# Distribution and functional implication of secretin in multiple brain regions

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**Abstract:**

Secretin is a polypeptide hormone initially identified for its gastrointestinal functions. However, emerging evidences show wide distribution of secretin and secretin receptor across various brain regions from cerebral cortex, hippocampus, hypothalamus to cerebellum. In this mini-review, we will firstly describe the region-specific expression pattern of secretin and secretin receptor in brain, followed by summary of central physiological and neurological functions mediated by secretin. Using genetic manipulation and pharmaceutical approaches, one can elucidate the role of secretin in mediating various neurological functions from simple behaviors such as water and food intake, to more complex functions including emotion, motor and learning or memory. At last, current weakness and future perspectives of secretin in central nervous system will be discussed, aiming to provide the potency of using secretin or its analog for treating various neurological disorders.

**Keywords: Secretin; Food and water intake; Motor learning; Stress; Anxiety; Transgenic**

**mice; Drug target**

**Expression of secretin and secretin receptor across brain regions**

Secretin has a unique place in the field of physiology as it is the first mammalian hormone proposed. Early work has established the release of secretin from duodenum to stimulate pancreatic secretion [1]. Later studies broaden its peripheral functions into fatty acid metabolism [2], glucose homeostasis modulation [3], bile acid secretion [4] and water reabsorption in renal collecting tubules [5]. In recent decades, multiple brain-gut peptide hormones such as vasoactive intestinal peptide (VIP), pituitary adenylate cyclase activating peptide (PACAP) and glucose-dependent insulinotrophic polypeptide (GIP) have been found to be expressed in various brain regions [6-8]. Secretin, sharing high degree of sequence homology with those gut peptide hormones, also presents a wide spectrum of distributions in central nervous system.

The study for brain expression of secretin was initiated in 1979, when secretin-like bioactivity was firstly identified in porcine brain extracts [9]. The presence of secretin-like activity has been demonstrated across various mammalian species including canine, porcine and rats [10]. Further examination found immune-reactive secretin in multiple brain regions from forebrain cortex to midbrain and brain stem [11,12]. Increasing evidences from *in situ* hybridization (ISH) and immunohistochemistry (IHC) staining reveal region-specific expression pattern of secretin inside the brain. In a quick summary: (1) In cerebral cortex, secretin transcript [13,14] and immunoreactivity [14] have been found at a relatively lower level; (2) Hippocampal and hypothalamic neurons have expression of secretin gene transcript [13,15] and peptide [15,16]; (3) Within limbic system, secretin exists in amygdala nuclei especially central amygdala (CeA) [17]; (4) Cerebellar Purkinje cells and basket cells have prominent expression of secretin gene transcript [14,15] and peptide [15,18,19]; (5) Within brain stem, secretin is expressed in medullar oblongata, pons [20], and nucleus of the tractus

47 solitary (NTS) [17]. These expression profiles are plotted mainly on rodent models, and a human
48 brain study revealed similar results as secretin resides in cerebellar Purkinje cells, deep cerebellar
49 nuclei, pyramidal neurons of motor cortex, plus hippocampal and amygdala nuclei [21].

50 The spatial expression of secretin receptor has also been investigated. Early studies showed
51 high affinity binding against secretin in rat brain membranes, indicating the existence of specific
52 secretin receptor [22]. Using the more sensitive auto-radiographic binding approach, secretin binding
53 sites have been found in brain stem, hippocampus, caudate, cerebellum, cingulate nuclei and
54 orbital cortex [23]. Consistently, the region-specific RT-PCR study has identified secretin receptor
55 within cerebellum, hippocampus, NTS, lateral dorsal thalamic nucleus, lamina terminalis, lateral
56 habenular complex, supraoptic nucleus (SON) and paraventricular nucleus (PVN) of
57 hypothalamus, and CeA [17,24]. Generally speaking, secretin receptor presents a much wider spatial
58 distribution than secretin ligand [14], indicating pleiotropic roles of secretin inside the brain via
59 specific receptor binding within certain regions. A summary for major findings of secretin and
60 secretin receptor across brain regions is shown in Figure 1.

