

# Yawning

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## ABSTRACT

Yawning is a common physiological event that can be divided into 3 distinct phases: a long inspiratory phase, a brief acme and a rapid expiration.

The aim of yawning is not yet well defined. However this semi-voluntary event increases vigilance and aims to alert when drowsiness occurs. Yawning probably has an important role for social communication as well. Yawning can be responsible for pain, luxation or even transient ischemic attack. Abnormal yawning is present in various pathologies: migraine, Parkinson's disease, tumors, psychiatric diseases, infections or iatrogenic pathologies.

The neuro-pharmacology of yawning is complex and knowledge of its mechanisms is incomplete. While under the control of several neurotransmitters, yawning is largely affected by dopamine. Dopamine may activate oxytocin production in the paraventricular nucleus of the hypothalamus, oxytocin may then activate cholinergic transmission in the hippocampus, and finally acetylcholine might induce yawning via the muscarinic receptors of the effectors. In fact, this scheme is over simplified. Many other molecules can modulate yawning, such as nitric oxide, glutamate, GABA, serotonin, ACTH, MSH, sexual hormones and opium derivate peptides.

Dopamine involvement in yawning could have practical applications in the study of new drugs or the exploration of neurological diseases such as migraine or psychosis.

## INTRODUCTION

Yawning is a common physiological event that has been described since antiquity. Hypocrates described yawning as an exhaustion of the fumes preceding fever. Modern medicine did not pay a great deal of attention to yawning until the eighties, with advances in neuropharmacology. Yawning is an easily observable and quantifiable phenomenon. Hence knowledge of the transmitters and mechanisms implicated in yawning would enable one to better investigate drugs that modify yawning and pathologies where yawning is abnormal.

In this review we chose to study, first, the normal yawn. We will focus on its description, its neuro-pharmacological basis and its determinism. In a second section, we will deal with the pathologies associated with abnormalities in yawning frequency.

## A DESCRIPTION OF YAWNING

In humans, yawning can be divided into 3 distinct phases [1], a long inspiratory phase (4 to 6 sec), a brief acme (2 to 4 sec) and then a rapid expiration. The maximum duration of a yawn is 10 seconds. Looking about, moving or arranging one's hair can precede yawning. Yawning can be accompanied by stretching of the neck and arms; the stretch can be more generalized, though less often. Once initiated, yawns cannot be stopped, but can be modulated; the mouth opening, the thoracic participation and the facial contraction can be partially inhibited. Several anatomical structures are implicated in the occurrence and the control of yawning : the neocortex, the brainstem reticular formation, the neostriatum and the hippocampus. The effectors' centers include the inspiratory bulbar centre, the motor nuclei of the 5th, 7th, 10th and 12th cranial nerves, the phrenic nerve and nerves of accessory respiratory muscles.

*The inspiratory phase:* During this phase the lower jaws open widely, then a deep inspiration drains air principally through the mouth. The superior airways must be maximally opened. As such, an elevation of nostrils and soft palate, a dilatation of nasopharynx, a maximal abduction of the vocal cords and a downward and backward displacement of the tongue occur. At this phase, stretching also begins.

*The acme :* The maximal inspiration position is maintained. Contraction of the mimic muscles is characteristic of this phase, salivation, lacrimation can occur. At this point, there is a relative sensorial isolation of the subject; indeed the eyes are closed, the closure of the Eustachian tubes produces a transient hypoacusia [2] and the maximal muscle extension can interfere with other proprioceptive sensations.

*The expiration :* The muscles involved in the two preceding phases relax, a quick passive expiration occurs and subsequently a brief apnea ensues.

## THE ROLE OF YAWNING

Yawning is present in all humans, in all mammals and at least its mandibular form occurs in all vertebrates. Nonetheless, the purpose of such a widespread behaviour is difficult to define. Gaping movements of fish, amphibians and reptiles simulate the oral component of yawning in humans [3], however it is unknown whether or not this gaping behaviour is accompanied by the respiratory component of yawning. In fact, gaping may have a dissuasive or an aggressive goal in these species (4). The data on birds are more complete. Birds gape often and this behaviour may be associated with unilateral or generalized stretching. In young birds, gaping is usually used to receive their parents' food, hence the respiratory component of yawning is also discussed in birds (1).

In mammals, yawning is widely admitted, with associated components of gaping, inspiration and stretching [1]. In nomadic mammals, yawning could signal tiredness of one member of the group thus prompting the group to halt its progression and sleep.

