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Yawning Behavior

Contents

Abstract

Yawning is a common phenomenon that is an expression of certain physiological and psychological states. This behavior is particularly interesting, because it can be elicited in laboratory animals by systemic administration of low doses of apomorphine or other dopaminergic agonists and cholinomimetic drugs, raising the concept that yawning is a behavioral consequence of inhibition of dopaminergic system and activation of acetylcholine system. This syndrome, which is also characterized by stretching and penile erection, can also be elicit by ACTH, MSH, oxytocin or some other peptides, suggesting that there are different neurotransmitter systems involved in the modulation of this behavior.

Key words: Yawning, dopaminergic system, acetylcholine, ACTH, MS, oxytocin, sleep.

Invited Review

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Introduction

Yawning is a common phenomenon that is an expression of certain physiological and psychological states. This behavior is characterized by gaping of the mouth that is accompanied by a long inspiration followed by a shorter expiration and often associated with stretching movements of the muscles of the trunk and extremities.

In order to yawn it is necessary to be conscious, but anything that tends to lower the normal level of consciousness is likely to induce yawning. The reduction in stimulation, which occurs in consequence of uninteresting events, underscores the importance of the effect of oxygen reduction as well as of the reduction in the critical awareness of external stimuli in producing yawning. It is well known that yawning is contagious, but it would appear to be so principally under conditions of reduced critical consciousness. Thus, the social and biological function of contagious yawning would be to heighten the consciousness of one's fellows by inducing yawning in them in a resulting reciprocally interstimulating situation (Montagu & Princeton, 1962).

Although there is much opinion about this phenomenon, little empirical evidence concerns why yawning occurs, what function yawning serves, and what environmental circumstances modulate yawning rate (Provine, 1986[a,b]).

Phylogenetically and ontogenetically, yawning is an old phenomenon. Dogs and cats yawn, turtles and birds show movements resembling yawning (see Lehmann, 1979 and references therein). Yawning and stretching seem to be intimately associated in their phylogenetic origins. In humans, stretching is also probably an essential part of the yawning act, but is often voluntarily suppressed. The early ontogenetic occurrence of yawning is confirmed by the observation that infants yawn when only a few days old (see Lehmann, 1979 and references therein).

Yawning is not a simple reflex of short duration, but has a complex spatio-temporal organization with facial, respiratory and other components. The neural structures necessary for yawning are presumably located in the brainstem near or within other respiratory and vasomotor centers. The internal physiological stimuli that evoke spontaneous yawning as well as its physiological functions are unknown, although a role in increasing oxygen-CO_2 exchange in the lung, in facial stretching and in normalizing internal ear pressure has been suggested (Provine, 1986[a], Provine *et al.*, 1987[a,b]; Argiolas & Melis, 1998). The physiological conditions that bring about yawning include: fatigue, drowsiness, anemia, hunger, hypoglycemic states, intoxication with barbiturates and other cerebral depressant and certain lesions of the central nervous system (CNS) (Lehmann, 1979).

There is considerable evidence that yawning occurs under various somatic conditions, most of which, for different reasons, are associated with diminished oxidative processes in the brain. Furthermore, yawning is a self-adjusting mechanism, a homeostatic reflex; the tonic contraction of large muscle groups improves the circulation in general and brain circulation in particular, thus compensating for defective brain metabolism (Lehmann, 1979).

Drugs-induced Yawning and Penile Erection

Penile erection and yawning are two different behavioral responses that often occur concomitantly in experimental animals (Holmgren *et al.*, 1985). Penile erection is one of the most important sexual responses in mammals, its achievement being essential for the success of reproduction. While the importance of penile erection in reproduction of mammals does not need to be stressed, it is pertinent to recall that yawning, alone or

associated with stretching, is considered a ancestral vestige surviving throughout evolution that subserves the purpose of arousal (Bertolini & Gessa, 1981). Several pharmacological agents can induce both penile erection and yawning in experimental animals.

Experimental Induction of Yawning

Yawning is particularly interesting, because it can be elicited in laboratory animals by several pharmacological agents including cholinergic agonists (Urba-Holmgren *et al.*, 1977; Wood *et al.*, 1979), by low doses of dopaminergic agonists (Mogilnicka & Klimek, 1977), and polypeptides such as α-MSH and ACTH (Ferrari *et al.*, 1963; Yamada & Furukawa, 1981; Lobo *et al.*, 1990), suggesting there are different neurotransmitter systems involved in the modulation of this behavior.

