

# Substance P and swallowing after stroke

**David G Smithard**

Stroke Physician,  
 William Harvey Hospital,  
 Ashford, Kent,  
 TN24 0LZ, UK  
 Tel.: +44 1233 61214  
 Fax: +44 1233 616662  
 david.smithard@ekbt.nhs.uk

Swallowing is essential for independent living. The swallowing center is based within the brain stem, generating a patterned swallow which is modified both by peripheral feedback and cortical input. The striatum and thalamus are intimately involved in swallowing initiation and control. Substance P, a neuropeptide, appears to play a pivotal role in swallowing. Centrally, it acts as a neuromodulator within the striatal–nigral pathway, but distally it may act as a neurotransmitter within the plexus of nerves in the pharyngeal epithelium in response to nociceptive stimuli. Inhibition of substance P, centrally, with direct antagonists or dopamine antagonists, interrupt the swallow. Peripherally, agents that deplete nerve endings of substance P also delay the swallow. It is proposed that the difficulties in swallowing, and any subsequent aspiration, after stroke may be related to reduced levels of substance P, which may be ameliorated by angiotensin-converting enzyme inhibitors, dopamine agonists and capsaicin, all of which increase substance P levels.

The ability to swallow is essential for independent survival; however it is often affected during the acute phase of stroke and for a small number of patients, the problem persists well into the rehabilitation phase. In many cases the ability to swallow safely returns within a matter of days, but for those where problems persist for more than 10 days, alterations to diet, mode of swallow or the use of enteral feeding may be required for a period of many years [1]. It is known that pharmacological agents frequently adversely affect the swallow, but there is increasing evidence for the use of a few that may facilitate the pharyngeal swallow. This paper describes the normal swallow and problems that occur following stroke. It discusses the role of pharmacological agents both in the management of swallowing and impairment of the ability to swallow safely.

## Swallow

### Normal swallow

The oropharyngeal swallow is a complex and highly coordinated process, the main purpose being the passage of the food/liquid bolus from the mouth to the stomach [2–8].

### Neurological control of swallowing

The neurological control of swallowing is complex, involving both the CNS (cerebral hemispheres, brain stem, cerebellum and cranial nerves [V, VII–XII]) and peripheral nervous systems. There is continuous feedback from the oropharynx to the cortex, resulting in

modulation of the sequential swallow that is generated by the brain-stem-swallowing centers [9–16] (Figure 1).

However, recent work by Bastian and Rigg studying patients with tissue transplant to the pharynx has suggested that sensation, and by inference, sensory feedback, may not be as important and that the swallow may merely occur as a result of a neuromuscular cascade [17].

