Neural basis of drug-induced yawning

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Colin T. Dourish and Steven J. Cooper

Introduction

In a study of human yawning Robert Provine (1986) remarked that yawning is a prominent stereotyped action pattem and releasing stimulus which "does not deserve its current status as a minor behavioural curiosity". Indeed, "yawning may have the dubious distinction of being the least understood, common, human behaviour". In contrast, a large body of experimental data has been collected during the past 30 years on drug-induced yawning in animals (particularly rodents). In this chapter we consider the neural basis of drug-induced yawning in rodents and discuss the relevance of this pharmacological phenomenon to "spontaneous" yawning in animals and man.

We propose that yawning may be controlled by a complex interaction of catecholaminergic, serotonergic, and peptidergic neuronal mechanisms. A model is put forward to explain how yawning may be caused largely by peptidergic and cholinergic excitation and dopaminergic inhibition. Furthermore, we present evidence which suggests that, in animals and man, yawning may be a marker of recovery from acute stress and that these responses may be closely associated with an inhibition of brain dopamine metabolism.

Historical perspective: peptide hormones

Drug-induced yawning and stretching were first reported in the 1950s by W.Ferrari and colleagues working at the University of Cagliari in Italy (Ferrari et al. 1955; Ferrari 1958; early studies are reviewed by Ferrari et al. 1963 and Gessa et al. 1967). Ferrari injected dogs intracistemally with adrenocorticotropic hormone (ACTH) and after about an hour observed recurrent yawning and stretching (see Fig. 4. 1). The behaviour persisted for 24 to 72 hours depending on the dose of ACT H given (Ferrari et al. 1963). The syndrome appeared to be centrally mediated as intra-arterial injections of large doses of ACTH did not produced yawning and stretching (Ferrari etal. 1963). After this initial discovery a large number of other peptides were tested for their ability to provoke the yawning syndrome, but of these only alpha-melanocyte stimulating hormone (a-MSH), beta-lipotropic hormone (bLPH) (Ferrari et al. 1963), and, more recently, oxytocin (Argiolas et al. 1985) produced a positive result. In subsequent studies, intraventricular or intracistemal injection of ACTH and a-MSH were found to elicit the syndrome in a wide variety of other species including cats, rabbits, monkeys, gumea-pigs, mice, and rats. Interestingly, in dogs and cats stretching was the dominant response, whereas in monkeys, rabbits, and rats yawning was more frequently observed (Gessa et al. 1967). In rats, excessive grooming is also an important feature of the ACTH-induced syndrome. Peptide induced grooming is discussed in detail by Isaacson and Gispen in Chapter 5 of this volume.

In an effort to identify the site of action of ACTH in producing the yawning-stretching syndrome, Gessa etal. (1967) examined the effects of intracerebral injection of the hormone into

various brain regions in cats. These experiments revealed two principal sites of action of ACTH in the brain which were the hypothalamic areas lining the third ventricle and the caudate nucleus. A hypothalamic site of action was not unexpected as another feature of the yawning-stretching syndrome is sexual arousal and there is considerable evidence that hypothalamic mechanisms are important in the control of sexual behaviour (Sandler and Gessa 1975). (A detailed consideration of the sexual arousal comportent of the syndrome is beyond the scope of this chapter. For further discussion of this subject the reader is referred to reviews by Bertolini et ai. 1975 and Bertolini and Gessa 1981) The most intense stretching and yawning was observed upon injection of ACTH into the anterior and ventromedial hypothalamic nuclei. Potent effects were also observed in the posterior and lateral hypothalamic nuclei and in the caudate nucleus (Gessa etal. 1967). Weak responses were produced by application of ACTH to the putamen, globus pallidus, and substantia nigra. This early observation that the hypothalamus and the eaudate nucleus play an important role in the mediation of stretching and yawning induced by ACTH is consistent with recent experiments showing that these regions are crucially involved in the control of yawning induced by dopamine agonists (see below for further discussion).

During the 10 years subsequent to the 1967 review of Gessa and colleagues little or no work was published on the neuropharmacology of yawning. However in the mid- 1970s interest in the yawning syndrome was rekindled by the discovery that certain pharmacological manipulations of either cholinergic or dopaminergic neurotransmitter systems could elicit yawning (Baraldi and Bertolini 1974; Urba-Holmgren et al. 1977; Mogilnicka and Klimek 1977). These seminal findings provoked a considerable research effort on the yawning syndrome and a consideration of the results of these studies and their theoretical implications forms the basis of the remainder of this chapter.