The involvement of dopamine (DA) in yawning was first suggested by the discovery that classical DA receptor agonists, such as apomorphine, bromocriptine, lisuride and others, were able to induce yawning often together with penile erection in male rats (Mogilnicka & Klimek, 1977; Yamada & Furukawa, 1980; Baggio & Ferrari, 1983; Mogilnicka *et al.*, 1984; Melis *et al.*, 1987; for review Argiolas & Melis, 1998). This finding was soon confirmed for other laboratory animals and extended to humans (Lal *et al.*, 1989).

Several evidences exist that drug-induced yawning in rats is a behavioral consequence of dopaminergic autoreceptor stimulation (Mogilnicka & Klimek, 1977; Yamada & Furukawa, 1980; Serra *et al.*, 1986), resulting in decrease of DA synthesis and release, impairment of dopaminergic transmission and consequent reducing the firing of DA neurons (Di Chiara *et al.*, 1976). It was also suggested that dopaminergic neurons, whose inhibition was responsible for the induction of yawning by DA D_2 receptor agonists, were nigrostriatal dopaminergic neurons since bilateral lesions of the nigrostriatal dopaminergic system by 6-hydroxydopamine prevent DA receptor agonist-induced yawning in rats (Dourish & Hutson, 1985; Stoessl *et al.*, 1987). Further studies supported this hypothesis showing that injection of high doses of DA receptor agonists in the striatum or the septum induce yawning in rats (Dourish & Hutson, 1985; Yamada *et al.*, 1986; Okuyama*et al.*, 1987). Controversially, recent findings led to the suggestion that DA D_2 receptor agonists induce yawning when injected in high doses in these sites because of their diffusion through the very nearby lateral ventricles, across the brain to the paraventricular nucleus of the hypothalamus, where they induce yawning by stimulating postsynaptic DA D_2 receptors (Melis *et al.*, 1987; for review, Argiolas & Melis, 1998).

There is evidence suggesting that irrespective of the agent eliciting the response, drug-induced yawning is subject to androgenic influences (Berendsen & Gower, 1986). The incidence of yawning produced by either apomorphine or physostigmine is lower in female than in male rats (Holmgren *et al.*, 1980; Beredsen & Nickolson, 1981; Hipólide & Tufik, 1995). Castration of male rats reduces the levels of yawning to that typically obtained in females. Moreover, enhancing the androgen levels by pretreatment with dihydrotestosterone (DHT) permits a level of drug-induced yawning in both female rats and in male castrates which is equivalent to that obtained in normal male animals. Similarly, testosterone treatment increases adrenocorticotropin (ACTH)-induced yawning in guinea pigs (Rodriguez-Sierra *et al.*, 1981). Concomitant with yawning, DA agonists and ACTH increase the incidence of penile erection in normal rats (Benassi-Benelli *et al.*, 1979; Bertolini & Baraldi, 1975). Spontaneous penile erection are markedly reduced or absent in chronically castrated rats but can be restored by testosterone or DHT (Davidson *et al.*, 1978; Gray *et al.*, 1980), suggesting that, like yawning, penile erection are androgen-dependent (Berendsen & Gower, 1986).

In addition to drugs that act via dopaminergic mechanism, peptidergic mechanisms are also involved in both penile erection and yawning: ACTH and melanocyte-stimulating hormone (MSH) were active in several species of mammals (Bertolini & Gessa, 1981, for review), and oxytocyn was active in rats (Argiolas *et al.*, 1986[a]). Indeed, ACTH and α-MSH induces excessive grooming and a peculiar syndrome characterized by recurrent episodes of yawning, stretching, penile erection and ejaculation (Argiolas *et al.*, 1986[a]). While grooming is also induced by other peptides (Gispen *et al.*, 1976, Katz, 1980; Miyamoto & Nagawa, 1977), the above syndrome is considered to be specific for ACTH-MSH peptides, since it is not induced by any other known peptide tested (Ferrari *et al.*, 1963; Bertolini *et al.*, 1975; Gispen *et al.*, 1975; O'Donohue & Dorsa, 1982).

