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Neurophamacology of Yawning

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Abstract

Yawning is a common behavioral event that is observed in humans, as well as other mammals, birds and reptiles. In humans, yawning often occurs just before bed and upon waking up, and is also associated with tedious or boring situations. Although the physiologic roles of yawning have yet to be fully elucidated, the past 50 years of research has led to a much greater understanding of the neuropharmacologic regulation of yawning. While many of the early studies concluded that yawning was primarily driven by changes in cholinergic neurotransmission, we now know that numerous neurotransmitters and neurohormones are involved in the mediation of yawning, including acetylcholine, dopamine, glutamate, serotonin, oxytocin, GABA, opioids, adrenergics, nitric oxide, as well as the proopiomelanocortin-derived peptides ACTH and α-MSH. Furthermore, antagonist interaction studies have clearly defined at least 3 distinct neural pathways involved in the induction of yawning, as well as the hierarchical order through which these different neurotransmitter systems interact to regulate yawning. The following sections will discuss the state of knowledge for each of the major neurotransmitters and neurohormones involved in the regulation of yawning, their interactions with one another, and their place in the hierarchical organization of yawning.

Yawning is a phylogenetically conserved behavior, observed in mammals, birds and reptiles; it is essentially defined as a paroxysm of the respiratory cycle characterized by a standard cascade of movements over a 5- to 10-second period [1], with 3 distinct phases. Yawning is initiated by a wide opening of the mouth with an ample, slow and deep inspiration, followed by a brief interruption of ventilation fluxes once the thorax is full (the so-called acme state, which is often is accompanied by limb stretching and eye occlusion) and concluding with a short expiration, accompanied by the relaxation of all participating muscles. In the case of humans, yawning is also accompanied by a great expansion of the pharynx and larynx, and a maximal abduction of the vocal cords, with inspiration occurring essentially through the mouth. Although the duration of a yawn in a given individual appears to be fixed, it can be modulated voluntarily. Furthermore, it is important to note that yawning is also accompanied by an

opening of the eustachian tubes, a brief lowering of hearing acuity, as well as the opening of the stomach cardia resulting in an influx of intragastric air that is responsible for the sensation of abdominal fullness occasionally associated with yawning. Thus, yawning should not be thought of simply as the opening one's mouth, but rather a generalized stretching of muscles, particularly those of the respiratory tract, such as the diaphragm, intercostals, and those of the face and neck [2].

Although yawning is often associated with tedious or boring situations such as reading, traveling on public transport, driving, waiting or watching monotonous videos [3–5], yawning should not be thought of as simply a sign of boredom. For instance, yawning is thought to act as an alarm signal to warn drivers about the risk of falling asleep while driving a vehicle, particularly on long straight highways [6–9], suggesting that yawning may play a role in affecting arousal states. In fact, in humans yawning occurs most frequently during the transition from one state of arousal to another, such as just before bedtime and immediately after waking up, with the later particularly associated with stretching of the forelimbs and trunk [4, 10, 11]. Interestingly, in anesthetized rats, instances of inspiration and mouth opening (i.e. yawning) were preceded by cortical arousal, further supporting the notion that yawning is associated with changes in arousal states [12].

In a series of studies, Anías et al. [13] have clearly demonstrated the influence of circadian rhythms on the frequency of yawning, as the peak incidence of yawning in an inbred high-yawning subline of rats occurred just before the dark phase, regardless of the light-dark schedule. The peak in yawning disappeared when rats were subjected to constant light conditions, suggesting that this pattern of yawning is not endogenously generated. Interestingly, when these rats were further subjected to a restricted feeding schedule of just 2 h per day, a significant increase in yawning was observed just prior to feeding, suggesting that the anticipation of food is capable of functioning as a zeitgeber for the circadian regulation of yawning [14]. Similar instances of anticipatory yawning have been reported just before feeding in zoo animals, such as carnivores, fish and monkeys, as well as in wild hyenas, which yawn repeatedly while circling a dead animal just before eating it [15, 16]. These peaks in yawning are correlated with increased corticoid levels.