### Cortex

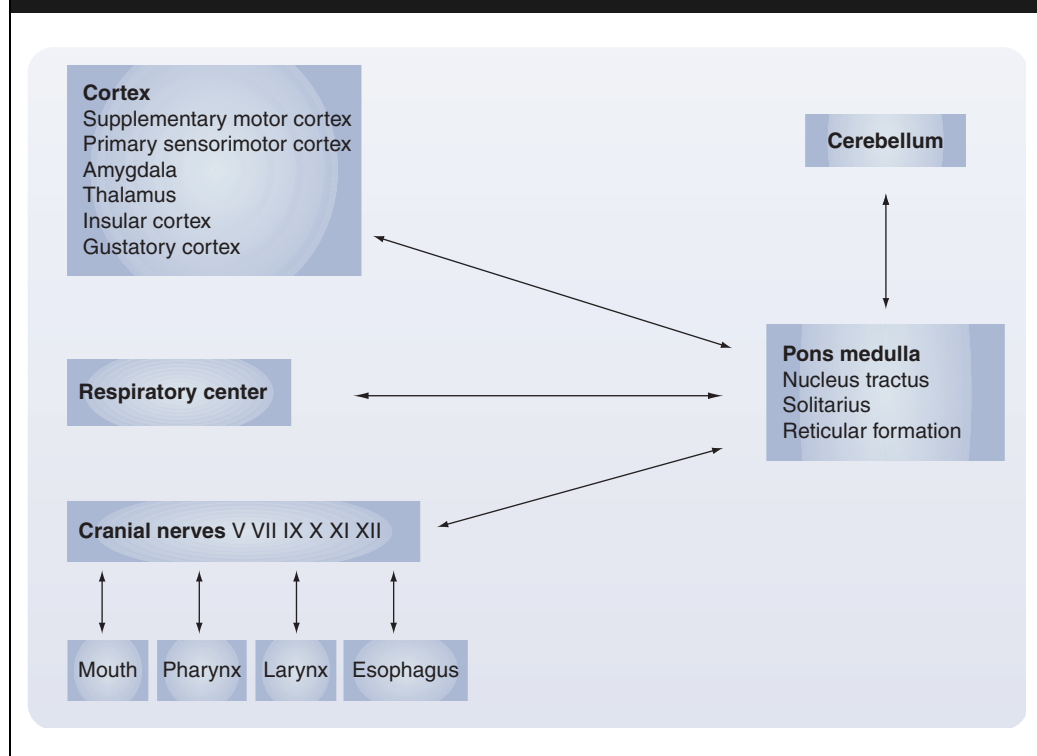
The cortical representation of swallowing is complex and bilateral, involving the activation of a number of discrete cortical areas (premotor cortex, sensorimotor cortex, primary gustatory cortex, amygdala, insula and basal ganglia/striatum) which may work in parallel rather than in series [18–21]. Dry, wet and repetitive swallows appear to activate different cortical areas, suggesting different types of swallowing processes [20,22,23].

### Brain stem

The paired swallowing centers are located within the pontine and medullary regions, between the posterior pole of the facial nucleus and the rostral pole of the inferior olive. They are a collection of interneurons (subnetworks) within the reticular formation, which may have the ability to function/operate independently [24,25]. Control of swallowing is likely a basic (repetitive) medullary program, modified by bolus volume and consistency via peripheral (afferents) or central feedback (cortical/ interneurons) mechanisms [21,22,26].

Keywords: stroke, substance P, swallow



**Figure 1. Neurological control of swallowing.**

#### Neurotransmitters/neuromodulators

The main neurotransmitters of the brain include serotonin, acetylcholine, dopamine (DA), norepinephrine and  $\gamma$ -aminobutyric acid (GABA) [27–29]. These may coexist in different networks or with neuromodulators, which are often peptides.

Afferents to the striatum are from the cortex, (including insula), amygdala and from the substantia nigra. The crucial pathways for the control of swallowing include the nigrostriatal, striatonigral and the striatopallidal pathways. Substance P (SP) and dynorphin are the primary neuropeptides within the nigrostriatal fibers [30–32], and enkephalin in the striatopallidal (via the subthalamic nucleus), although the final transmitter in all cases appears to be GABA. These two pathways provide a tonic input to the substantia nigra. The subthalamic nucleus stimulates the substantia nigra, inhibiting the swallowing process, whereas the striatonigral pathway inhibits the substantia nigra, facilitating the swallow (Figure 2).

SP can be found in many different areas of the CNS and in the case of swallowing, is considered to be a neuromodulator rather than a transmitter [33,34]. Evidence from animal models using DA antagonists and agonists, suggests that DA is critical for the expression of SP, increasing it at the cellular level (both within the cell body and