Several lines of experimental evidence suggest that a central DA-oxytocin link plays a key role in the expression of such symptomatology (Melis *et al.*, 1992[a]). Oxytocin, peptide extract from a rat hypothalamic produced the above syndrome when injected into the lateral ventricle of a recipient rabbit (Bertolini et al., 1975) as well as in rat (Argiolas *et al.*, 1986[a]). Accordingly, apomorphine (DA agonist) and oxytocin induce penile erection and yawning when unilaterally injected in the paraventricular nucleus (PVN) of the hypothalamus (Melis *et al.*, 1986; Melis *et al.*, 1987); lesions of the PVN abolish apomorphine and oxytocin responses (Argiolas *et al.*, 1987); DA receptor antagonists prevent apomorphine but not oxytocin effects (Argiolas *et al.*, 1988). These and additional data support the hypothesis that apomorphine and other dopaminergic agonists induce penile erection and yawning by releasing oxytocin in the CNS by acting in the PVN (Melis *et al.*, 1992[a]), the site of the brain most sensitive to oxytocin or apomorphine for the induction of penile erection and yawning (Melis *et al.*, 1986; Melis *et al.*, 1987); and raised the possibility that some other active substance might be present in the hypothalamus in addition to ACTH and α-MSH (Argiolas *et al.*, 1986[a]).

Among known pharmacological manipulations that prevent oxytocin- and apomorphine-induced penile erection and yawning, morphine is certainly one of the most effective (Argiolas *et al.*, 1986[a]; Beredsen & Gower, 1986). The ability of morphine to markedly inhibit the activity of paraventricular oxytocinergic neurons (Pittman *et al.*, 1980) raises the possibility that opiate prevents apomorphine and oxytocin effect by acting in the PVN (Melis *et al.*, 1992[b]). To test this hypothesis, Melis and colleagues evaluated the effect of morphine and an opiate agonist into the PVN on the apomorphine- and oxytocin-induced penile erection and yawning. The results suggest that morphine prevents apomorphine- and oxytocin-induced penile erection and yawning by inhibiting the activity of oxytocinergic neurons in this hypothalamic nucleus.

The assumption of acetylcholine involvement in the expression of yawning is also based on pharmacological experiments showing that cholinomimetic drugs are effective to induce yawning when administered in rats (Urba-Holmgrem *et al.*, 1977; Yamada & Furukawa, 1980; Ushijima *et al.*, 1985; Yamada *et al.*, 1989). Evaluating the ability of acetylcoline muscarinic agonists elicit yawning, Gower (1987) reported that yawning was induced by the cholinesterase inhibitor, physostigmine, and the direct agonists, RS86 and pilocarpine, but oxotremorine, arecoline, bethanecol had marginal or no effect.

Acetylcholine is also thought to be involved in the yawning response induced by ACTH-MSH and related peptides, because an increase in acetylcholine turnover was found to occur in the hippocampus during the ACTH-induced stretching-yawning syndrome (Wood *et al.*, 1978, 1979) and because ACTH responses are prevented by selective antagonists of the muscarinic M1 and M2 receptors (Poggioli *et al.*, 1991). Interestingly, D_2 receptor agonists and oxytocin are also prevented by muscarinic receptor antagonists

(atropine and scopolamine), but not nicotinic antagonists (mecamylamine) as demonstrated by Urba-Holmgren *et al.* (1977), Yamada & Furukawa (1980), Argiolas *et al.* (1986[a]) and Yamada *et al.*(1989). These data give support that cholinomimetically induced yawning seems to be due to the stimulation of central muscarinic receptors, because it is rapidly and completely blocked by scopolamine. Otherwise, doses of nicotine did not induce yawning (Urba-Holmgren *et al.*, 1977). These studies led to more precise characterization of the involvement of the muscarinic M1 and M2 receptors in cholinomimetic-induced yawning (Fujikawa *et al.*, 1996 and references therein). Many of these studies, suggested that yawning induced by DA D_2 receptor agonists was mediated by the stimulation of central cholinergic transmission, secondary to the inhibition of dopaminergic neurons by the activation of DA D_2 autoreceptors as described above (for review Argiolas & Melis, 1998). Accordingly, scopolamine inhibits apomorphine-, pilocarpine-, and physostigmine-induced yawning (Yamada and Furukawa, 1980); sulpiride (a D_2 receptor antagonist) inhibits apomorphine-induced, but not physostigmine-induced yawning (Gower *et al.*, 1986), indicating that yawning appears to be a result from a balance between inhibition of dopaminergic and activation of cholinergic systems (Yamada & Furukawa, 1980).