Rodents are the most usual animal model of the neuro-physiology and neuro-pharmacology of yawning. Males yawn more than females and in males yawning is often associated with an erection. In carnivores, primates and domestic animals we can distinguish two types of yawn: a passive yawn, with closed eyes, when the animal is tired, bored or hungry ; an active yawn, during which the animal keeps its eyes open, shows its teeth and threatens its adversary (5). In primates, males yawn more than females and dominant males more than the other males (6). In animals, thus, yawning is mostly a group behaviour with high social and communicative significance.

In humans, the earliest yawn recorded to date was observed in a 15 week old embryo during an obstetrical sonogram [7]. In the second half of the pregnancy yawns become common. In new-borns, a yawn occurs a few minutes after the first breath and the first oral cues. Infants under a year frequently yawn without stretching, whereas children stretch often when yawning. Yawning decreases in frequency with maturation, and adults often yawn without stretching, this voluntary inhibition being acquired because of social rules. The neo-cortex should be responsible of these behaviours, with the frontal neo-cortex as the best candidate.

In humans, men do not yawn more often than women (13). During the day, yawns occur more often before sleeping or after waking (8). In fact before sleeping we yawn without stretching and after waking we often stretch without yawning (9), and we don't yawn when sleeping (10). Lal et al. (11) showed that yawning frequency increased after both apomorphine and placebo when given in the morning compared with responses in the afternoon. These results suggest a diurnal variation in dopamine receptor sensitivity. Greco (12), in 1993, recorded the yawning behaviour of 28 students during a week. Yawns were associated with relative passive activities like attending class, reading and watching television, but were also observed during driving. Several discrepancies emerged between what students thought about their yawns and their actual behaviour, for instance, they believed they yawned more in the afternoon, which is in fact the period when the percentage of daily yawns fell to its lowest level.

Yawning can be observed in various non-pathological contexts such as before eating (hypoglycemia could be a cause) or after eating (in a drowsiness context, almost always after alcohol absorption), in a stressful situation, in motion sickness or altitude changes [21]. Other classical situations are associated with yawning: boredom and drowsiness are the more frequent ones, hunger is also common. This introduces the debate about the aim of yawning. For some authors it has a respiratory aim, for others it modulates attention and lastly, some authors think that its main goal is a communicative one.

*The respiratory hypothesis of yawning* : During the respiratory phase of yawning, contraction of the diaphragm induces an increase of splanchnic venous return, by compression and by inducing a thoracic depression. Contraction of the lateral pterygoids and the soleus muscles empties the rich venous plexus. Contraction of the muscles of the limbs during stretching induces an increase of venous return to the heart. The deep inhalation stretches the bronchial musculature that stimulates the vagal terminals and the cholinergic pathway that dilates arterioles, and thus enhances cerebral blood flow (3). Dilation of superior airways and stretching of the terminal bronchioles and alveoli induce an exhalation of CO<sub>2</sub> and an hyperoxy. This increase of cerebral blood flow associated with hyperoxy improves cerebral oxygenation and decreases CO<sub>2</sub> concentration, so the aim of yawning could be almost a respiratory one.

However, it has been demonstrated that neither breathing pure O<sub>2</sub>, nor breathing gases high in CO<sub>2</sub> has a significant effect on yawning frequency, and that physical exercise sufficient to double breathing rate has no effect on yawning. These two studies suggest that yawning does not serve a primary respiratory function (14). Furthermore, studies on the vasomotor reaction of healthy volunteers and patients (Raynaud's and Burger's disease) have shown that yawning induces a transient distal vasoconstriction of vegetative origin, and not a vasodilation [9].

*The alertness goal of yawning* : this second theory was more developed. Yawning often occurs when we must maintain a high level of vigilance in the absence of environmental stimulation. Yawning could be a reflex answer of the brainstem reticular formation to increase the cortical level of vigilance. Indeed, yawning induces sensory afferences from the terminals of the fifth facial nerve that stimulates the brainstem. Monitoring jugular O<sub>2</sub> partial pressure, and electroencephalograms (EEG) in thrombotic patients, Karasawa (15) found that yawning appeared when the posterior activity slowed on the EEG, and when the oxygen monitoring showed a decreased O<sub>2</sub> partial pressure. Moreover yawning was followed by an acceleration of the EEG. Sato-suzuki produced yawning by electrical and chemical stimulation of the paraventricular nucleus of the hypothalamus. A stereotyped yawning response occurred, but after a systematic fall of blood pressure and an EEG arousal (16). Recording wrist movements and yawns in healthy volunteers during several days, Baeninger [17] showed that yawns were followed by an increase of wrist motions, which confirmed the alertness goal of yawning.