Acetylcholine

Yawning induced by cholinergic agents

In 1977 Holmgren and his colleagues observed that small doses of pilocarpine (a cholinergie agonist) or physostigmine (which inhibits acetylcholine metabolism) produced yawning in infant rats. Each yawn was preceded by salivation, licking of the forepaws and cleaning movements of the snout, chewing movements, or forelimb stretching (Urba-Holmgren et al. 1977). The yawn consisted of a slow wide opening of the mouth with marked protrusion of the tongue and had a maximum frequency of 8-10 responses in 15 min and a duration of 3-4 seconds.

The response appeared to be centrally mediated since the peripheral cholinergic agonist neostigmine methylsulphate did not induce yawning. Furthermore, the yawning seemed to involve muscarinic receptors as the response was inhibited by the muscarinic antagonist scopolamine and was not produced by nicotine (Urba-Holmgren et ai. 1977). Furthermore, the nicotinic receptor blocker mecamylamine had no effect on yawning induced by pilocarpine or physostigmine (Ushijima et al. 1984a). Yawning induced by cholinergic agonists is critically depenilent on the age of the animal during testing. Thus, physostigmine-induced yawning is highest in early postnatal days and tends to decline from the seventh day onward (Holmgren and Urba-Holmgren 1980). (It should be noted that this developmental sequence contrasts with that of yawning induced by dopaminergic drugs which does not appear until 11-15 days of age and is maximal in adults.) There has been disagreement is subsequent studies as to whether pilocarpine significantly increases

yawning in adult rats. Yamada and colleagues (Yamada and Furukawa 1980; Ushijima et al. 1984a, 1985) have reported that pilocarpine induces a peak yawning response in adult rats at a dose of 4.Omg/kg. However, Salamone etal. (1986) disagree and suggestthatUshijimaetal.(1984a, 1985) may have recorded an exaggerated yawning response by scoring 'gaping' responses as yawns.

Gaping is a rapid opening and closing of the mouth which is wide enough to see the teeth. In contrast, yawning has been defined as a gradual opening of the mouth, followed by a retention of the open position, frequently accompanied by a lifting back of the head, and usually finished with a closure of the mouth more rapid than the orginal opening (Salamone et al. 1986). Since Ushijima et al. (1984a) recorded yawns as total number of mouth openings, it is possible that gaping responses may have been scored as yawns in their study.

Ushijima et al. (1984a, 1985) have suggested that spontaneous physiological yawning and yawning induced by physostigmine are very similar in appearance. Both responses are reported to be characterized by a slow wide opening of the mouth (3.6 s in duration) with the head moving mainly upward (Ushijima et al. 1985). Thus, they have speculated that physiological yawning may be mediated by endogenous acetycholine.

Responses associated with yawning induced by cholinergics

Some attention has also been paid to two other components of the cholinergic yawning syndrome, i.e. tongue protrusion and chewing mouth movements. It has been proposed that tongue protrusion (in contrast to yawning) may be mediated by nicotinic receptors since this response is inhibited by the nicotinic antagonist mecamylamine (Ushijima et al. 1984a, 1985). Chewing mouth movements (described as teeth chattering by some authors) have been observed after pilocarpine and physostigmine; like yawning, these responses are attenuated by scopolamine but unaffected by the peripheral muscarinic antagonist methyl scopolamine (Ushijima et al. 1984a; Salamone et al. 1986). The frequency of chewing is considerably higher than that of yawning with as many as 40 responses per minute being observed at some doses (Salamone et al. 1986). The chewing response has been proposed by Salamone and colleagues (1986) as a reliable index of central muscarinic agonist activity in rats.

Chewing mouth movements have also been observed in rats treated acutely and chronically with certain neuroleptic drugs including haloperidol and sulpiride (Rupniak et al. 1983a). This response was decreased by anticholinergics and increased by cholinergic agonists (Rupniak et al. 1983a, 1985). It has been suggested that this chewing response may be an acute dystonic reaction (Rupniak et al. 1983a, 1985).

Yawning and associated behaviours elicited by cholinergic agonists are sensitive to dopaminergic drug treatments. For example, the dopamine antagonists spiroperidol and fluphenazine potentiated yawning induced by physostigmine (Holmgren and Urba-Holmgren 1980; Yamada and Furukawa 1980). Thus, a dopaminergic-cholinergic link has been implicated in the control of yawning (see pp. 105-8).

