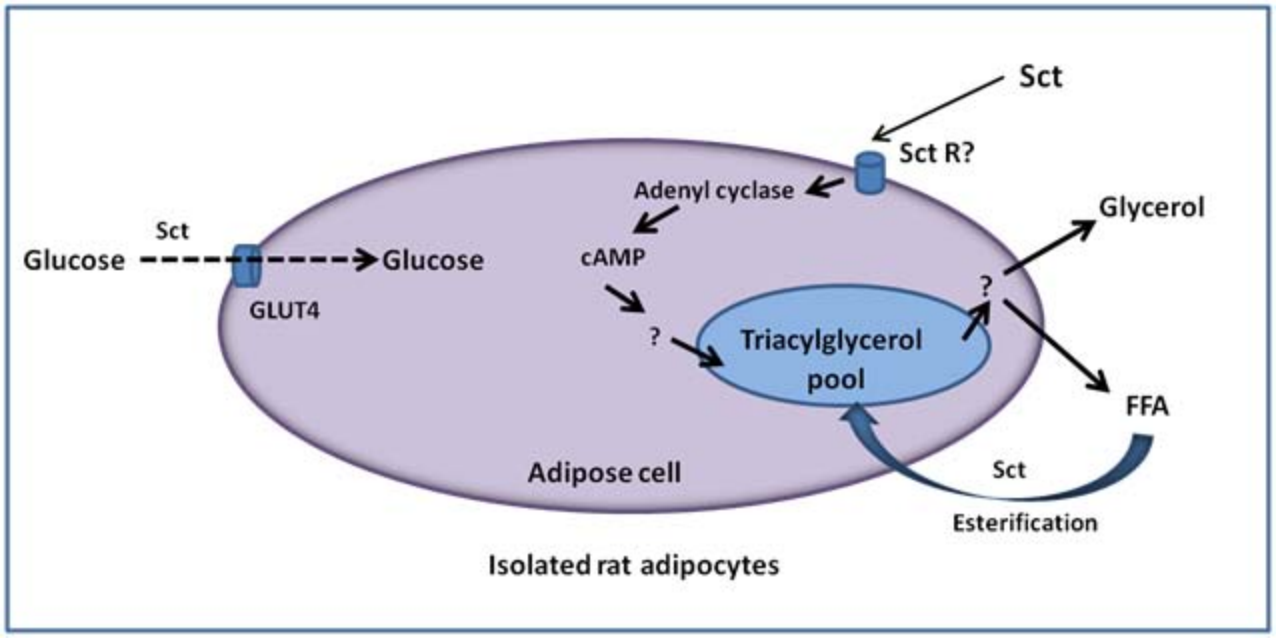
BLOOD?



Isolated rat adipocytes