In fact the 2 theories are not really opposite. We can speculate that decrease of vigilance induces hypoxia and hypercapnia that stimulate the brainstem reticular formation, which in turn induces yawning. Then, this yawning increases somesthetic afferences and O<sub>2</sub> blood concentration, and stimulates various brain areas thus increasing vigilance.

*Yawning has a primarily a communicative aim* : During a boring conference for instance, an auditor may yawn in order to maintain attention despite the boring surroundings. This type of yawning is an alertness signal to the speaker who realizes that s/he is not interesting. Yawning during a conversation could also express a refusal to participate in the dialogue, a loss of interest. In these situations, yawning, a semi-voluntary act, clearly has a non-verbal communicative status [18]. Yawning is easily elicited by interactive situations like suggestion. Bell [19] was able to induce yawning in students by instructing them to think about it, through imitation, or thoughtful preoccupations with yawning: Charcot [20] prevented his students from yawning during a lesson about yawning. In humans, thus, yawning remains a group behaviour with high social significance and non-verbal communicative aim.

## PHARMACOLOGY OF YAWNING

Yawning is under the control of several neurotransmitters and neuropeptides. While its neuropharmacology is complex and not yet fully understood, it could have useful applications.

### DOPAMINE

In rats, dopamine receptor agonists--such as apomorphine and bromocriptine--are able to induce yawning, often together with penile erection in rats. This response is induced by selective D2 receptor agonists but not by type D1 (21). Extremely low doses of a dopamine receptor agonist (quinpirole), that has 100 fold greater affinity for D3 than D2 receptors, induced yawning behaviour in absence of other effects. Therefore the authors have suggested that yawning may be a D3 mediated process (23). Logically, dopamine receptor antagonists like classical neuroleptics (22) block these responses.

The implication of dopamine presynaptic autoreceptor agonists has been amply discussed. For instance, Morelli (24) demonstrated that a dopamine receptor agonist with high D1 receptor affinity was able to significantly reduce yawning evoked by apomorphine. Since dopamine autoreceptors are type D2, a D1 receptor antagonist is not expected to interact with them. Furthermore, Stalhe et al. demonstrated that apomorphine can induce hypomotility and yawning even when amphetamine elevated the extracellular level of dopamine (25). They showed, moreover, that apomorphine-induced yawning does not follow autoreceptor-induced reductions in neurotransmitter metabolism in the striatum (26). Lynch et al. obtained the same result in the mesolimbic region (27). These results suggest that D2 post synaptic receptors are involved in induced yawning, but that presynaptic autoreceptors, or D1 receptors are not. Proof of a possible involvement of D3 receptors must await further investigation.

The site of action of dopamine receptor agonists is the paraventricular nucleus of the hypothalamus (21). This hypothalamus nucleus contains dopaminergic nerve endings; immunocytochemical studies have showed that dopaminergic synapses impinge on the cell bodies of oxytocinergic neurones in this nucleus (28). Moreover, oxytocin receptor antagonists prevent apomorphine induced yawning (29). These results suggest that dopamine receptor agonists induce yawning by activating oxytocinergic neurones.

In healthy humans, we demonstrated that low doses of apomorphine also induce yawning (30), and various pathologies mainly related to dopaminergic system dysfunction show variations of spontaneous yawning frequency. Typical neuroleptics that have a dopamine receptor antagonist action, such as haloperidol, prevent apomorphine induced yawning (31). Concerning atypical neuroleptics, while certain authors have concluded that they do not prevent apomorphine-induced yawning (32), others have ascertained the contrary (33, 34). In a double-blind placebo controlled study conducted in 1995, we investigated the effect of a pretreatment with amisulpiride (a D2-D3 blocker) on apomorphine induced yawning in healthy volunteers. Amisulpiride (300mg), which has been shown to improve negative symptoms in schizophrenic patients with predominant negative signs, and was therefore suggested to block dopamine presynaptic D2 receptors did not block apomorphine induced yawning. Several explanations might be proposed, among them are the following : yawning is not related to either D2 presynaptic receptor stimulation, or D3 receptor stimulation.