61 In addition to spatial expression across brain regions, the temporal distribution of secretin and
62 secretin receptor during development has also been investigated. Both secretin and secretin
63 receptor gene display age-dependent expression patterns, with peak levels at early postnatal phase
64 (before P7) in most of the brain regions examined [17]. During embryonic development, RT-PCR
65 analysis has shown the existence of the secretin gene transcript in midbrain mesenchyme and
66 tegmentum, cerebellar primordium and choroid plexus as early as E10.5 [25]. Using a similar ISH
67 approach, the secretin receptor transcript is expressed in similar regions as those for secretin gene
68 [26]. The early and persistent expression of secretin and secretin receptor since neural tube formation

strongly supports the role of secretin in neurodevelopment and neurological functions, as we will revise in later sections.

**Hypothalamic pathways for mediating water and food homeostasis**

As the regulating center for basic needs and vital functions of the body, hypothalamus is crucial for homeostatic control such as body osmolality, food intake, and energy expenditure. The known expression of secretin [13] and secretin receptor [17] within hypothalamus thus suggests the involvement of secretin in mediating body homeostasis. Indeed, the earliest evidence for central functions of secretin comes from hypothalamic regions, as intracerebroventricular (ICV) perfusion of secretin stimulates prolactin (PRL) and luteinizing hormone (LH) release [27,28]. These results were in line with electrophysiological recordings showing that secretin alters the firing rate of hypothalamic PVN neurons [29], indicating the participation of secretin in activity-dependent neuroendocrine cell secretion. To elucidate whether it is peripheral or central originated secretin that plays a role, cultured hypothalamic explants were depolarized by KCl and endogenous release of secretin occurred in a calcium channel-dependent manner [30]. Therefore, secretin can be secreted from hypothalamic nuclei under stimuli to exert physiological or neurological functions via receptor binding inside the brain.

Secretin mediates water homeostasis via a central pathway. Secretin and secretin receptor are prominently distributed in posterior pituitary (pars nervosa) and in magnocellular neurons of hypothalamic SON and PVN [31]. Under plasma hyper-osmolality challenge, secretin is released from posterior pituitary, and can activate PVN and SON neurons to release vasopressin into the general circulation [31]. Further studies attribute angiotensin II (ANGII) as the upstream factor

mediating secretin's effect, as disruption of secretin-secretin receptor axis abolishes the dipsogenic effect of ANGII [32]. These two studies establish secretin as the linkage between ANGII and vasopressin, and the activation of ANGII-secretin-vasopressin axis counteracts hyper-osmolality stress by enhancing renal water reabsorption [33] and increasing water intake [34]. Such effects on water homeostasis are likely to be contributed by centrally but not peripherally released secretin, as ICV but not intraperitoneal (i.p) injection of secretin can induce water intake behavior [35]. These results plus early findings that identify secretin's direct role in facilitating renal tubular water reabsorption [5] thus demonstrate a dual role of secretin in water homeostatic regulation via both central and peripheral routes. However, these studies cannot answer the question of whether secretin directly regulates water intake via specific neural circuits. Previous findings showed that ICV-secretin infusion strongly activated subfornical organ (SFO) neurons [35], whose activation is known to produce thirst sensation and water intake behavior [34]. Therefore, the hypothesis that secretin participates in water intake circuits can be tested in future, using selective activation of SFO neurons with secretin receptor expression.