Dopamine

Early studies

In recent years, the role of dopamine in yawning has been the subject of more attention than that of any other neurotransmitter. This is due in part to the fact that yawning and related behaviours have been used to examine the functional role of certain dopamine receptor subtypes in the CNS which were identified by receptor binding and neurochemical studies (see Carlsson 1975; Seeman 1980; Stoof and Kebabian 1984 for further details of the biochemistry and pharmacology of multiple dopamine receptors). Therefore, a correspondingly large section of this chapter is devoted to a consideration of the role of dopaminergic mechanisms in yawning.

The first reports of yawning induced by dopaminergic agents came from Baraldi and colleagues (Baraldi and Bertolini 1974; Baraldi and BenassiBenelli 1975) who observed that apomorphine and amantadine produced yawning and penile crections in male rats. SubsequentIy, Mogilnicka and Klimek (1977) discovered that a large number of dopamine agonists, including piribedil, nomifensine, and L-dopa, when given in small doses produced yawning, stretching, chewing, and penile erection in rats. The list of dopamine agonists which have since been reported to produce the yawning syndrome is extensive and the rank order of potency of some of these compounds is shown in Table 4. 1.

Yawning induced by dopamine agonists appears to be mediated by an action on dopamine receptors as it is prevented by pre-treatment with small doses of dopamine antagonists (Mogilnicka and Klimek 1977; Protais et al. 1983; Gower et al. 1984). The yawning syndrome contrasts with the weIlknown effects of high-dose dopamine agonist treatment (consisting of hyperactivity and stereotyped sniffing, rearing, headbobbing, and oral movements) which are mediated by stimulation of postsynaptic dopamine receptors located in striatum and nucleus accumbens (Emst 1967; Kelly et al. 1975).

Is yawning mediated by dopamine autoreceptors?

Mogilnicka and Klimek (1977) suggested that yawning was mediated via the activation of presynaptic inhibitory dopamine receptors caused by low-dose dopamine agonist treatment. These presynaptic receptors (named autoreceptors by Carlsson 1975), located on the cell bodies, dendrites, axons, and presynaptic terminals of dopamine neurones (see Fig. 4.2), are considerably more sensitive to dopamine and dopamine agonists than postsynaptic dopamine receptors and are, therefore, activated by very small drug doses. Stimulation of dopamine autoreceptors was shown by Carlsson (1975) to inhibit both the synthesis and release of dopamine and consequently to functionally decrease brain dopaminergic neurotransmission. Numerous subsequent studies have supported the autoreceptor explanation advanced by Mogilnicka and Klimek (1977) and some authors have proposed that yawning behaviour may be a useful index of brain dopamine autoreceptor activation (Gower et al. 1984; Stahle and Ungerstedt 1984, Dourish and Cooper 1985). Indeed, there is a good correlation between the potencies of drugs in producing yawning and their potencies in biochemical tests thought to identify dopamine autoreceptor activity (Gower et al. 1984). In addition, yawning is elicited by certain novel dopamine agonists, including (±)-3-P P P, T L-99, and B-H T 920 which are claimed to act selectively on dopamine autoreceptors (Gower et al. 1984; Mogilnicka et al. 1984; Ferrari 1985). Another novel drug (+)-A J 76 which is thought to be a selective dopamine autoreceptor antagonist (Svensson et al. 1986) blocks yawning induced by apomorphine (Dourish et al. 1988).

Dopamine depletion produced by bilateral 6-hydroxydopamine (6-OHD A) lesions of the striatum or the substantia nigra prevents yawning induced by a low dose of apomorphine (Dourish and Hutson 1985; Stoessl et al. 1987). Similarly, apomorphine-induced yawning is prevented by chronic haloperidol treatment which potentiates stereotyped sniffing and oral behaviour induced by a high dose of the drug (Ushijima et al. 1984b). These findings support mediation of yawning by dopamine autoreceptors since it is well established that postsynaptic dopamine receptors become supersensitive to dopamine agonists after treatments with neuroleptics or denervation by 6-O H D A (Ungerstedt 1971; Rupniak et al. 1983b).