### OXYTOCIN

Oxytocin, a neuropeptide of the neurohypophysis, is mainly implicated in parturition and lactation. In fact, it is also present in the hypothalamus and is able to induce penile induction and yawning when injected in the central nervous system and especially in the paraventricular nucleus of the hypothalamus, in rats (36). This oxytocin-induced yawning is abolished by both atropine and scopolamine, which are antimuscarinic drugs, but not by dopamine D2 receptor antagonists such as neuroleptics. We can thus speculate that dopamine receptor agonists induce yawning by releasing oxytocin (37), which subsequently activates cholinergic transmission in another brain area. Experimental studies suggest that, in the paraventricular nucleus of the hypothalamus, oxytocin induces yawning by activating its own transmission. One of the oxytocinergic pathways, activated by oxytocin itself, which projects to extrahypothalamic areas and whose activation induces yawning, might be a hypothalamo-hippocampus pathway (38). However, oxytocin also projects endings to the pons and to the medulla oblongata.

### NITRIC OXIDE

Nitric Oxide (NO) is produced from arginine by Nitric Oxide Synthetase (NOS), a calcium-calmodulin dependent enzyme. Many compounds that induce yawning such as dopamine receptor agonist, NMDA, oxytocin increase NOS activity and thus NO production (40). Yawning induced by dopamine receptor agonists, NMDA, oxytocin is prevented by calcium channel blockade (w-conotoxin), a NOS inhibitor and oxytocin receptor antagonist (38-39). A NO-releasing compound injected in the medial part of the paraventricular nucleus of the hypothalamus (PVN) induces the stereotypical yawning response (16). The paraventricular nucleus of the hypothalamus is one of the brain areas richest in NOS activity (41). In the PVN, parvocellular and magnocellular neurons contain NOS (42). Parvocellular cells in the PVN send descending axons to the lower brainstem (43). These results suggest that dopamine D2 receptor agonists, NMDA,

Oxytocin induce yawning by increasing intracellular calcium, which in turn activates NO synthesis, in the parvocellular cells of the paraventricular nucleus of the hypothalamus. These parvocellular neurons would project to respiratory, cardiovascular, motor and arousal systems in the lower brain stem (16).

#### ACETYLCHOLINE

Cholinergic drugs (physostigmine, pilocarpine ...) induce yawning and muscarinic receptor antagonists prevent yawning induced by dopamine receptor agonist, ACTH,  $\alpha$ MSH, oxytocin (44). These results suggest that yawning induced by these four drugs is mediated by cholinergic activation. In fact, M1 type muscarinic receptors are involved in this reaction (45). Cholinergic transmission has therefore been suggested being the final step of the neuronal pathway involved in yawning (46). The site of the brain where acetylcholine receptor agonists induce yawning may well be the hippocampus; indeed mesoseptal dopaminergic neurons play a role in the control of the hippocampal cholinergic neurons. Moreover  $\alpha$ MSH, when inducing yawning, increases acetylcholin turnover rate in the hippocampus of the rat (47).

However, in humans, Skorzevska (48) did not find a significant correlation between yawning and a muscarinic receptor antagonist injection.

#### ACTH and $\alpha$ MSH

The central administration of adrenocorticotropin hormone (ACTH) or  $\alpha$ melanocyte stimulating hormone ( $\alpha$ MSH) induced recurrent episodes of yawning and stretching in different animal species (49). Beta adrenoceptor agonist (salbutamol) and muscarinic M1 receptor antagonist inhibit yawning produced by these two neuropeptides, but not by dopaminergic activation or inhibition. Hence, ACTH and  $\alpha$ MSH produce yawning via activation of a cholinergic mechanism (45). Recent studies have led to the cloning of the ACTH- $\alpha$ MSH receptor genes. They are present in several brain areas including the hypothalamus, the midbrain and the brainstem (50). One of these sites is probably involved in the yawning-stretching syndrome. ACTH and  $\alpha$ MSH induced-yawning and stretching (when injected into the hypothalamus periventricular region of the third ventricle) is prevented by a selective melanocortine 4 (MC4) receptor antagonist (51). A MC1 receptor selective agonist was able to induce yawning and stretching (52).

ACTH- $\alpha$ MSH induced yawning is prevented by calcium channel blockade and by nitric oxide synthetase inhibitor (38), suggesting that these neuropeptides probably exert their effect via nitric oxide activation.

In humans, Melaton II, a non selective melanocortin receptor agonist, induces erections, increase of sexual desire, nausea and stretching-yawning behaviour (53).