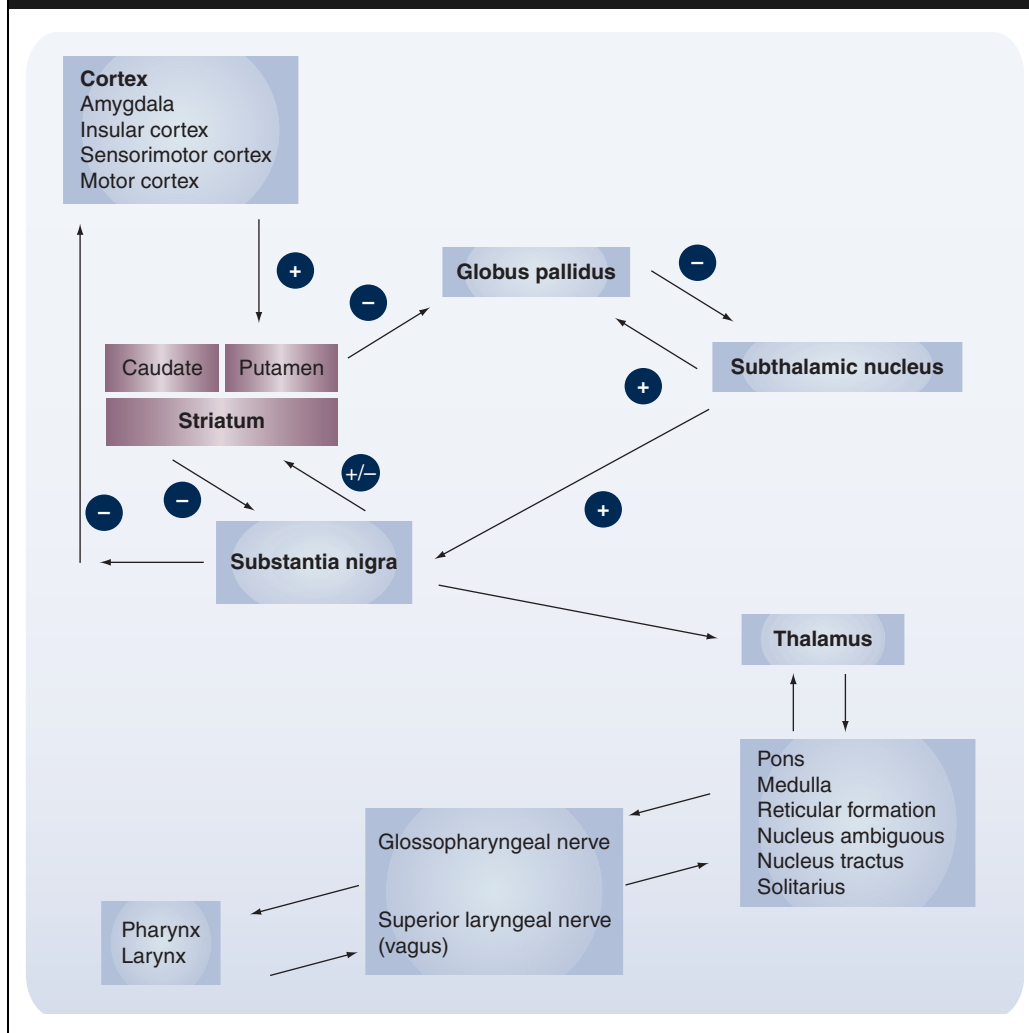
nerve terminals). This effect was demonstrated by DA agonists administered to rats, which resulted in an increase in striosomal expression of SP [32]. Conversely, when DA antagonist ( $D_1$  and  $D_2$ ) were administered in the same setting, a decrease in SP expression was observed [35]. Compounds that inhibit DA pathways also cause an increase in the activity and expression of enkephalin, due to a reduction in the usual inhibitory tone [31]. Output from the substantia nigra occurs via the thalamus, superior colliculus and the pedunculopontine nucleus [31]. These pathways provide input into the medullary swallowing centers in addition to the premotor cortex.

SP is also found in the glossopharyngeal and superior laryngeal nerves (sensory motor), the neurological supply to the pharynx and the non-myelinated C fibers found in the pharyngeal wall, suggesting an integral role for SP in the peripheral regulation of swallowing [36]. In addition, there is also an extensive plexus of nerves containing SP in the laryngeal and tracheal epithelium [30,35].