In addition, yawning has recently been hypothesized to play a role in thermoregulation dysfunctions, insofar as increases in yawning are observed when brain and/or core body temperatures are elevated, and decreases in yawning are observed as temperatures return to normal, suggesting that yawning may provide a compensatory cooling mechanism [17]. Similar effects are seen with D_2-like agonists which increase yawning over low doses, and induce hypothermia at higher doses that also corresponded to decreases in yawning [18]. Although a causal relation was not implied, these findings provide further support for the notion that there is an association between the regulation of core body temperature and the frequency of yawning.

Finally, it is well know that yawning is contagious in humans. Provine [19] has reported that 55% of spectators viewing a brief video of 30 successive yawns yawned

themselves within a period of a few seconds to 5 min. Additionally, it appears that observing the complete face of the yawner is necessary to induce yawning, as viewing only part of the face, such as a wide-open mouth, failed to trigger replication. Thus, Provine et al. [19, 20] concluded that contagious yawning in humans depends on a multimodal perception of the entire facial configuration, combined with audible respiratory movements and the coordinating dynamics. Studies in macaque monkeys have linked this ability to imitate behaviors to a group of neurons within the ventral premotor cortex, called mirror neurons, whose activity is correlated not only with the performance of specific behaviors, but also the observation of these behaviors in other individuals, suggesting that mirror neurons may provide the neurophysiologic foundation for contagious yawning in monkeys as well as humans [21].

Clearly, yawning is not a simple behavior, but rather a common response to a variety of environmental and physiologic stimuli, many of which will be described in greater detail in other chapters of this book. This chapter will instead focus on what is known about the neuropharmacologic regulation of yawning, as well as the hierarchical organization and interactions of the major neurotransmitter systems involved in the induction and regulation of yawning (fig. 1; table 1).

Major Neurotransmitters Involved in the Induction of Yawning

Adrenocorticotropic Hormone and α-Melanocyte-Stimulating Hormone

One of the earliest accounts of pharmacologically-induced yawning was provided by Ferrari et al. [22], who described a series of behavioral effects characterized by increases in stretching, yawning and grooming that occurred following the intracisternal administration of either adrenocorticotropic hormone (ACTH) or α-melanocyte-stimulating hormone (α-MSH): two of the centrally active peptide hormones that are formed by the processing of proopiomelanocortin (POMC) in the brain and pituitary. Although the fact that yawning is abolished by hypophysectomy suggests that an intact pituitary gland is necessary for ACTH to induce yawning [23], other studies have suggested that the hypothalamus is the primary site of action as increases in yawning are observed following the microinjection of ACTH into several hypothalamic nuclei [24], including the paraventricular nucleus (PVN), dorsomedial nucleus, ventromedial nucleus and anterior hypothalamus [25]. Dose-dependent decreases in yawning induced by the intra-PVN administration of ACTH are observed following microinjection of the melanocortin-4 receptor antagonist, HS014, into the PVN suggesting that activation of melanocortin-4 receptors within the PVN is sufficient for ACTH to induce yawning [25]. However, as yawning induced by the intracerebroventricular (ICV) administration of ACTH is not affected by the electrolytic lesion of the PVN [26], it is likely that multiple hypothalamic nuclei are involved in the mediation of ACTH- and α-MSH-induced yawning.