Feeding or appetite control is known to be regulated by the melanocortin system in paraventricular nucleus (PVN) and arcuate nucleus (Arc) of hypothalamus [36]. Based on expression data of secretin and secretin receptor in these regions [30,37], it is reasonable to speculate the function of secretin in mediating food intake behavior. Central administration of secretin activates Fos expression in PVN and Arc, and suppresses food intake in mice [38]. Further investigations demonstrate up-regulation of the melanocortin-4 receptor (Mc4r) pathway in PVN plus reduced agouti-related protein (AgRP) transcript levels in Arc [38]. These studies thus illustrate the anorectic role of secretin via central modulation on the melanocortin system. Unlike the scenario in water

intake, peripheral administration of secretin exerts similar effects on food intake suppression, PVN and Arc neuron activation, and Mc4r activation plus AgRP suppression in mice [38]. These results suggest that central and peripheral pathways co-exist to mediate food intake in parallel manners. Following studies find that peripheral secretin suppresses food intake via vagal afferent pathways projecting to Arc region [39]. In summary, secretin depresses appetite and food intake via both central modulation on the melanocortin system and vagal afferent pathways. However, whether it is central or peripheral secretin that plays more prominent roles in food intake regulation has not been resolved, and this can be differentiated using site-specific ablation of secretin. Moreover, the effect of secretin on food intake may be explained from other regions, as the stereotaxic injection of secretin into rat CeA also suppresses feeding behavior [40].

**Fine motor control and motor learning by secretin in cerebellum**

Both secretin and secretin receptor are prominently expressed in cerebellum, which is known to regulate complex motor tasks and related motor learning. In early studies, secretin gene transcript [14] and immunoreactivity [19] have been found to be present in rat cerebellum. Secretin binding affinity [23] and secretin receptor gene transcript [17] are also identified in rodent models. Later work using human cerebellar slices further reveals existence of secretin in Purkinje neurons, and secretin receptor in Purkinje cells plus basket interneurons [21,41]. Moreover, secretin is also found to be sparsely expressed in deep cerebellar nuclei [15,19]. It is thus proposed that secretin may modulate cerebellar function at multiple levels within local circuits.

The earliest evidence of secretin on cerebellar modulation comes from an electrophysiological study, in which secretin potentiates inhibitory postsynaptic current (IPSC) on Purkinje neurons of

135 cultured rat cerebellar slices [18]. Later studies confirm the release of secretin from Purkinje cells
136 under KCl-induced depolarization [42]. Based on the presence of secretin immunoreactivity mainly
137 in soma and proximal dendrites of Purkinje cells [15,18,41], secretin is proposed to be released from
138 excited Purkinje cells, and bind with its receptor on presynaptic basket interneurons, where it
139 activates the cAMP-protein kinase A (PKA) pathway to open specific calcium channel for
140 potentiating GABAergic transmission [18]. An alternative cellular pathway has been postulated as
141 secretin can stimulate the release of glutamate from unknown sources to activate presynaptic
142 GABAergic interneurons [42]. A third possible explanation states that secretin may suppress
143 intracellular trafficking of Kv1.2 potassium channel in basket cells for potentiating presynaptic
144 excitability [43]. Although the definitive cellular pathway has not been resolved, such retrograde
145 neuromodulator function of secretin to potentiate GABAergic synaptic transmission [44] may help to
146 prevent Purkinje cell from over-excitation by parallel fiber input, and may play crucial roles in
147 maintaining firing patterns for timely and precise motor coordination and motor learning
148 functions.

149 In consistent with these neuromodulation functions, behavioral evidences further support the
150 role of endogenous secretin in mediating fine motor coordination and motor learning. When
151 secretin receptor gene is deleted, those transgenic mice present impaired motor learning abilities
152 on Rota-rod task [45]. A human study provides more convincing evidences as secretin infusion helps
153 to improve eye blink conditioning, which is one classical cerebellar dependent learning [46]. Our
154 group has developed a Purkinje-cell specific secretin mouse model using Cre-Loxp recombination
155 approach and finds impaired performance on complex motor tasks such as vertical climbing, plus
156 significant deficits in Rota-rod learning [15]. In another commonly applied behavioral paradigm for

157 evaluating cerebellar motor learning, eyeblink conditioning has also been found to be dependent
158 on secretin, as acquisition but not extinction performance is impaired with infusion of a secretin
159 receptor antagonist [47]. These behavior assays all support the role of cerebellar secretin in
160 mediating complex motor tasks and motor learning.