#### SEROTONINE

Post-synaptic serotonergic 5HT1a receptor agonists have an inhibitory effect on yawning induced by dopamine receptor agonists (46). Inhibitory serotonergic receptors seem to be located on the terminal dopaminergic neuron on the striatum (54). Depletion of serotonin potentiates dopamine receptor agonist induced yawning (55). Serotonergic 5HT1c receptor agonist, mCPP and TFMPP induced yawning in both the rat and humans (56). These yawns are inhibited by NOS inhibitor but not by oxytocin receptor antagonist. As such, nitric oxide seems to be implied in this induced yawning (38).

#### OPIOID PEPTID

Morphine, an opioid receptor agonist inhibits dopamine receptor agonists (*i*(bromocriptine), ACTH and cholinergic drugs (physostigmine, pilocarpine) induced-yawning in rats (57). Naloxone reverses this effect. The paraventricular nucleus of the hypothalamus contains endogenous opioid peptides and mu subtype opioid receptors. Moreover, a decrease of nitric oxide was measured, during in-vivo microdialyse, concomitant to the inhibition of yawning behaviour (60). This decrease could result from a decrease of the calcium influx in the oxytocinergic cells which in turn would induce a decrease in nitric oxide synthetase.

In humans, yawning is a frequent withdrawal sign in heroin addicts (58-59).

#### SEXUAL HORMONES

In rats, spontaneous yawning is more frequent in males than in females. Dopamine receptor agonists and oxytocin induced yawning is abolished by castration. It can be restored by substitution therapy with estradiol alone or with estradiol and testosterone. In intact male rats, estrogen inhibits dopamine receptor agonist induced yawning, and testosterone has no effect (61). Sexual hormones modulate both spontaneous and induced yawning behaviour. Luteinizing hormone releasing hormone (LHRH) has been reported to antagonize induced yawning.

However, in humans yawning frequency does not differ between men and women (13).

#### Adrenalin and noradrenalin

Yawning induced by dopaminergic and cholinergic agents, ACTH,  $\alpha$ MSH and oxytocin, is facilitated by beta adrenoceptor blockade (propranolol, pindolol). However, pindolol has also 5HT1a blocking properties that

might explain yawning facilitation. In contrast, yawning is inhibited by alpha<sub>2</sub> pre-synaptic receptor blockade, which increases noradrenaline release (62). The central adrenergic may thus take part in the regulation of the yawning.

N.methyl-d-aspartic acid (NMDA)

NMDA, an excitatory amino acid agonist of NMDA receptor subtype, induces yawning (61). NMDA induces this behavioural response by increasing intracellular calcium concentration in the oxytocinergic neurons, thus activating nitric oxide synthetase, nitric oxide synthesis and hence oxytocinergic transmission (63).

Gama amino butyric acid (gaba)

GABA-B receptor agonists (baclofen 3mg/kg) inhibit the yawning response by modulating acetylcholine transmission (64). GABA-A receptor activation also inhibits yawning (65)

Neurotensin

Neurotensine has been reported to antagonize drugs that induce yawning.

In conclusion of this part, the literature review shows that the pharmacological mechanisms underlying yawning are complex and that many systems and neuro-mediators are involved. Nonetheless, knowledge of the pharmacology of yawning could be useful for the experimental pharmacology of new drugs. First, it enables the study of the actions of psychotropic drugs on the different brain systems (66). For instance, a drug that produces yawning but antagonizes dopamine receptor agonist induced yawning may be a dopamine receptor partial agonist. It is also possible to functionally discriminate between central and peripheral beta adrenoceptor antagonists. If apomorphine-induced yawning is increased by a beta adrenoceptor antagonist, it means that it has a central action. As clinical evaluation of new psychoactive drugs is difficult and animal screening is difficult to transpose to humans, knowledge of their central pharmacological action could be useful. Moreover, hypotheses about the biological basis of severe psychiatric illness have been stimulated by knowledge of the mechanism of action of psychotropic agents. Lastly, the neuro-pharmacology of yawning provides information about the physiology of yawning and hence the physiopathology of diseases associated with abnormal yawning behavior.

## YAWNING AND HUMAN DISEASES (table 1)

### PATHOLOGIES CAUSING BY NORMAL YAWNING

Yawning could be responsible for pain, luxation and even transient ischemic attack.

Myofacial pain, click, and crepitation during yawning may indicate a temporo-mandibular joint disturbance (67). Discomfort when yawning may also be encountered in patients with gross calcifications of the styloïd ligament.