However, some recent findings have cast doubt on whether the receptors which mediate yawning induced by dopamine agonists are autoreceptors. The racemic form of 3-PPP has been resolved into two stereoisomers which have different pharmacological properties. (+)-3-PPP is a "classical" yawning is inhibited (Urba-Holmgren et al. 1982). Similarly, it has been noted that treatments with high doses of neuroleptics can cause the appearance of yawning in rats treated with a high dose of apomorphine (Protais et al. 1983). Presumably, blockade of hyperactivity, stereotyped sniffing, headbobbing, etc. allows the expression of yawning in animals given a large dose of apomorphine. Systemic administration of high doses of haloperidol alone does not produce yawning. However, injection of the drug in microgram amounts into the septal area produces yawning and penile erections in rats (Nickolson and Berendsen, unpublished data cited in Niekolson and Berendsen 1980). This suggests that the expression of septallymediated yawning after peripheral haloperidol may be blocked by various effects of the drug at other brain sites.

Responses associated with yawning induced by dopamine agonists

Yawning induced by dopamine agonists is generally accompanied by tongue protrusion, chewing, and stretching .

Tongue protrusion induced by dopamine agonists is probably mediated by an indirect action on nicotinic receptors since it is most effectively blocked by the nicotinic antagonist mecamylamine (Ushijima et al. 1985). Chewing almost invariably precedes and succeeds yawning induced by peripheral or central dopamine agonists and is blocked by treatments (ie. neuroleptics, scopolamine, 6-OHD A lesions) which also prevent yawning (Yamada and Furukawa 1980; Dourish et al. 1985; Dourish and Hutson 1985).

The principal distinction between the profiles of yawning induced by dopaminergic and cholinergic agonists is that the dopaminergic syndrome includes a sexual arousal comportent (ie. penile grooming, erection, ejaculation) whereas the cholinergic syndrome does not (Gower et al. 1984; Holmgren et al. 1985). There appears to be an important association between yawning and sexual arousal elicited by dopamine agonists and, interestingly, both responses are abolished by striatal 6-0 H DA lesions or haloperidol pretreatment (Gower et al. 1984; Dourish et al. 1985; Dourish and Hutson 1985). Recently, Holmgren et al. (1985) have bred a Sprague-Dawley derived rat strain which exhibits a high incidence of spontaneous yawning behaviour. Observation of these animals after saline or dopamine agonist treatments suggests that yawning and penile erection are regulated by a common dopaminergic mechanism (for further discussion of dopamine autoreceptor modulation of sexual behaviour see Gessa et al. 1980; Napoli-Farris et al. 1984).

Sexual arousal is also associated with peptide-induced yawning (see above). Recent lesion studies have enabled the differentiation of the yawning and sexual arousal components of the syndrome induced by dopamine agonists and peptide hormones.

Sex hormones appear to modulate yawning. Thus, yawning induced by apomorphine is less intense in female than in male rats (Berendsen and Nickolson 1981). Further, castration of male but not female rats reduces yawning. Testosterone treatment counteracts this effect and increases yawning in both intact and ovariectomized female rats (Berendesen and Nickolson 1981). Therefore, Berendsen and Nickolson (1981) have proposed that apomorphine-induced yawning is under androgenic influence and that oestrogens play little or no part.

Brain pathways invoived in dopamine agonist-induced yawning

There is strong evidence that yawning induced by dopamine agonists is a phenomenon which is mediated centrally. First, yawning induced by systemic agonist administration is abolished by central dopamine receptor antagonists such as haloperidol and pimozide (Mogilnicka and Klimek 1977; Protais etal. 1983) whereas the peripheral dopamine antagonist domperidone has no effect on the response (Gower etal. 1984; Stahle and Ungerstedt 1984). Second, intracerebral injections of dopamine agonists elicit yawning in rats (Dourish et al. 1985; Dourish et al. 1986; Melis et al. 1987; see Fig. 4.3).

Bilateral application of piribedil or apomorphine to the caudate nucleus produces yawning, chewing, stretching, and sexual arousal, a syndrome which is identical to that observed after systemic administration of these drugs (Dourish et al. 1985). Systemic administration of a low dose of the dopamine antagonist haloperidol prevents yawning induced by intrastriatal piribedil. Yawning was induced by intrastriatal application of piribedil at doses which were 25 times lower than those required to elicit the response by systemic injection (see Fig. 4.4). Furthermore, the intrastriatal response had a shorter latency to onset and a longer duration than that produced by systemic administration of piribedil. This strongly suggests that the behaviour is centrally mediated.