161 Such motor modulation effects by secretin can also be interpreted by developmental regulation,
162 in addition to neuromodulator functions as abovementioned. Secretin [25] and secretin receptor [26]
163 expression has been found to exist in cerebellar primordium in early embryonic phase, and in
164 postnatal phase [17]. We have recently studied juvenile mouse cerebellum and find that secretin and
165 secretin receptor show peak expression level at early postnatal phase (P4-P7) [48]. IHC staining
166 reveals secretin expression in the Purkinje cell body and proximal dendrite, whilst secretin
167 receptor is distributed in Purkinje cell and granular cell progenitors [48]. As phenotypic evidences,
168 we have shown that knockout of secretin gene from Purkinje cells results in a late onset of right
169 reflex and negative geotaxis reflex, which are two motor reflexes highly dependent on cerebellar
170 functions [15]. All these evidences support the involvement of secretin in cerebellar development.
171 We thus perform morphological examinations on secretin-deficient mice, which show decreased
172 number of Purkinje neurons, impaired dendritic arborization, plus lower spine density [48]. In a
173 further examination of granular progenitor cells, we have shown their early onset of migration
174 from external granular layer (EGL) toward internal granular layer (IGL) [48]. These results
175 demonstrate that secretin modulates the postnatal development of both Purkinje cells and granular
176 cells, thus affecting the formation and synaptic transmission of cerebellar cortical circuits. As
177 Purkinje cell regulates the proliferation and maturation of granular cells [49], further studies should
178 be performed to delineate the role of Purkinje-derived secretin in mediating granular cell

progenitor proliferation and migration via cell-specific secretin gene deletion.

While regulating cerebellar neuron development, secretin may also have neuroprotective effects. An early study has shown that the deprivation of secretin receptor significantly elevated ethanol-induced apoptosis of EGL progenitor cells in cerebellum during early postnatal period [50]. Elevated apoptosis has been recently found by our studies in the cerebellar EGL and IGL in secretin-deficient mice [48]. Further mechanistic investigations show that secretin could activate both PKA and extracellular signal regulated kinase (ERK) pathways to suppress apoptosis for protecting granular cell progenitors [48]. In summary, our studies have illustrated the indispensable role of secretin in mediating cerebellar-related motor coordination and motor learning functions, which may be achieved via neuromodulator, neurodevelopmental and neuroprotective functions. Recently, cerebellum has been proposed to be involved in multiple psychiatric disorders such as autistic spectrum disorder (ASD) [51] or schizophrenia [52], and has been shown to mediate cognitive functions such as reward prediction [53]. Therefore, it should be valuable to further explore both motor and non-motor functions of secretin in cerebellum.

**Cognitive, emotional and social functions regulated by secretin**

In addition to water or food homeostasis by hypothalamus, and motor learning control in cerebellum, secretin and secretin receptor are also found to be expressed across various regions in limbic system, including hippocampus [16] and amygdala nuclei [17]. The hippocampus is known to mediate spatial memory, whilst amygdala plays crucial roles in fear and anxiety control. Studies have been performed to investigate the functional role of secretin in these regions. Using secretin receptor-deficient mouse model, secretin has been demonstrated to modulate spatial memory

within Morris water maze task [45]. The authors proposed that such deficits in spatial memory were due to the impaired hippocampal CA1 spine formation and long-term potentiation (LTP) maintenance [45], the latter of which can be replicated in a secretin-deficient mouse model [16,54]. Besides the CA1 region, the dentate gyrus (DG) also shows decreased neurogenesis and lower volume at early postnatal phase with secretin gene deletion [54]. These results on DG neurogenesis and CA1 neural plasticity all help to illustrate the function of secretin in spatial memory.