Some studies have shown that drug-induced yawning can also be influenced by drugs that act on other neuronal systems, *i.e.* y-amminobutyric acid (GABA), noradrenaline, serotonin and neurotensin, suggesting a role for these systems in the expression of yawning.

Adrenergic seems to be participated in inhibiting occurrence of yawning because β-adrenoceptor blockades and inhibition of central adrenaline synthesis caused by administration of synthesis enzyme inhibitor similarly facilitate the occurrence of yawning induced by dopaminergic and cholinergic agonists (Yamada *et al.*, 1989; Kimura *et al.*, 1996).

Concerning serotonin, Matsumoto *et al.* (1989) suggest that yawning is evoked by stimulation of DA D_2-receptors having a high affinity and consequent muscarinic activation, and that the yawning induced by DA receptor agonists is potentiated by decreases in serotonergic neuron activity.

The influence by GABAergic neurons of yawning behavior in the rat was explored with GABA-activity-active drugs by Doger *et al.* (1989). The data show that $GABA_B$ receptors play a role in yawning behavior by modulating acetylcholine release, and that $GABA_A$ receptors may modify yawning frequency by modulating inhibitory influences on acetylcholine neurons.

Yawning and Paradoxical Sleep Deprivation (PSD)

Concerning PSD and DA, yawning behavior was used to evaluate the sensitivity of DA and acetylcholine receptors of PS deprived rats (Tufik *et al.*, 1987). The results demonstrated that PSD significantly decreases the yawning response by presynaptic doses of apomorphine and by small doses of physostigmine and pilocarpine suggesting that PSD induces subsensitivity of presynaptic DA receptors and/or postsynaptic acetylcholine receptors.

In respect with the evidence mentioned above, these findings led to the hypothesis that PSD induces an up-regulation of dopaminergic receptors (Tufik *et al.*, 1978, 1981[a,b], 1987). However, because apomorphine is a mixed D_1/D_2 agonist, it was not possible to determine from those experiments which subtype of dopaminergic receptor is unregulated after PSD. Thus, Nunes *et al.* (1994[a]) using autoradiographic analysis provide the evidence that PSD increases D_2 but not D_1 receptor binding in brain, suggesting that

the unregulated D_2 receptors can account for the previously reported changes in apomorphine-induced behaviors after PSD. An increase in DA release in PS deprived group will exhibit greater dopaminergic-mediated effects due to up-regulation of DA receptors in the striatum of PS deprived rats compared to control group (Farooqui *et al.*, 1996), giving further support to the early studies on behavioral effects of dopaminergic stimulants in PS deprived animals (Tufik *et al.*, 1978; Clark *et al.*, 1987; Asakura *et al.*, 1992).

Since activity of both neurotransmitter systems is also altered by stress (De Kloet, 1991), animals were chronically exposed to different stress modalities and the evaluation of yawning induced by dopaminergic and cholinergic drugs show that immobilization caused suppression of this behavior, whereas forced swimming and footshock increased the number of yawns suggesting that yawning is differently altered by constant and intermittent stressors (Tufik *et al.*, 1995).

As these stressful manipulations altered drug-induced yawning, Hipólide *et al.* (1999) investigated the effects of single and repeated treatments with a synthetic glucocorticoid, dexamethasone (DEXA) on apomorphine- and pilocarpine-induced yawning in rats. Neither single nor repeated treatment with DEXA altered apomorphine-induced yawning. On the other hand, single injection of DEXA caused in an increased number of yawns induced by pilocarpine. Repeated treatment with DEXA led to a decreased number of yawns induced by pilocarpine. The authors concluded that dopaminergic and cholinergic are distinctly altered by DEXA, in terms of yawning behavior. Furthermore, yawning behavior was evaluated to examine whether concomitant treatment of PSD with DA agonists could reverses PSD effects (Lobo *et al.*, 1995) as observed with stereotypy and aggressiveness (Troncone *et al.*, 1988). Atropine increased yawning of PS deprived rats induced by pilocarpine, but not by apomorphine. Treatments with methamphetamine and haloperidol did not change PSD effect on pilocarpine- and apomorphine-induced yawning, revealed that reversal of PSD-induced yawning inhibition is mediated distinctly by both acetylcholine and DA systems (Lobo *et al.*, 1995).