These experiments also provide clues to the location of the central site of action of dopamine agonists (and possibly other compounds) in producing yawning. Apomorphine-induced yawning appears to be depenilent on the integrity of dopaminergic innervation of the striatum, since the response to a small dose of the drug given systemically, is abolished by bilateral 6-O H DA lesions of the striatum (Dourish and Hutson 1985) or the substantia nigra (Stoessl et al. 1987). Striatal involvement in yawning is also supported by observations that the caudate nucleus is one of the most effective brain sites for producing yawning in response to piribedil and apomorphine (Dourish etal. 1985, 1986) or ACTH (Gessa etal. 1967). In addition, yawning is elicited by injections of dopamine agonists or ACTH into other dopamine-rich brain regions (ie. putamen, globus pallidus, substantia nigra, nucleus accumbens) with dense neuronal projections to and/or from the caudate nucleus (Gessa et al. 1967; Dourish et al. 1985, 1986).

Yawning is also elicited by injection of small doses of apomorphine into the paraventricular nucleus of the hypothalamus (P V N) (Melis et al. 1987). Indeed yawning can be induced by P V N injections of doses of apomorphine that are 1000-fold lower than the doses of the drug required to induce yawning by intrastriatal injection. Injection of peptide hormones (ACTH, oxytocin) into various regions of the hypothalamus also induces yawning (Melis et al. 1986). Thus,

there may be indepenilent striatal and hypothalamic dopaminergic mechanisms involved in the mediation of yawning (sec pp. 105-8).

Environmental influences on the temporal characteristics of apomorphine-induced yawning

In a recent study (Cooper, de Mars, and Dourish, unpublished results) we examined the temporal characteristics of apomorphine-induced yawning in rats tested under either novel or familiar conditions. The frequency and duration of yawning, stretching, penile grooming, face and body grooming, resting, chewing, rearing, and locomotion were determined from videotape recordings of behaviour. The results are illustrated in Fig. 4.5 which shows the time of occurrence of each yawn in indîvidual rats during a 60-min test. The numbers at the right of each figure give the total number of yawns for each rat. On occasions yawns occurred so closely together that it was not possible to represent each response separately on the chosen time scale. Under both experimental conditions yawns occurred in bursts.

In animals tested in familiar conditions there were few episodes of yawning after vehicle injection (range 0-4 responses). These animals exhihited locomotion and rearing during the first 10 min of the test but were generally inactive thereafter. When injected with 0.025 mg/kg apomorphine, yawnîng was evident early in the test (0-20 min) and late in the test (40-60 min). At higher drug doses most yawning occurred within 20-25 minutes of injection. After the yawning episodes these animals became inactive, like controls.

In animals tested in a novel environment, yawning occurred in all animals after vehicle injection (indeed two animals attained high scores, 24 and 48 responses). In the novel situation the animals also showed high levels of grooming and were very active during the first 30 min of the test. Yawning and inactivity occurred late in the test. Thus, these animals showed a sequence of behaviour consisting of activity/expIoration succeeded by yawning and resting. Apomorphine-treated animals tested in novel conditions showed a great deal of yawning. With increasing drug dosage, the onset of yawning seemed to occur earlier in the test. Thus, apomorphine considerably reduced the “hyperactivity” phase exhibited by vehicle-treated animals exposed to novelty and attenuated novelty-induced excessive grooming.

Our interpretation of these data is that low doses of apomorphine attenuate responses produced by novelty (ie. increased rearing, locomotion, and grooming) and increase yawning and associated behaviour. This suggests that yawning is associated with a decreasing level of arousal (or stress). We propose that novelty may be associated with increased dopamine release causing activation of postsynaptic dopamine receptors. The resulting behavioural responses of this “arousal” or “stress” state are increased. grooming, rearing, and locomotion. Low doses of apomorphine attenuate novelty-induced behavioural responses and produce a calming effect which results in yawning and resting. Interestingly, it has recently been reported that low doses of apomorphine have an anxiolytic action in an animal model of anxiety (Hjorth etal. 1986). In addition, beneficial effects of low-dose dopamine agonist treatment have been reported in patients suffering from mania (Post 1976). The diminishing arousal and anxiolytic effects of apomorphine may be mediated by an agonist action at dopamine autoreceptors (Carlsson 1975) or at postsynaptic inhibitory dopamine receptors (Cools and Van Rossum 1976).