Emerging evidences have shown the participation of secretin in regulating emotions such as anxiety or fear. An early study using ICV perfusion of secretin into rat lateral ventricles found remarkably decreased locomotor activity in the open filed [55]. The authors argued that such hypo-activity was due to suppressed propensity to initiate locomotor behaviors [55], providing the first evidence of secretin in mediating emotional function. Another study has found that secretin infusion decreases the magnitude of fear conditioned startle reflex in rats [56]. Fear conditioning is well-known to be encoded by amygdala nuclei, and previous studies showed peripheral secretin injection activated Fos expression in rat CeA region [57], providing a possible explanation for secretin-suppressed fear responses. In similar with fear regulation, secretin may also mediate anxiety or depressive behaviors. Central perfusion of secretin activates Fos expression in various brain regions including CeA, bed nucleus of the stria terminalis (BNST), external lateral subnucleus of parabronchial nucleus (PBel), locus coeruleus (LC), ventral periaqueductal gray (vPAG), paraventricular hypothalamus (PVH), lateral septal complex and anterior prefrontal cortex (PFC), and attenuates Fos immunoreactivity in dorsal periaqueductal gray (dPAG), lateral amygdala (LA), and parietal association cortex [58]. Those brain regions have been demonstrated to be involved in anxiety and depression disorder [59], secretin thus may play crucial roles for mood

control. More interestingly, peripheral infusion of secretin exerts similar effects in a vagal dependent pathway [57,60], suggesting the potency of gut-brain axis for emotion control. In consistent with animal studies, a human trail demonstrates amygdala activation after secretin infusion under affective stimuli [61]. In summary, secretin is highly related with the regulation of anxiety or depressive behaviors.

The role of secretin in mediating stress or anxiety can also be interpreted from neuromodulator and neuroendocrine aspects. The disruption of serotonin (5-HT) or dopamine systems has been implicated in psychiatric disorders such as major depression disorder (MDD). In studying the development of serotonergic neurons, it is interesting to find a transient expression of secretin in those nuclei since E14 to birth [62], suggesting that secretin may be involved in the formation of brain 5-HT system, thus mediating emotion functions. Although no direct study has performed to examin the 5-HT level in secretin or secretin receptor knockout mouse, and those mice presented normal anxiety level at resting state [15], future studies are still valuable to test the resilience toward environmental stress under deprivation of endogenous secretin. For dopamine metabolism, an early study found that secretin could increase the activity of tyrosine hydroxylase (TH) in rat superior cervical ganglion (SCG) [63]. A clinical finding shows that secretin infusion elevates brain dopamine turnover [64]. As TH is the rate-limiting step for biosynthesis of catecholamine including dopamine, epinephrine and norepinephrine, this mechanism may help to explain secretin's potential effects on modulating emotions. In summary, secretin potentially activates 5-HT and dopamine pathways across various brain regions to mediate anxiety or depressive behaviors, although direct evidence is still lacking. On the other hand, secretin may also work as one stress-induced hormone to mediate the hypothalamus- pituitary- adrenal (HPA) axis, which is

245 critical for both central and peripheral responses toward acute or chronic stress. Supporting
246 evidences include that secretin could inhibit the release of adrenocorticotropic hormone (ACTH)
247 release and depress glucocorticoid responses to ACTH, thereby suppressing the HPA axis [65]. In
248 addition, secretin is found to be up-regulated in rat hypothalamus under colchicine-induced stress
249 [37]. These results collectively indicate that secretin may help to reduce stress and anxiety by
250 mediating the 5-HT or dopamine system and the HPA axis.

251 Social function regulated by secretin has drawn a wide range of research interests. Using
252 secretin receptor-deficient mouse model, it has been demonstrated that secretin modulates social
253 behavior as reflected by the tube dominance and social recognition tests [45]. The wide spatial
254 distribution of secretin further suggests that it could regulate social behavior at multiple nuclei.
255 Currently available evidences mainly support the neuroendocrine module of secretin in social
256 function. For example, peripheral secretin infusion activates oxytocin and vasopressin neurons in
257 SON via the noradrenergic pathway [66]. As both oxytocin and vasopressin are known to mediate
258 social behaviors, secretin thus may help to mediate social behavior via an endocrine manner.
259 Further evidences reveal that central secretin activates SON neurons to release oxytocin into
260 medial amygdala (MeA), where it binds with the local oxytocin receptor to improve social
261 recognition in both rats and mice [67]. This study attributes secretin as the upstream mediator for
262 oxytocin activation, and provides an alternative explanation for secretin's effects on social
263 function. Besides those neuroendocrine functions, secretin may also mediate social behavior by
264 directly regulating related neural circuits, since it is expressed in hippocampus, amygdala and
265 hypothalamus.