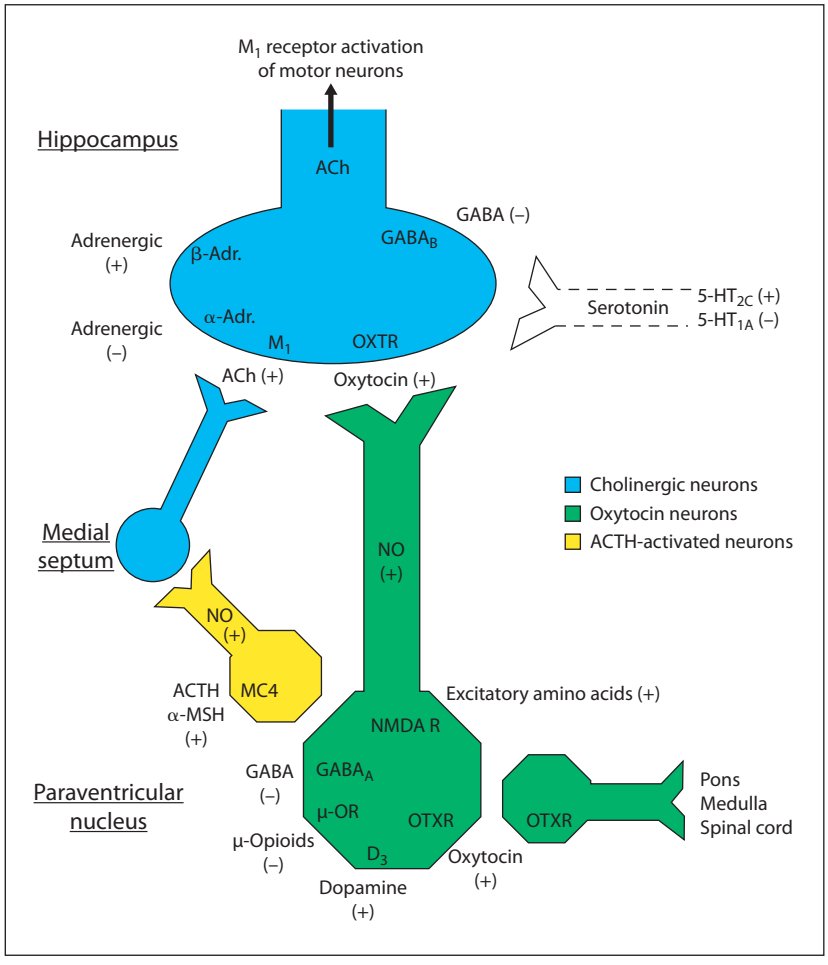

Fig. 1. Schematic representation of the neurotransmitters and receptor subtypes involved in the mediation of yawning. The main neural pathways that have been hypothesized to be involved in the regulation of yawning include: (1) two separate groups of oxytocinergic neurons projecting from the PVN to the CA1 region of the hippocampus, or the pons, medulla or spinal cord; (2) ACTH-/α-MSH-activated neurons projecting from the PVN to the hippocampus via activation of septo-hippocampal cholinergic neurons; (3) direct activation of septo-hippocampal/hippocampal cholinergic neurons; (4) a serotonergic-cholinergic pathway that has yet to be identified. Neurotransmitter systems/receptors that are capable of inducing or enhancing yawning are denoted by a (+), whereas those that are involved in the inhibition of yawning are denoted by a (–). See text for details regarding the interactions of these neurotransmitter systems.

Despite the fact that the hypothalamus, and in particular the PVN, is known to be involved in the induction of yawning by a variety of pharmacologic stimuli, including dopamine and oxytocin (see later sections), it is important to note that ACTH-induced yawning is not affected by dopamine D_2-like or oxytocin receptor antagonists [27, 28]. Although these findings suggest that the neurons involved

Table 1. Neurotransmitters involved in the regulation of yawning

Neurotransmitter	Effect of yawning	Receptor(s)	Brain region
ACTH/MSH	stimulatory	MC_4	hypothalamus
Acetylcholine	stimulatory	M_1	HI
Oxytocin	stimulatory	OXTR	PVN, HI
Nitric oxide	stimulatory	n.a.	PVN, others
Dopamine	stimulatory inhibitory	D_3 D_2	PVN
Excitatory AA	stimulatory	NMDA	PVN
Serotonin	stimulatory inhibitory	5-HT_{2C} 5-HT_2/5-HT_{1A}	n.d. n.d.
Opioid	inhibitory	μ-opioid	PVN, others
GABA	inhibitory	$GABA_A$/$GABA_B$	PVN, HI
Adrenergic	enhancing inhibitory	α_2-adrenergic β-adrenergic	n.d. n.d.

HI = Hippocampus; PVN = paraventricular nucleus of the hypothalamus; AA = amino acids.

in the mediation of ACTH-induced yawning are independent of those that mediate dopaminergic and oxytocinergic yawning, the induction of yawning by ACTH and α-MSH does not occur via completely autonomous mechanisms. For instance, similar to yawning induced by oxytocin, or D_2-like agonists, yawning induced by ACTH and α-MSH is inhibited by centrally active anticholinergics, such as atropine [22]. In total, these findings suggest that ACTH- and α-MSH-induced yawning results from the activation of melanocortin-4 receptors within a variety of hypothalamic nuclei, and although these receptors appear to be located on neurons that are distinct from those that involved in other forms or yawning (i.e. dopaminergic or oxytocinergic), ACTH-induced yawning appears to be mediated by a downstream activation of cholinergic neurotransmission that may be common for all forms of yawning.