Serotonin and noradrenalin

There is evidence that both serotonergic and noradrenergic neurones may influence yawning. Urba-Holmgren et al. (1979) reported that the serotonin uptake inhibitor Lu 10-171(sertralin) potentiates yawning induced by physostigmine at doses which have no effect on behaviour when given alone, suggesting that serotonin exerts a positive modulating effect on yawning. Similarly, it has been observed that the serotonin antagonist methysergide supresses yawning induced by alpha-MSH or piribedil (Yamada and Furukawa 1981). Since serotonergic neurones may tonically inhibit nigrostriatal and mesolimbic dopamine neurones, Yamada and Furukawa (1981) have suggested that methysergide could decrease piribedil-induced yawning by causing disinhibition of dopaminergic neurones. The consequent increase in dopamine release produced by methysergide would prevent yawning.

In cats and monkeys (but not rats) the serotonin agonists LSD and N,Ndimethyltryptamine elicit yawning which can be blocked by methysergide (Jacobs et al. 1977; Trulson and Jacobs 1979; Marini 1981). Thus, data on the whole tend to support a facilitatory role of serotonin in yawning. In contrast, noradrenalin appears to have an inhibitory influence on peptide-induced yawning. Thus, yawning induced by ACTH in rats is potentiated by the alpha2-adrenoceptor antagonist yohimbine but blocked by the alpha2-agonist clonidine (Poggioli etal. 1984, 1985).

Interactions of alpha2-adrenoceptor agonists and antagonists with apomorphine-induced yawning are not so straightforward. Thus, Gower et al. (1986) report that the alpha2-antagonists piperoxan and idazoxan and the alpha2-agonist clonidine all inhibit apomorphine-induced yawning. Although there seems to be some doubt regarding the exact nature of the dopaminergic-noradrenergic link in yawning, the identity of the adrenoceptor population involved has been clearly established as being of the alpha2 subtype, as the alpha1antagonists prazosin and phenoxybenzamine have no effect on apomorphine-induced yawning (Gower et al. 1986).

Interaction of brain dopaminergic, cholinergic, and peptidergic neurones in the mediation of yawning: an hypothesis and a model

It is clear from the preceding pages that yawning behaviour is influenced by a number of interacting; neurotransmitter systems. Major influences are exerted by brain dopaminergic, cholinergic, and peptidergic neurones and in this section we propose a hypothesis which explains how these various neurotransmitter mechanisms may interact to control yawning and associated behaviours.

There is strong evidence for the involvement of dopaminergic inhibition and cholinergic excitation in yawning. Thus, yawning induced by dopaminergic drugs is probably caused by activation of dopamine autoreceptors (or inhibitory postsynaptic dopamine receptors) which reduces dopamine synthesis and release. In contrast, yawning induced by cholinergic agents appears to be due to increased release of acetylcholine and stimulation of postsynaptic muscarinic receptors.

In cross-blocking studies, it bas been shown that dopamine agonist induced yawning; is

attenuated or abolished by treatment with muscarinic receptor antagonists (Yamada and Furukawa 1980, 1981; Holmgren and Urba-Holmgren 1980). In contrast, dopamine antagonists potentiate yawning induced by physostigmine (Yamada and Furukawa 1980; Holmgren and Urba-Holmgren 1980). Therefore, these authors have proposed that yawning is produced by the release of cholinergic neurones from tonic dopaminergic inhibition. This disinhibition may be caused by activation of dopamine autoreceptors at presynaptic neuronal sites induced by low doses of dopamine agonists (see Fig. 4.2). Thus, the same functional effect (ie. increased yawning) is produced by stimulation of postsynaptic cholinergic receptors or presynaptic (inhibitory) dopamine receptors. Blockade of postsynaptic dopamine receptors by a dopamine antagonist would also activate cholinergic neurones and this probably accounts for the potentiation of physostigmine-induced yawning by neuroleptics (Yamada and Furukawa 1980).