#### What is the role of SP in swallowing?

Studies using DA antagonists reduced the synthesis of SP both in cell bodies and nerve terminals, synthesizing and transporting SP to the periphery [30,31]. Clinical studies investigating patients with bilateral basal ganglia infarcts have

**Figure 2. Interplay between the substantia nigra and striatum in the control of swallowing.**



revealed a reduction in DA metabolism, with a consequent reduction in SP in the superior laryngeal and glossopharyngeal nerves. These findings suggest that DA signalling is important both centrally and peripherally [30,31].

Supporting this, depletion of SP in the pharynx results in an impaired cough reflex and a delay of the pharyngeal swallow in addition to an increase in pharyngeal transit time [36] which increases the risk of silent aspiration [37], whereas compounds that increase SP appear to reduce the risk of aspiration and reduce pharyngeal transit times [38].

Clinical studies suggest that local irritation of the pharynx, by water, capsaicin or other substances, including electrical stimulation [39] may result in the release of SP initiating a swallow. In this instance, SP depolarizes axon membranes by increasing nonselective cationic disturbances/discharges, which may be part of the unmyelinated

C fibres. Interestingly, the frequency of electrical stimulation in the pharynx is important [39] and does play a role, could tachyphalaxis be occurring or do high doses/frequencies result in inhibition rather than facilitation.

Ebihara and colleagues have noted that patients with advanced Parkinson's disease have a low sputum SP ( $911.2 \pm 8.4$  pg/ml) compared with non-Parkinson's patients ( $35.6 \leq 15.4$  pg/ml) and early disease ( $28.5 \pm 16.4$  pg/ml). They postulated that a loss of SP neurons in the striatum and brain stem as well as low levels of SP in the pharynx contributes to impaired sensory, as well as motor components [40].

### Stroke & swallowing

The cortical representation of swallowing is diffuse and the effect of stroke on swallowing depends on the lateralization of this representation and the

ability of the nondominant hemisphere to increase in size, which has been demonstrated by Hamdy and colleagues [41].

Cortical lesions affecting the precentral gyrus or internal capsule [21] result in spasticity of pharyngeal and laryngeal support musculature and peristaltic dyscoordination, which may in turn lead to aspiration. In addition, bilateral lesions may result in more severe dysphagia [43–45].

Recent work has suggested that cortical ischemia (periventricular lucencies/multiple infarcts) may disrupt the connections between the anterior and posterior cortical regions and deep connections, resulting in a disordered pharyngeal swallow [46]. The effect would be to reduce the inhibitory effect of the dopaminergic/SP pathways, leading to a reduced/absent pharyngeal swallow and hyperreflexia of the cricopharyngeus muscle [11,47].

Brain-stem lesions will also result not only in weakness of pharyngeal musculature, but also in coordination of the swallow which in turn causes pharyngeal dysmobility and asymmetry, incomplete laryngeal closure, vallecula pooling, vocal cord palsy and incomplete relaxation or spasm of the cricopharyngeus [48–50].

### Aspiration & pneumonia

Aspiration is a generic term referring to any material (solid or liquid) penetrating the larynx and entering the airway below the true vocal cords. Silent aspiration is defined as penetration of saliva or food below the level of the true vocal cords, without cough or any other outward sign of difficulty [51–53]. The presence or absence of a cough may be related to respiratory muscle function and hence the occurrence of a cough reflex [54]. Aspiration frequently accompanies dysphagia.

Pneumonia is a common cause of death in elderly people. In those patients with oropharyngeal dysphagia, the risk of pneumonia and mortality is increased [55]. Patients with recurring pneumonia may also have recurrent aspiration resulting in a reduction in protective mechanisms, including the cough reflex [37,56–59]. Nakagawa and colleagues noted that patients with basal ganglia infarcts had a high incidence of pneumonia, likely secondary to nocturnal aspiration and reduced cough reflex [60]. It has been postulated that DA metabolism causes reduced SP expression, resulting in pharyngeal latency and reduced cough reflex [60].

### Medication, aspiration & SP

Pharmacological agents can adversely affect the ability to swallow, both at a local level (oropharyngeal) and centrally. A number of medications

have been reported to be of benefit for those with mild-to-moderate dysphagia. Interruption of the dopaminergic system and consequently, SP, may affect the ability to swallow safely.