Tesfay (68) described a recurrent subluxation of the lower jaw induced by yawning in a 25 year old woman. After 2 temporo-mandibular luxations during yawning, the woman learned to control and voluntarily inhibit her yawns. Despite this, there were four occasions over the ensuing 34 years during which subluxations of the jaw recurred.

This type of accident, although rarely reported, seems to be relatively frequent and well known to practitioners. An anatomical abnormality of the temporo-mandibular articulation is very often present.

Handa (69) reported a substantially less frequent incident, transient ischemic attacks induced by yawning in a patient who underwent a temporal mid-arterial cerebral artery by-pass operation. Yawning provoked recurrent cerebral ischemia by kicking the donor artery with each wide mouth opening.

### ABNORMAL YAWNING CAUSED BY PATHOLOGIES

#### CENTRAL NERVOUS SYSTEM AETIOLOGIES

##### MIGRAINE

Spontaneous yawning is a frequent symptom before, during and after migraine attacks. Apomorphine, a dopamine receptor agonist, when injected at very low dose (5 µg/kg, i.e. 1% of the dose that improves Parkinson's disease) induced a significantly higher number of yawns in migraine patients than in a control group of healthy volunteers (70-71). So, migraine patients may have dopaminergic hypersensitivity, and apomorphine-induced yawning could be a sensible test to detect this hypersensitivity. A growing body of pharmacological evidences indicate that dopaminergic neurotransmission is a major patho-physiological component of migraines. Low doses of apomorphine (5-10 µg/kg) increase systolic velocity and mean velocity

in the middle cerebral artery in migraine patients compared to control subjects (74). Apomorphine has a cerebral vasodilatory effect and increases blood flow significantly in the middle cerebral artery in migraineurs (75). Dopamine receptors have been localised directly in vascular beds of cerebral arteries, they are believed to be involved in migrainous pathogenesis (76). Dopamine receptor antagonists are effective in the acute and chronic treatment of migraines. Prochlorpromazine, a potent dopamine D2 receptor antagonist, has demonstrated a high degree of efficacy (82 to 88 %) in the acute treatment of migraine in a placebo-controlled clinical trial, with minimal side effects and no headache recurrence (72). Flunarizine, initially developed as a calcium channel blockade, displays significant dopaminergic antagonist properties and a moderately high affinity for the D2 subtype receptor. It is marketed as an anti-migraine drug in many countries.

In general, headache is not a common side effect of dopamine agonists. However in the treatment of Parkinson's disease, in elderly patients with a past history of migraine, low doses of apomorphine (1 mg) have been reported to induce migraine headaches (73).

Considerable evidence thus supports an involvement of the dopaminergic system in migraine through dopamine hypersensitivity (78). Recent genetic advances should elucidate the mechanism of this hypersensitivity. An increased density of dopaminergic D5 receptors in peripheral blood lymphocytes of migraine patients has been reported recently (77). The frequency of a familial predisposition to migraine suggests the presence of a genetic factor. In 1993, a gene for the familial hemiplegic migraine has been mapped on the chromosome 19p13. The gene encodes an alpha-1-subunit of a voltage gated calcium channel. In 1997, Peroutka (79) reported an association between migraine with aura and dopamine D2 receptor (DR D2) related genes. He suggested that the presence of the DR D2 Nco1 IC allele has a significant effect on dopamine susceptibility of migraine patients with aura, as compared to a control group as well as to patients with migraine without aura. In 1998, another allele of DR D2 gene was associated with dopamine hypersensitivity in migraine patients without aura. Del Zompo et al. took a sample of Sardinian families with migraine (Migraine with or without aura). A subgroup of «dopaminergic migraine patients» was selected according the presence of both nausea and yawning before and during the pain phase (80). They demonstrated a positive association between the presence of the allele 1 of the DR D2 gene (the less common form of DR D2 alleles ) and a subgroup of «dopaminergic migraine patients without aura». Dopaminergic hypersensitivity in migraine is most likely multi-factorial, and several genes could be implicated. Apomorphine-induced yawning could be a sensitive test to detect «dopaminergic migraine patients».

#### BASAL GANGLIA DISORDERS

Pathologies with dopaminergic system dysfunction should induce abnormal yawning.