Acetylcholine

A role for cholinergic neurons in the mediation of yawning was first suggested after dose-dependent increases in yawning were observed following systemic administration of the acetylcholinesterase inhibitor, physostigmine, and the direct muscarinic

receptor agonist, pilocarpine [29], effects that have been replicated with a variety of centrally active, but not peripheral acetylcholinesterase inhibitors [30–32]. Further support for a role of central muscarinic receptors in the induction of yawning was provided by antagonist interaction studies in which dose-dependent decreases in physostigmine-induced yawning were observed following administration of the centrally active cholinergic muscarinic receptor antagonist, scopolamine, but not the peripherally active muscarinic receptor antagonist methylscopolamine or the nicotinic receptor antagonist mecamylamine [29, 33, 34]. A specific role for the muscarinic M_1 receptor subtype in the induction of yawning was later proposed based on the findings that M_1 receptor agonists, such as RS-86 and YM796, induced dose-depended increases in yawning, whereas moderately selective M_1 antagonists, such as pirenzepine, inhibited yawning induced by either physostigmine or direct M_1 agonists [35–37].

In addition to supporting a role for M_1 cholinergic receptors in the induction of yawning, antagonist interaction studies have also provided evidence suggesting that septo-hippocampal cholinergic neurons play an important role in the mediation of yawning induced by a variety of pharmacologic agents. For instance, not only does ACTH- and α-MSH-induced yawning correspond to an enhancement of hippocampal acetylcholine turnover rates, but these ACTH- and α-MSH-induced increases in yawning are also blocked by centrally active cholinergic antagonists, such as scopolamine and atropine [22, 36, 38]. In addition, muscarinic antagonists have also been shown to inhibit yawning induced by oxytocin, dopamine D_2-like agonists, such as apomorphine, and 5-HT_2 receptor agonists, such as trifluoromethylphenylpiperazine (TFMPP) [33, 34, 36, 39, 40]. When taken together with the fact that decreases in apomorphine-induced yawning are observed after medial-septal lesions which interrupt the septo-hippocampal pathway [41], these findings point to a central role of septo-hippocampal cholinergic neurons as a site of action for the induction of cholinergic yawning, as well as a common downstream mediator of yawning induced by a variety of pharmacologic mechanisms.

Oxytocin

The first evidence in support of a direct role for oxytocin receptors in the induction of yawning was provided by microinjection studies in which dose-dependent increases in yawning were observed following microinjection of oxytocin into the PVN, as well as the CA1 region of the hippocampus [42], effects that were blocked by the ICV or intra-PVN administration of oxytocin receptor antagonists, such as d(CH2)5Tyr(Me)-[Orn8]vasotocin [26, 27, 36, 43, 44], as well as the systemic administration of anticholinergics [36, 39]. In addition to their capacity to inhibit oxytocin-induced yawning, oxytocin antagonists have also been shown to inhibit yawning induced by dopamine D_2-like agonists, such as apomorphine and N-methyl-D-aspartic

acid (NMDA); however, these effects are only observed following ICV and not intra-PVN administration [44], suggesting that these effects are mediated by blockade of oxytocin receptors outside of the PVN. In addition, although electrolytic lesion of the PVN is capable of inhibiting the induction of yawning by the ICV administration of either oxytocin or apomorphine [26], medial-septal lesions inhibited apomorphine-induced yawning (intra-PVN or ICV), but failed to affect yawning induced by either intra-PVN or ICV oxytocin [41]. When taken together with the finding that the induction of yawning by D_2-like agonists, such as apomorphine, also corresponds to increases in hippocampal oxytocin [26, 27, 45], these findings suggest that oxytocin neurons originating in the PVN and projecting to the hippocampus play an integral role in the mediation of yawning induced by D_2-like agonists and NMDA, the details of which will be described in later sections. However, the fact that medial-septal lesions failed to inhibit oxytocin-induced yawning suggests that a functional septo-hippocampal pathway is not necessary for oxytocin to induce yawning, raising the possibility that oxytocinergic neurons projecting from the PVN to structures such as the pons, medulla oblongata or spinal cord may also be capable of inducing yawning when stimulated by oxytocin [41 and references therein].