266

**Implication of secretin in neurological diseases and pharmaceutical usage**

Due to its initially discovered peripheral functions, currently approved clinical usage of secretin mainly includes the intervention on gastrointestinal disorders. However, based on these abovementioned neurological functions, potential values of secretin in treating psychological or neurological disorders can be expected. The earliest report comes from intravenous infusion of secretin on ASD children, who are claimed to have improved social and communication behaviors [68]. A second study also shows improved scores in 7 out of 12 ASD children after secretin infusion [64]. Such results are somehow controversial as following similar clinical trials cannot replicate the improvement at most of the time. One pilot study even reports worsening scores of ASD patients during secretin treatment course [69]. Therefore, human studies still show controversial results regarding secretin's effects on ASD [70]. These are in sharp contrast with previous animal results showing modulation of social function by secretin [45,67]. Similar phenomena occur when secretin is used on schizophrenia patients: a single intravenous secretin injection leads to transient amelioration of symptoms, although overall scores are not improved [71]. In examining eye blink conditioning in schizophrenia patients, secretin has been found to improve such conditioned learning [46]. Secretin also partially reverses phencyclidine-induced deficits in prepulse inhibition (PPI) in an animal model [72], suggesting its potential value as antipsychotics. We argue that the lack of persistent effects from secretin on ASD or schizophrenia patients may be due to the rapid metabolism of secretin, whose single injection thus cannot achieve long-lasting behavioral improvements. The development of new drug delivery approaches to achieve chronic release of secretin, or innovation of secretin analogs with a slow metabolic rate, may help to improve therapeutic effects.

289 To address the delivery route issue of secretin, the permeability of secretin across blood brain
290 barrier (BBB) should firstly be addressed. General opinions agree that secretin could penetrate
291 BBB via a non-saturation transmembrane diffusion [73]. Besides direct penetration across BBB,
292 secretin may also activate the vagal system and mediate central neuron activation along vagal
293 afferent nerves from brain stem to midbrain and limbic regions [60]. To avoid the blockade by BBB,
294 another approach is to use intranasal drug delivery like those having been used for oxytocin [74]. It
295 is interesting to find that intranasal application of secretin suppresses hyperactive and repetitive
296 behaviors in mice, with even more significant effects comparing to ICV injection [75]. Therefore,
297 intranasal administration may provide an alternative route for clinical usage of secretin.
298 Besides neuromodulator function, secretin may also work as a neuroprotective reagent. An
299 animal study shows that secretin protects cerebellar and striatal neurons from ethanol-induced
300 apoptosis at early postnatal phase [50]. In the hippocampal dentate gyrus (DG) region,
301 secretin-deficient mice present decreased neurogenesis and lower volume at early postnatal phase,
302 indicating reduced survival of neural progenitors [54]. These results are in line with our recent
303 developmental studies showing that secretin could protect cerebellar granular progenitors from
304 apoptosis during early postnatal phase [48]. Indeed, secretin-like neuropeptides have been identified
305 as neuroprotective factors. For example, PACAP, with high sequence similarity with secretin,
306 exerts strong neuroprotective effects against neural injury [76,77]. Therefore, secretin may be used as
307 a drug candidate for protecting neurons.
308 In studying pharmaceutical potency of secretin, one should further illustrate the site-specific
309 effects of secretin at cellular or even sub-cellular scale, plus its molecular pathway inside neurons.
310 Emerging evidences are showing that secretin modulates neuron activity in region/cell-specific