Indeed yawning seems to be abnormally infrequent in Parkinson's disease and more frequent than in general populations in Huntington's disease, in supra-nuclear palsy (21-81) without an accompanying sleep disturbance or somnolence. Subcutaneous apomorphine injections in Parkinsonian patients usually induce yawning just before or at the beginning of the motor response, with or without sedation (82-83). Otherwise, L.Dopa induced yawning is much less frequent. Goren (84) described 2 patients, whose L.Dopa-induced «on» periods were always preceded by yawns. The yawns generally preceded turning «on» by 3 to 6 minutes. They were often associated with stretching and were not associated with a change in the level of arousal.

#### FOCAL BRAIN LESIONS

Abnormal repetitive yawning may be the consequence of various central nervous system focal lesions such as tumor, apalic syndrome, cerebral malformations and transtentorial herniation (85). Frontal lobe, mesodiencephalic and bulbar lesions are the most often involved in excessive yawning.

Poster (86) reported a patient with excessive yawning, hemi-paresis and facial paresis as a relapse symptom of multiple sclerosis. Yawning occurred 4 times per minute and there were multiple lesions of the brainstem on the MRI. With a steroid therapy the yawning syndrome disappeared, as did the other acute symptoms.

Loawerse (87) observed prolonged bouts of intensive and uncontrolled yawning in 23 of 200 patients with ALS. All 23 patients had signs of bulbar paresis. For Loawerse, uncontrolled yawning could be a sign of pseudo-bulbar syndrome akin to forced crying or laughing.

Another phenomenon is widely described in the literature, such being the presence of spontaneous yawning in locked-in syndrome, or the presence of spontaneous stretching of the plegic arm that accompanies spontaneous yawning. For instance, the case of a patient with a transecting glioma of the pons was reported, who, despite a locked-in syndrome (he could not open or close his mouth voluntarily), was able to yawn (88). Bauer (89) observed involuntary movements, such as sighing and groaning in locked-in syndrome patients with bilateral transverse lesions at the pontine or midbrain level. Anencephalic new-borns that have only midbrain structures still yawn. These structures thus seem to be sufficient to produce yawns (90).

Several observations of hemiplegic patients who could stretch both arms when yawning have been reported (91-92). Mulley (93) studied 40 stroke patients, 80% of whom had associated reactions affecting the hemiplegic arm. Involuntary arm movements often occurred when yawning in these patients. 25% of these patients had no voluntary arm movements, and they could have false hope, believing that these involuntary

movements were a sign of recovery. This phenomenon shows the functional efficiency of the pathway projecting directly from the stimulated basal ganglia to the lower motor systems of the brainstem and the cervical medulla (92).

#### EPILEPSY

In partial epilepsy, yawning has been described as a possible aura of epileptic seizure (18). More recently, yawning has been observed in infantile spasms (94)

#### NARCOLEPSY AND MYASTHENIA

These two diseases are regularly mentioned as potential causes of yawning, particularly in Forte's PhD thesis (95). However a medline search using yawning and narcolepsy/myasthenia did not provide any references.

#### INTRA CRANIAL HYPERTENSION

Yawning is one of the common signs of intra-cranial hypertension; it could be the sign of a diencephalic disorder.

#### PSYCHIATRIC DISORDERS

Charcot (20) described hysterical patients with unceasing yawns throughout the day. They only stopped yawning when sleeping, and yawning frequency could decrease when they sustained attention.

In early schizophrenia, yawning has been considered a good prognosis. It indicates that the patient desires to maintain contact with the real world. In chronic schizophrenia, however, it would indicate poor prognosis [3].

In 1995, We studied central dopaminergic system responsiveness in schizophrenic patients with predominant negative symptoms. Schizophrenic patients fulfilling DSM IV diagnostic criteria and healthy volunteers were included. We administered 2 micrograms/kg of apomorphine. Subjects were left alone in a room for 60 minutes and videotaped. The mean number of yawns per group were analyzed as a non-parametric variable using the Kruskal and Wallis Test. We found a significant difference between the two groups at the basal state and during the total test period. Patients yawned less than healthy volunteers, before and after apomorphine injection (see Figure). In depression, excessive yawning could be associated with other neuro-vegetative disorders. Sismotherapy could provoke bouts of yawning as well [1].