#### *Central effects*

There have been many case reports of neuroleptic agents both old (haloperidol) and new (olanzapine) causing dysphagia. It is thought that the primary mode of action is via the blockade of D<sub>1</sub> DA receptors, resulting in reduced levels of SP and an imbalance between the striatopallidal and striatonigral systems [62–65], which in turn causes defective tongue movements, slowed oral fine movement, delayed triggering of the swallow, irregular epiglottic movement and increased transit time.

Benzodiazepines depress the deglutitive system via overexpression of GABA, resulting in a disassociation of the oropharyngeal from the esophageal phase. It is thought that opiates may inhibit the release of SP [66], possibly via the dopaminergic pathways [27].

#### *Local/peripheral effects*

Anesthetic sprays, often used during endoscopy, may impair the swallow. It has been reported that as a result of the use of these sprays, pharyngeal transit times are increased which results in a lack of feedback from the pharynx, leading to a swallow that is not coordinated [39,67,68]. However, recent work examining the transposition of colonic tissue to the pharyngeal region has put this theory into question [16], and may support a role for a local action of SP initiated by direct irritation of cell fibers.

#### *Pharmacological agents with a positive effect on swallow*

There is an increasing amount of literature reporting the beneficial effects of a number of pharmacological agents on swallow. However, most suffer from either small numbers, nonrandomized trials and/or poor blinding.

#### *Central effects*

Perez and colleagues studied 17 patients with moderate dysphagia, in a randomized, placebo-controlled trial [69]. At 2 weeks following stroke onset, patients with difficulties swallowing, but who were able to take items orally, were randomized between a treatment arm (long-acting [LA] nifedipine 30 mg once-daily) and placebo. A total of 2 weeks after stroke onset, patients with mild-to-moderate dysphagia were

randomized to placebo or slow-release (SR) nifedipine, 30 mg daily for 4 weeks. Those randomized to the treatment arm demonstrated improvements in mean pharyngeal transit times (-1.34 s, 95% confidence interval [CI]: -2.56, -0.11) and mean swallow delay (-1.91 s, 95% CI: -3.58, -0.24). It is unclear whether this was a local effect (pharyngeal muscle being striated) or a global improvement in neurological function. The mode of action here is uncertain; however, it is known that SP is secreted in a calcium-dependent manner. Therefore, can it be assumed that calcium-channel blockers in effect increase synaptic calcium and facilitate SP release?

In Japan, a great deal of attention has been given to angiotensin-converting enzyme inhibitors (ACEIs). It was found that the use of ACEIs and stimulation of the oral cavity by simple oral care, which are both effective in increasing SP levels, reduced the incidence of aspiration pneumonia [37]. Sekizawa noted that those patients with stroke treated with an ACEIs had less pneumonia than those treated with other antihypertensive agents (7 vs 18%) [56].

Shibuya and colleagues noted that in a study of 143 patients with cerebrovascular disease who had an unsafe swallow and who were taking ACEIs for hypertension, aspiration occurrence was lower than if another agent was used [61]. Angiotensin-receptor blockers (ARBs), despite blocking the same system, do not have the same effect. This may be because ARBs act at a receptor level and consequently do not affect the production of SP.

In 1998, Arai and colleagues found similar results in their study of patients with nocturnal silent aspiration using Tc-labelled tin colloid applied via nasal catheter to note silent aspiration in sleeping patients which was reduced in frequency by the use of ACEIs [70]. Patients with silent aspiration/symptomless dysphagia were given imidapril or losartan. SP was measured in the pharynx before and after the administration of medication. Results showed that patients given the ACEI demonstrated increased levels of SP from 26.5–82.91 pg/ml accompanied by a reduction in symptomless dysphagia [70,71].

It is thought that the action of ACEIs in the cyclooxygenase pathways results in an increased production of SP, thus enhancing the swallow action. This is supported by the fact that patients with a cough secondary to the use of ACEIs have raised SP levels [72].