It seems that the striatum may be the central locus for this dopaminergic-cholinergic neuronal interface. The striatum in the rat receives innervation from approximately 3500 dopaminergic neurones located in the zona compacta of the substantia nigra (Andén et al. 1964, 1966). The terminals of these dopamine neurones make synaptic connections with striatal interneurones (which represent the majority of striatal neurones) and neurones which innervate the substantia nigra and globus pallidus. Acetylcholine is a major striatal transmitter and most of it is located in interneurones (Hassler 1978). The dopaminergic nigrostriatal neurones make synaptic contact with these cholinergic neurones (Hattori etal. 1976) and inhibit their firing (Roth and Bunney 1976; Trabucchi et al. 1975). In contrast, there is no apparent dopaminergic-cholinergic link in other major dopamine terminal regions such as nucleus accumbens and olfactory tubercles (Ladinsky et al. 1975).

In yawning experiments, it has been shown that the striatum is very sensitive to dopamine agonist treatments and that 6-OHDA lesions of the striatum. or substantia nigra abolish yawning induced by a small dose of apomorphine (Dourish et al. 1985; Dourish and Hutson 1986; Stoessl et al. 1987). Furthermore, yawning induced by intrastriatal injection of piribedil is abolished by blockade of either dopamine autoreceptors (with low-dose haloperidol) or postsynaptic muscarinic receptors (with scopolamine) (Dourish et al. 1985). At this point, our yawning model comprises striatal cholinergic excitation and dopaminergic inhibition. We noted earlier that the peptide hormones ACTH, a-MSH, beta-LPH and oxytocin are potent yawning inducers. Therefore, the question arises as to how peptidergic mechanisms interact with neuronal dopamine and acetylcholine to control yawning.

There is evidence that ACTH and alpha-MSH injection can activate cholinergic neurones (Torda and Wolff 1952; Marx 1975). Accordingly, yawning induced by ACTH and alpha-MSH is paralleled by a twofold elevation of acetycholine turnover in hippocampus (Wood et al. 1978). This is consistent With evidence that peptide-induced yawning is suppressed by cholinergic antagonists and neuroleptics (Ferrari et al. 1963; Yamada and Furukawa 1981). These data suggest that yawning is associated with cholinergic and peptidergic excitation and dopaminergic inhibition.

Indeed it is known that alpha-M S H-producing cells in the pituitary are under the inhibitory control of dopaminergic neurones originating from the arcuate nucleus of the hypothalamus (Tilders and Smelik 1977). Therefore, it is possible that inhibition of dopamine release (caused by low-dose dopamine agonist treatment) may indirectly result in release of newly synthesized peptides (ACTH, alpha-M S H, betaLPH, oxytoxin) from the pituitary or from

peptidergic neurones (Serra et al. 1983a).

The importance of the pituitary in mediating yawning is illustrated by the observation that hypophysectomy prevents yawning induced by apomorphine (Serra et al. 1983a). Similarly, apomorphine-induced yawning is prevented by treatment with the protein synthesis inhibitor cycloheximide (Serra et al. 1983b).

The observation of Wood etal. (1978) that ACTH and alpha-MSH specifically increased acetylcholine turnover in the hippocampus indicates that this brain region may be of importance in the control of yawning. This idea is supported by evidence from lesion studies in which it has been demonstrated that partial ablation of the hippocampus potentiates ACTH-induced yawning whereas total hippocampectomy abolishes the response (colbern et al. 1977). This study also implicated the amygdala and the mammillary bodies in the control of yawning since lesions in these areas modified the response to ACTH.

Interestingly, lesion studies have also enabled the differentiation of the yawning and sexual arousal components of the ACTH-induced syndrome. Thus, pre-optic lesions, destroying structures which take up labelled testosterone, abolished penile grooming and erection but did not affect yawning (Bertolini et al. 1975).

The model we propose to explain the neural control of yawning is illustrated in Fig. 4.7. It is clear that there are cholinergic, peptidergic, serotonergic (all excitatory), dopaminergic, and noradrenergic (both inhibitory) inputs to the system. At this point it is unclear whether the final step in the pathway is peptidergic or cholinergic (hence the reciprocal connections with question marks in Fig. 4.7). However, it is noteworthy that all of these influences may precede a mechanism illustrated on the bottom right portion of Fig. 4.7. Cortical spreading depression was shown to produce yawning and sexual arousal by Huston (1971). In a subsequent study, Jakobartl and Huston (1977) observed that intracranial injection of ACTH produced spreading depression and that the hippocampus was more sensitive to the peptide than the cortex. Thus, it is possible that yawning and related behaviour elicited by ACTH could be secondary to hippocampal spreading depression.