#### IATROGENIC YAWNING

Excessive yawning without a decrease of the arousal level has been noted with various drugs. Almost all of these treatments have a central nervous system action. Sodium valproate was administered to a patient with post anoxic myoclonus. Myoclonus disappeared, but uncontrolled yawning occurred. Yawning stopped when the treatment was stopped and recurred when the sodium valproate was reintroduced. Finally, yawning was abolished when sodium valproate was associated with pimozide, a dopaminergic antagonist (96). Excessive yawning has also been reported with antidepressants. For instance, clomipramine induces sexual excitation and very frequent yawns (97), fluoxetine (98) and imipramine also induces abnormally frequent yawning. Van Sweden (99) reported a 40 year old woman who presented excessive continuous yawning of acute onset, 7 days after onset of a new estrogenic therapy. Ten days following estrogen withdrawal, yawning disappeared. This case points to the influence of sexual hormones in yawning. Finally, yawning associated with sneezing, profuse sweating and vomiting is the well-known syndrome of opiate withdrawal.

#### INFECTIOUS DISEASES

Fever by itself can induce yawning. Frequent yawning is present in all encephalitis with vigilance disorders: listeria, tuberculosis encephalitis are classical examples, the same for trypanosomiasis wherein vigilance disorders are a major component (95-100). In Von Economo epidemic encephalitis, excessive yawning was included in a more generalised dysautonomic syndrome (101). Excessive yawning had also been observed in typhoid fever, measles, and herpes virus encephalitis.

#### METABOLIC DISORDERS

Acidocetosis, renal insufficiency, severe hepatic failure, hypo-glycemia (3) and thyroidal insufficiency (100) have been incriminated as excessive yawning etiologies.

#### SOPITE SYNDROME

The sopite syndrome is a possible manifestation of motion sickness (102); typical symptoms are frequent yawning, drowsiness, disinclination for work, lack of participation in group activities. It could be meshed with the other classical symptoms of motion sickness, like nausea, or it could be isolated. Unlike motion sickness, there is no adaptation phenomena.



## GASTRO-INTESTINAL DISEASES

Excessive yawning has been reported in gastro-intestinal diseases, especially with gastro-duodenal ulcer, where yawning crises can parallel pain exacerbations (103). In infants with gastro-esophageal reflux, Feranback (104) demonstrated that the reflux events were closely temporally associated with various behaviours such as emissions of gas or liquid, yawning, stretching or mouthing. Evans (105) reported cases of acute pharyngeal obstruction in infants, with yawning lasting until the obstruction was relieved. He suggested that the pharyngeal obstruction provoked a vagal stimulation, which induced yawning.

## CONCLUSION

Until the eighties, progress on the neuro-physiology and neuro-pharmacology of yawning was limited. Today, most of the neurotransmitters and anatomical structures implied in yawning are known. In the future, we will have to devote efforts to the understanding of the relationship between the different systems implied in the modulation of yawning. We also must keep in mind that most of our knowledge comes from animal experimentation and that the greatest care must be taken in extrapolating it to humans. Nonetheless, yawning has proved to be a valuable tool in studying the physio-pathology of diseases and the action of new drugs in humans. For instance, apomorphine-induced yawning allows one to evaluate dopaminergic reactivity. As this reactivity could be modified in pathological conditions, this test could evaluate putative treatments, for instance in migraine. Apomorphine-induced yawning could also be used in the study of the pharmacodynamics of new molecules. It could be used, in particular, for the exploration of the dopaminergic pathways, for instance the dose-effect relation of dopamine antagonists or dopamine partial agonists.

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Table 1 : YAWNING AETIOLOGIES

PHYSIOLOGICAL:

drowsiness, boredom  
imitation, thinking about  
hunger

PATHOLOGICAL:

NEUROLOGICAL:

- dopaminergic dysfunction: Parkinson's disease (unfrequent yawns), Huntington's disease, supranuclear palsy, migraine (frequent yawns).

focal lesions of the frontal lobe, mesodiencephalic or bulbar lesion:

tumor  
multiple sclerosis  
stroke  
intracranial hypertension  
myasthenia  
narcolepsy  
epilepsy

PSYCHIATRIC:

hysteria  
schizophrenia  
depression

IATROGENIC

opiate withdrawal  
anti-depressant (clomipramine, imipramine)  
sodium valproate  
estrogens

INFECTIOUS

fever by itself  
trypanosomiasis, typhoid fever  
various encephalitis drowsiness: herpes virus encephalitis, measles encephalitis ...  
meningitis: listeria, tuberculosis

METABOLIC DISORDER

acidocetosis  
renal insufficiency  
severe hepatic failure  
thyroid insufficiency  
hypoglycaemia

SOPITE SYNDROME

GASTRO-INTESTINAL DISEASE:

gastro-duodenal ulcer  
gastro-oesophageal reflux  
acute pharyngeal obstruction