Iwasaki and colleagues used a Chinese herbal medicine, Banxia Houpo Tang (BHT), in patients with Parkinson's disease [73]. Results

demonstrated that the swallowing reflex before treatment was significantly delayed. Swallowing reflex before BHT treatment was  $3.66 \pm 0.98$  s, and it improved significantly, to  $2.27 \pm 0.54$  s ( $p < 0.0001$ ) after BHT treatment.

L-dopa does improve the ability to swallow in patients with Parkinson's disease however, studies have not been conducted in the field of stroke. Where there are bilateral basal ganglia infarcts, the synthesis of DA is low [60], theoretically L-dopa should be effective. Amantadine, a DA agonist, should have a similar effect. Both L-dopa and amantadine should work by increasing central levels (striatal) of SP. Interestingly amantadine and folic acid may potentiate DA neurones and prevent aspiration pneumonia [22]. Kanda and colleagues have reported that the combination of ACEIs and amantadine reduces the duration of antibiotic use and length of infection by methicillin-resistant *Staphylococcus aureus* in elderly pneumonia patients with a previous history of stroke [74]. Since amantadine is a cerebral stimulant, could it be that it has a general effect on wakefulness rather than directly on swallowing?

#### Local effects

In 2005, Ebihara and colleagues, in a randomized, controlled study of nursing home residents, noted that those given capsaicin reduced their swallowing latency time of the swallow reflex and improved their cough reflex [75]. A study using citric acid diluted with water has seen a change in pharyngeal transit times [76].

#### Expert commentary

SP is a pivotal neuromodulator for swallowing. Its effects are local to the pharynx and central to the substantia nigra and the striatum. Further work is required to investigate whether the use of agents to increase SP should be used routinely in patients with a stroke.

Swallowing is a complicated process. Although the actual swallow is a complex all-or-nothing reflex [77], modulation and cortical control is complex involving many areas of the brain [21]. Despite this, crucial areas would appear to be the amygdala, insular cortex and basal ganglia. The limited evidence presented so far would suggest that the best approach to the pharmacological management of dysphagia would be via the DA/SP route. SP and DA receptors are found both centrally and peripherally. SP levels at the pharyngeal level may be responsive to

direct irritation as well as a systemic effect. This is suggested by a rise in pharyngeal SP from distilled water and capsaicin. It can be hypothesized that the mechanism of action of pharyngeal stimulation [42,78,79] is via nociceptive, unmyelinated C fibres, to increase SP. DA and ACEIs, although having a peripheral effect, are more likely to exert their effect centrally. By increasing the level of SP in the nigrostriatal pathway, swallowing is more likely to occur in patients who are deficient in DA. L-dopa and DA agonists act first

to increase DA at the striatal level and second, SP. ACEIs may act at the substantia nigra or the nigrostriatal pathway to increase SP via the angiotensinogen pathway. ARBs do not have any effect since they block the effect of angiotensin rather than its synthesis and hence do not drive the pathway to produce SP.

## Outlook

Perez and colleagues reported the beneficial effects of calcium channel blockers [69]. Although their action as smooth muscle relaxants is known, this does not explain their effect on the pharyngeal phase of swallowing (skeletal muscle). As SP release is calcium-dependent, could there be a synergistic effect between the two?

Further work needs to be carried out to explore the effect of pharyngeal stimulation on SP and whether the success noted for ACEIs on nocturnal aspiration can be replicated during the day.

## Highlights

- Swallowing is a complicated process.
- Substance P (SP) is a pivotal neuromodulator for swallowing.
- Limited evidence currently available suggests that the best approach to the pharmacological management of dysphagia would be via the dopamine(DA)/SP route.
- By increasing the level of SP in the nigrostriatal pathway, swallowing is more likely to occur in patients who are deficient in DA.

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**Affiliation**

David G Smithard  
Stroke Physician,  
William Harvey Hospital,  
Ashford, Kent,  
TN24 0LZ, UK  
Tel.: +44 1233 61214  
Fax: +44 1233 616662  
david.smithard@ekbt.nhs.uk