311 manners. For example, secretin can potentiate synaptic transmission of NTS neurons [78] or
312 cerebellar inhibitory interneurons [18]. In hypothalamus, secretin potentiates the firing rate of nearly
313 half of PVN neurons whilst suppressing the other ~20% neurons' firing [29]. In similar, secretin
314 infusion into CeA elevates half of neuron's firing rates whilst inhibits some neurons [40]. These
315 diverged cell behaviors illustrate heterogeneous of neuron sub-populations, and the role of secretin
316 is proposed to be dependent on cell identity and related electrophysiological properties. In
317 studying intracellular pathways of secretin in brain, it is necessary to delineate the molecular
318 mechanism of secretin receptor. Some interest findings challenge the classical belief that secretin
319 receptor is activated on its monomer form. In specific, secretin receptor can form heterodimer with
320 related G-protein coupled receptor (GPCR) such as AGNII receptor AT1aR, and such receptor
321 dimer can bind with both ligands to activate the cAMP pathway in a synergistic way [79]. Using
322 transmembrane peptides to specifically suppress the formation of such receptor heterodimer, an *in*
323 *vivo* assay shows that secretin receptor dimerization plays a crucial role in facilitating water intake
324 behavior [79]. This concept of receptor dimerization highlights the potency of secretin to modulate
325 the physiological function of other related neuropeptides, by means of regulating receptor
326 complex dynamic. For intracellular messengers of the secretin pathway, putative secretin receptor
327 has been described in association with adenylate cyclase [80], indicating the cAMP pathway as
328 potentially downstream effectors. Such proposed model was later substantiated as adenylate
329 cyclase activation occurs in frontal cortex [81], hypothalamus and hippocampus under secretin
330 infusion [82]. In summary, secretin activates cell surface receptor, probably in a hetero-dimer form,
331 to elevate the intracellular cAMP level, which can further mediate various protein kinase pathways
332 to affect neuron activity, neuroendocrine secretion and other cell behaviors.

## Conclusion and future perspective

Since the discovery of secretin in brain extracts [9], the central functions of secretin have been investigated for almost 40 years. To date, progresses of secretin as a neuropeptide mainly reside in the hypothalamic function of mediating food and water homeostasis, spatial memory related with hippocampus, plus cerebellar modulation for motor coordination and motor learning. In other behavioral paradigms, such as anxiety or depressive behavior, and social functions, incomplete or sometimes controversial evidences exist. A brief summary of well-established neural functions of secretin is listed in Table 1. Future studies should be performed to plot a more complete picture of secretin's expressional and functional profiles. For example, the function of secretin in cortex still lacks of comprehensive studies. One can observe expression of secretin [21] and secretin receptor [23] in cortical neurons especially pyramidal neurons. However, the exact role of secretin in cortical region is unknown yet.

One interesting question remains to be resolved, as whether there is a cell type-specific pattern of secretin expression. So far, the only partial answer comes from cerebellum, where secretin is found to be prominently in inhibitory Purkinje cells and some basket cells [15]. This issue is of critical importance for resolving central function of secretin, as brain nuclei is of high heterogeneity, and different cell subtypes play unique or sometimes antagonistic roles in mediating behaviors. The sub-typing of neurons by differential expression of neuropeptides has been well recognized. VIP, for example, is now regarded as one important marker for the specific sub-type of inhibitory neurons with unique electrophysiological property and circuitry connection. Secretin is thus expected to work in a similar way for differentiating between neuron sub-populations.

More importantly, these secretin-positive neurons are expected to have specific neural circuitry connection, which can help to elucidate specific neural functions.