Nitric Oxide

In addition to their work demonstrating the importance of oxytocin in the mediation of yawning, Drs. Melis and Argiolas have also provided clear evidence of a central role of nitric oxide (NO) in the mediation of yawning [for review, see: 46]. Early evidence suggested that NO-induced yawning resulted from increased oxytocinergic neurotransmission, as yawning induced by the intra-PVN administration of NO donors, such as sodium nitroprusside, hydroxylamine and nitroglycerin, was blocked by the ICV administration of oxytocin antagonists [47, 48]. Further support for a role of NO in the mediation of yawning was provided by studies in which the intra-PVN administration of NO synthase inhibitors, such as NG-nitro-L-arginine methyl ester (L-NAME), were shown to be capable of inhibiting yawning induced by either apomorphine or oxytocin [49, 50], suggesting that in addition to stimulating yawning, NO signaling also plays an important role in the mediation of yawning induced by a variety of other mechanisms. This notion was later confirmed by studies in which a clear correspondence between the induction of yawning (by apomorphine, oxytocin and NMDA) and increased levels of NO_2 (a reliable indicator of NO production) within the PVN was demonstrated [51, 52]. However, it is important to note that while the intra-PVN administration of L-NAME blocks yawning that is mediated by activation of oxytocinergic neurons within the PVN (i.e. D_2-like agonist-, NMDA- and oxytocin-induced yawning), the ICV administration of L-NAME has also been shown to block yawning that is not mediated by PVN oxytocinergic neurons (i.e. ACTH- and 5-HT_{2C} agonist-induced yawning [53, 54]). Together, these studies

suggest that increases in NO signaling likely play a more general role in the mediation of yawning induced by a variety of mechanisms, the details of which will be described in later sections.

Dopamine

Although a variety of neurotransmitter systems are known to be involved in the regulation of yawning, perhaps none has received as much attention as the capacity of dopaminergic drugs to induce yawning. Since it was initially described by Mogilnicka and Klimek [55], hundreds of studies have investigated the phenomenon of D_2-like agonist-induced yawning, with many of the early studies focusing on the interactions of dopaminergic and cholinergic systems in the induction of yawning. For instance, in addition to being inhibited by centrally active D_2-like antagonists, such as spiroperidol, haloperidol and sulpiride, D_2-like agonist-induced yawning is also blocked by centrally active anticholinergics, such as scopolamine. Moreover, when combined with the inability of D_2-like antagonists to inhibit physostigmine-induced yawning, these studies support the notion that dopaminergic yawning is mediated by a downstream increase in cholinergic activity [56–58], similar to what has been described for ACTH- and oxytocin- induced yawning. Although early microinjection studies suggested that the induction of yawning by D_2-like agonists may be mediated by their actions in the striatum or septum [59, 60], subsequent studies demonstrated that apomorphine was capable of inducing yawning when injected into the PVN at doses approximately 5–40 times lower than those that were required to induce yawning in the striatum or septum [61], suggesting that the PVN may play a central role in the mediation of dopaminergic yawning, as had been previously described for oxytocin [42].

Subsequent studies by Drs. Argiolas and Melis provided several lines of evidence that clearly demonstrate the involvement of PVN oxytocinergic neurons in the mediation of D_2-like agonist-induced yawning. For instance, in addition to increasing yawning, apomorphine has also been shown to increase hippocampal oxytocin levels, two effects that are similarly inhibited by D_2-like antagonists [45]. Moreover, although apomorphine-induced yawning is prevented by electrolytic lesion of the PVN or the ICV administration of the oxytocin antagonists [26, 43], D_2-like antagonists fail to alter oxytocin-induced yawning [27, 42], suggesting that oxytocin plays an important role in the downstream mediation of dopaminergic yawning. Similarly, the induction of yawning by apomorphine also corresponds to increased NO_2 levels within the PVN, an effect that is blocked by D_2-like antagonists and NO synthase inhibitors, but not oxytocin antagonists, which only block yawning [52]. Collectively, these studies suggest that dopaminergic yawning is induced via activation of D_2-like receptors within the PVN, resulting in NO- and oxytocin-dependent increases in hippocampal cholinergic activity.