Based upon the PSD effects on both systems (cholinergic and dopaminergic) and that the septal-hippocampal cholinergic neurons are necessary to elicit the stretching-yawning syndrome following ACTH or α-MSH (Wood *et al.*, 1978, 1979), Lobo *et al.* (1990) proposed to study the effects of PSD on ACTH-induced yawning by injecting the peptide immediately after the PSD period or after 24 h of recovery. PSD for 96 h impaired ACTH-induced yawning, but a 24-h recovery period restores the system responsible for the displaying of yawning after the central administration of ACTH, suggesting an involvement of the acetylcholine receptor after ACTH treatment (Lobo *et al.*, 1990).

In spite of several papers reporting PSD alters drug-induced behaviors, very little is known about the relationship between PSD and the effect of theses drugs in female rats. In this context, Hipólide and Tufik (1995) reported that, as in males, PSD in females resulted in increased apomorphine-induced stereotypy; however unlike males, no apomorphine-induced aggressiveness or apomorphine- and pilocarpine-induced yawning were observed in PS deprived females.

More recently, the effects of Δ^8- and Δ^9-tetrahydrocannabinol (Δ^8 and Δ^9-THC) were examined both acute and chronically on yawning induced by pilocarpine or apomorphine. The data suggest that cannabinoid agonists inhibited yawning induced by cholinergic or dopaminergic agonists. In addition, the increased frequency of spontaneous yawning following cessation of chronic administration of a cannabinoid agonist may be of importance as a withdrawal sign for these drugs (Nakamura-Palacios *et al.*, 2002).

Cannabis also induces aggressive behavior in PS deprived rats probably related to brain catecholamines with DA playing an agonist role and NOR an inhibitory one (Carlini *et al.*, 1977).

Several evidences exist that drug-induced yawning in rats is a behavioral consequence of dopaminergic autoreceptor stimulation, resulting in decrease of DA synthesis and release, impairment of dopaminergic transmission and consequent removal of the inhibition that DA neurons exert upon cholinergic neurons (Yamada & Furukawa, 1981). Testing animals after a recovery period of 24 h, Neumann *et al.* (1990) observed that apomorphine-induced yawning was still significantly reduced, whereas pilocarpine-induced yawning had returned to normal, suggesting that PSD alters these systems in different ways, it seems that the interference on the dopaminergic system is prior and stronger than on the cholinergic system, thus its recovery demands more time.

On the other hand, the decrease in yawning behavior induced by cholinergic agonists (Tufik *et al.*, 1987) led to investigate the cholinergic receptors after PSD. Again, a autoradiographic study show that PSD resulted in a generalized down-regulation of M-type muscarinic receptors in rat brain, corroborating to the notion that pontine M-type receptors may participate, but not necessarily play a special role, in effects associated with PSD (Nunes *et al.*, 1994[b]).

Conclusion

The studies mentioned show that yawning is under the central control of several neurotransmitters and neuropeptides. Yawning behavior can be induced in rats by systemic administration of low doses of apomorphine or other dopaminergic agonists and cholinomimetic drugs, raising the concept that yawning is a behavioral consequence of inhibition of dopaminergic system and activation of acetylcholine system. This syndrome, which is also characterized by stretching and penile erection can also be elicit by ACTH, MSH, oxytocin or some other peptides, suggesting that there are different neurotransmitter systems involved in the modulation of this behavior.

The functional significance of yawning is still unknown, although it has been hypothesized that yawning is a self-adjusting mechanism, the tonic contraction of large muscle groups improves the circulation in general and brain circulation in particular, thus compensating for defective brain metabolism. Furthermore, the role of yawning could be that of increasing attention when sleep is pressing due to fatigue or boredom, but cannot be engaged in, as in dangerous situations or social circumstances.

Among the behaviors altered by PSD, yawning is particularly interesting, because it can be used to study different neurotransmitter system modulations that are modified by PSD. Indeed, PSD inhibits yawning elicited by drugs that act on different systems, such as apomorphine, physostigmine, pilocarpine and ACTH. The effects of PSD on yawning response are possibly mediated by the stressful condition produced by the procedure itself. This overview of such studies show PSD is reasonable way to study and contribute to the understanding of the neurophysiology and neurochemistry of this phylogenetically old event.

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