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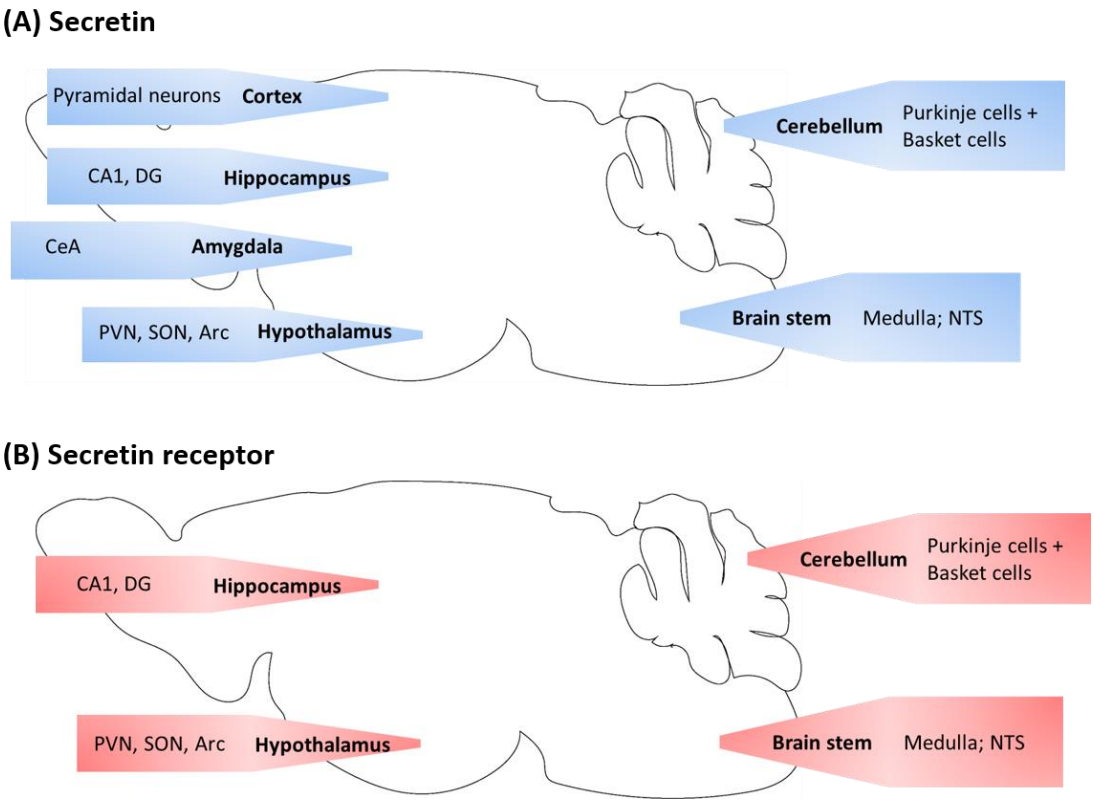


584

585 **Figure 1 Spatial distribution of secretin and secretin receptor across major brain regions.**
586 This illustration is based on at least two independent studies revealing consistent results for either
587 protein or gene transcript expression. See main text for references. Abbreviations: CeA, central
588 amygdala; PVN, paraventricular nucleus; SON, supraoptic nucleus; Arc, arcuate nucleus; NTS,
589 nucleus of the tractus solitary.

590

**Table 1 Summarized neurological functions of secretin**

| Behavioral modules | Major functions | Brain regions involved | References |
|---|---|---|---|
| 1. Water intake | Facilitation of water intake and renal water reabsorption | SFO, SON and PVN | 31,32,35 |
| 2. Appetite | Suppressing food intake via mediating AgRP and Mc4r system | PVN and Arc | 38,39 |
| 3. Motor learning | Mediating motor coordination and motor learning in Purkinje neurons | Cerebellar cortex | 15,18,48 |
| 4. Spatial memory | Necessary for normal spatial memory via hippocampal synaptic plasticity | Hippocampal CA1 | 45,54 |
| 5. Social | Modulating social interaction and social recognition | Hippocampus, SON | 45,67 |

**Abbreviations**: SFO, subfornical organ; SON, supraoptic nucleus; PVN, paraventricular nucleus; Arc, arcuate nucleus.