In addition to studies aimed at elucidating the neurotransmitters and pathways involved in the mediation of D_2-like agonist-induced yawning, a significant effort has

been put forth to identify the receptor(s) responsible for the induction and subsequent inhibition of yawning by D_2-like agonists. Early hypotheses attributed the induction of yawning to increased cholinergic activity resulting from the activation of pre-synaptic D_2 receptors, whereas the subsequent inhibition of yawning was thought to be mediated by post-synaptic D_2 receptors or the concomitant activation of D_1 receptors [34, 62, 63]. However, based on the inability of pharmacologic manipulations that alter synaptic dopamine levels to affect D_2-like agonist-induced yawning, as well as the finding that apomorphine-induced yawning did not correspond to changes in synaptic dopamine levels, Stahle and Ungerstedt proposed that the biphasic nature of D_2-like agonist-induced yawning was mediated by multiple post-synaptic D_2 receptors with differing sensitivities, and not pre-synaptic D_2 receptors [34, 62–68].

Subsequent to this change in thinking, a number of studies reported dose-dependent increases in yawning following administration of a wide variety of D_3-preferring agonists, such as pramipexole, PD-128,907, 7-OH-DPAT, quinpirole and quinelorane, but not the D_2-preferring agonist sumanirole [18, 40, 69], raising the possibility that the D_3 receptor was involved in the mediation of yawning. Specific roles for the D_3 and D_2 receptors in the mediation of yawning were later confirmed by a series of antagonist studies in which D_3-selective antagonists, such as PG01037 and SB-277011A, were shown to selectively inhibit the induction of yawning; the D_2-preferring antagonist L-741,626 was shown to selectively reverse of the inhibition of yawning; and mixed D_2/D_3 antagonists, such as haloperidol and raclopride, were shown to produce rightward shifts in both the ascending and descending limbs of the dose-response curves for D_3-preferring agonist-induced yawning [40, 69–72]. Thus, while dopaminergic yawning involves downstream increases in oxytocin, NO and acetylcholine signaling, these findings strongly suggest that the induction of yawning is mediated by the selective activation of D_3 receptors, whereas the inhibition of yawning observed with higher doses of D_2-like agonists is mediated by the concomitant activation of D_2 receptors.

Excitatory Amino Acids

As mentioned in previous sections, excitatory amino acids (such as NMDA) are also capable of inducing yawning, an effect that was first described following the intra-PVN administration of NMDA for the purpose of studying grooming behavior [73]. Although it was unclear at the time, these increases in yawning were later shown to be NMDA-specific, as yawning was observed following the intra-PVN administration of NMDA, but not α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) or (±)-1-aminocyclopentane-trans-1,3-dicarboxylic acid (ACPD) agonists of the AMPA and metabotropic glutamate receptors, respectively [44]. Furthermore, in addition to being blocked by variety of NMDA receptor antagonists, including MK-801 [44, 74], NMDA-induced yawning has also been shown to be dose-dependently inhibited by the ICV, but not intra-PVN, administration of oxytocin antagonists, as well as the

ICV or intra-PVN administration of L-NAME [44, 75, 76], suggesting that NMDA-induced yawning is mediated by the activation of oxytocinergic neurons within the PVN in a NO-dependent manner. Importantly though, NMDA-induced yawning is not blocked by D_2-like antagonists, just as apomorphine-induced yawning is not blocked by NMDA antagonists [74, 76]. Thus, although NMDA- and D_2-like agonist-induced yawning appear to be similarly mediated by the activation of oxytocinergic neurons with in the PVN, in an NO-dependent manner, the influences of NMDA and dopamine on yawning appear to be independent of each other. Moreover, these findings provide further evidence for a central role of oxytocinergic neurons within the PVN insofar as they are responsible for the integration of inputs from a variety of neurotransmitter systems that are involved in the mediation of yawning.

Serotonin

Serotonin (5-HT) was first proposed to be involved in the regulation of yawning by Urba-Holmgren et al. [77], who described an enhancement of physostigmine-induced yawning following treatment with the selective 5-HT reuptake inhibitor citalopram, an effect that was blocked by the 5-HT receptor antagonist, metergoline. Although the mechanism by which 5-HT affected yawning was unclear at the time, more recent studies have suggested that 5-HT may play multiple roles in the mediation of yawning. For example, dose-dependent increases in yawning are observed following the systemic, but not intra-PVN, administration of 5-HT_{2C}-preferring agonists, such as m-CPP, TFMPP and MK 212, effects that are blocked by 5-HT_2 receptor antagonists, such as mianserin and ritanserin [40, 53, 78, 79]. However, unlike with D_2-like agonist- and NMDA-induced yawning, 5-HT_{2C} agonist-induced yawning is not reduced by D_2-like antagonists, oxytocin antagonists or the intra-PVN administration of NO synthase inhibitors [40, 53, 79], suggesting that serotonergic yawning is mediated by the activation of 5-HT_{2C} receptors located outside the PVN, rather than an interaction with oxytocinergic neurons within the PVN. However, it is interesting to note that despite these important differences, reductions in m-CPP- and TFMPP-induced yawning are observed following the ICV administration of NO synthase inhibitors [53], suggesting that serotonergic yawning is mediated by increases in NO signaling, although not within the PVN. In addition, m-CPP- and TFMPP-induced yawning appears to be mediated by the downstream activation of cholinergic systems as yawning is inhibited by the systemic administration of anticholinergics, such as scopolamine [40, 80]. Although it is unclear if serotonergic yawning is mediated by septo-hippocampal cholinergic neurons, these findings provide further support for a integral role for cholinergic neurotransmission in the coordination of yawning induced by a variety of neurotransmitter systems.

In addition to its role in the stimulation of yawning, several lines of evidence have suggested that 5-HT may also have a more general role in the tonic inhibition of

yawning. For instance, although depletion of endogenous 5-HT by p-chlorophenylalanine or the selective lesioning of serotonergic neurons by 5,7-dihydroxytryptamine has been shown to result in an enhancement of D_2-like agonist- and physostigmine-induced yawning, enhancing serotonergic activity through treatment with the 5-HT precursor 5-hydroxytryptophan has been shown to inhibit D_2-like agonist- and physostigmine-induced yawning [81, 82]. Similar inhibitions of dopaminergic, serotonergic and cholinergic yawning have also been observed with 5-HT_{1A} receptor agonists, such as 8-OH-DPAT, S 14506, and S 20499 [80, 83]. Thus, although activation of 5-HT_{2C} receptors results in the induction of yawning through a mechanism unrelated to oxytocin neurotransmission in the PVN, 5-HT_{1A} receptors appear to mediate the general inhibitory effect of 5-HT on yawning induced by a variety of mechanisms.

Major Neurotransmitters Involved in the Modulation of Yawning

Opioids

As discussed previously, the POMC-derived peptides ACTH and α-MSH were some of the first compounds to be shown to induce yawning in laboratory animals [22]; however, it is worth noting that β-endorphin, a POMC derived peptide with μ-opioid agonist activity, has been shown to inhibit ACTH-induced yawning [84, 85], suggesting an inhibitory role for the μ-opioid receptor on yawning. This notion is further supported by a number of studies that have demonstrated the capacity of morphine, a non-peptidic μ-opioid agonist, to inhibit yawning induced by a variety of mechanisms, including ACTH, physostigmine, D_2-like agonists, NMDA and oxytocin, effects that are reversed by the μ-opioid receptor antagonist naloxone [86–90]. Interestingly, although microinjection studies suggest that the inhibitory effects of morphine result from the activation of μ-opioid receptors on oxytocinergic neurons within the PVN [87, 88], the fact that systemically administered morphine is also capable of inhibiting yawning that is not mediated by oxytocin neurotransmission (i.e. ACTH and physostigmine) [22, 89] suggests that μ-opioid receptors in other brain regions may also be involved in the tonic inhibition of yawning. In addition, it is interesting to note that increases in yawning have been used for the identification and characterization of morphine withdrawal in humans and laboratory animals dating back to the 1930s [91–93].

GABA

Although it has not been extensively studied, a handful of studies have suggested that γ-amminobutyric acid (GABA) is also involved in the regulation of yawning. Curiously, although the γ-amminobutyric acid transaminase inhibitor, γ-acetylenic-GABA, has

been shown to increase spontaneous yawning, studies of the effects of $GABA_A$ and $GABA_B$ agonists on yawning have generally suggested that GABAergic receptors have an inhibitory rather than stimulatory influence on yawning [94]. For example, systemic administration of $GABA_A$ agonists, such as muscimol, or the $GABA_B$ agonists, such as baclofen, have been shown to inhibit physostigmine-induced yawning, effects that are reversed by the $GABA_A$ antagonist bicuculline and the $GABA_B$ antagonist phaclofen, respectively [94, 95]. Despite the similarities in these effects, however, several lines of evidence suggest that $GABA_A$ and $GABA_B$ receptors may be exerting their inhibitory effects at different stages of the pathway(s) responsible for the induction of yawning. For instance, although the intra-PVN administration of the $GABA_A$ agonist muscimol inhibits apomorphine-, NMDA- and oxytocin-induced yawning in a NO-dependent and bicuculline-sensitive manner, baclofen fails to affect apomorphine-, NMDA- or oxytocin-induced yawning when administered into the PVN [51, 96]. Thus, although $GABA_A$ receptors located on oxytocinergic neurons in the PVN may be capable of inhibiting yawning, it also appears as though $GABA_B$ receptors located outside of the PVN are capable of inhibiting yawning, possibly through a $GABA_B$ receptor-mediated inhibition of hippocampal acetylcholine activity [97].

Adrenergic

Similar to the capacity of drugs that act on GABA and μ-opioid receptors to affect yawning without inducing it, a variety of adrenergic drugs have been shown to modify yawning induced by other mechanisms. Despite their inability to induce yawning, centrally active β-adrenergic antagonists have generally been shown to enhance yawning, whereas α_2-adrenergic antagonists generally inhibit yawning induced by D_2-like agonists, oxytocin, cholinomimetics, M_1 agonists as well as α-MSH [36, 37, 63, 98, 99]. Curiously, and somewhat less convincingly, α-adrenergic agonists have been reported to inhibit yawning, and β-adrenergic agonists to enhance yawning induced by D_2-like agonists and cholinomimetics [99–101]. Despite these peculiarities, the fact that these adrenergic antagonists are capable of modifying yawning induced by a variety of pathways (i.e. ACTH/α-MSH, PVN oxytocinergic stimulation, and direct cholinergic activation), suggests that the effects of β- and α_2-adrenergic antagonists on yawning likely results from an interaction of adrenergic systems with the septohippocampal cholinergic neurons that has been shown to be involved in the coordination and mediation of yawning induced by a variety of neurotransmitter systems.

Conclusions

Although the phenomenon of yawning has fascinated man throughout time, most of the significant advances towards our understanding of the neuropharmacologic

regulation of yawning have been made during the past 50 years. We now know that a variety of neurotransmitters and neurohormones are involved in the induction and regulation of yawning, including acetylcholine, dopamine, glutamate, serotonin, oxytocin, GABA, opioids, adrenergics, nitric oxide, as well as the POMC-derived peptides ACTH and α-MSH. Despite this diverse set of neurotransmitters, the majority of yawning is mediated by at least 3 distinct pathways, all of which appear to converge on cholinergic neurons within the hippocampus. In addition, the elegant work of Drs. Argiolas and Melis has demonstrated the importance of the hypothalamus in the regulation of yawning, as many of these neurotransmitters appear to affect yawning through their interactions with oxytocinergic neurons within the PVN. For instance, activation of these oxytocinergic neurons by dopamine, glutamate, nitric oxide and oxytocin is known to induce yawning, whereas inhibition of these neurons by μ-opioids and GABA has been shown to reduce the frequency of yawning. It is important to note that although the effects of ACTH and α-MSH are also mediated by the hypothalamus, the induction of yawning by these peptides does not involve oxytocinergic neurons. Similarly, the induction of yawning by serotonin is also known to occur independently of oxytocinergic neurons within the PVN; however, the brain region(s) responsible for serotonergic yawning are currently unknown. Despite the great advances that have made towards our understanding of the neuropharmacologic regulation of yawning, further studies are needed to fully elucidate how these neurotransmitter systems interact with each other, as well as the specific receptor subtypes and brain regions involved in the induction and inhibition of yawning. Such an understanding would not only advance the use of yawning as a tool for the pharmacologic characterization of receptor subtype-selective agonists, partial-agonists and antagonists, but also further our understanding of how a variety of environmental and pharmacologic manipulations (i.e. dietary conditions or chronic drug treatments) affect the receptor systems involved in the mediation of yawning [71, 102–104]. In addition, a more complete understanding of the neuropharmacologic regulation of yawning could also provide insight into the specific roles of different neurotransmitter systems and/or receptor subtypes in the occurrence of yawning under a variety of physiologic conditions and disease states in which changes in the frequency of yawning are known to occur.

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