Conclusions

In this chapter we have described how drug-induced yawning is mediated by the interaction of various brain neurotransmitter systems. Dopaminergic, peptidergic, and cholinergic neurones appear to be primarily responsible for the control of yawning. At the pharmacological level yawning and sexual arousal appears to be useful as a model for identifying drugs with agonist activity at inhibitory dopamine receptors (Gower et al. 1984). Similarly, chewing mouth movements have been proposed as a useful index of agonist action at central muscarinic receptors (Salamone et al. 1986).

In behavioural terms, the evidence suggests that in most cases pharmacologically-induced yawning bears a close resemblance to spontaneous, physiological yawning. Thus, the posture of rats yawning in response to physostigmine or apomorphine is very similar to that of spontaneous physiological yawning in rats (Ushijima et al. 1985). Furthermore, apomorphine

induced yawns in rats occur in clusters (Szechtman 1984; Cooper, de Mars, and Dourish, unpublished results) which is consistent with anecdotal reports that yawning in humans occurs; in bures (Barbizet 1958).

The only comprehensive study to date on physiological yawning in animals was carried out by Anias et al. (1984) who produced a “high yawning frequency” line of Sprague-Dawley rats through selective breeding. They found a clear circadian pattem in spontaneous yawning with the highest frequency being evident during the last hour of the light period. Interestingly, this coincides with the time of the lowest daily dopamine turnover rate (Cahill and Ehret 1981) which suggests some form of dopaminergic control of spontaneous yawning.

Spontaneous, physiological yawning is a behaviour categorized by ethologists as a “stereotyped action pattem” (see Provine 1986 and references therein). In humans, yawns can be released by observing yawns, thinking about yawning, or even reading about yawning (Provine 1986). There have been a number of speculations concerning the function of yawning. One proposal is that yawning is useful for “stretching the face”. By causing contraction of the facial muscles, yawning forces blood through cerebral vessels to the brain which may have an alerting effect (Heusner 1946; Barbizet 1958). Similarly, it has been suggested that yawning may increase blood oxygen levels during the deep air inspiration which accompanies the response (Bartlett et al. 1971). However, a study by Provine (1986) has cast doubt on the respiratory hypothesis since there was no correlation between yawn duration and interyawn interval (ie. infrequent yawners did not compensate by producing yawns of longer duration).

Yawning is also of clinical interest since it has been reported to be associated with a number of disorders including epilepsy, epidemic encephalitis and Huntington's chorea (Heusner 1946), hysteria and brainstem lesions (Barbizet 1958) and adrenoleucodystrophy (which interestingly is accompanied by high blood ACTH levels; Kataoka et al. 1980). Yawning is also reported to be associated with opiate withdrawal in man (Himmelsbach 1939). In contrast, it has been reported that apomorphine-induced yawning in rats is reduced by the opiate antagonist naloxone (Szechtman 1984). However, it appears that the effects of naloxone on yawning may not be opiate-receptor-mediated (Berendsen and Gower 1986).

It seems likely that yawning may have an important social function both in apes (Hadidian 1980) and in humans (Barbizet 1958). In man, yawning is often regarded as an expression of indifference and/or boredom although social etiquette demands that the yawn is hidden by putting one's hand over one's mouth.

We believe that yawning and stretching may signal the termination of stressful experience or of sustained concentration. Experimental evidence is lacking, but there are anecdotal observations which suggest that yawning and stretching may be behavioural features of recovery from at least certain forms of stress. For example, one of us (SJQ sat amongst a large class of students in Northern Ireland who were being addressed by a visiting rescarch worker. He wanted them to answer direct questions about the impact of the “Troubles'” (ie. the period from 1969 to the present day during which there has been widespread violence) on their personal lives, and on those of their families and friends. The effect of his talk on the behaviour of the students was startling. Under normal circumstances, like students anywhere, his audience would have shown periodic fidgeting, whispering, looking-about, coughing, and so on. On this occasion, however, the entire

class sat motionless, and expressionless, when it became clear that they were being asked about widespread fears and anxieties, and about injuries and deaths which may have befalien members of their families, their friends, and neighbours. There was a palpable feeling of tension throughout the lecture room. As the speaker came to an end of his talk and signalled this by some closing comments, the behaviour of the class changed remarkably. They relaxed their body postures, they turned to classmates and looked at each other, they smiled, and most strikingly, there was a widespread outbreak of yawning and stretching. These changes were closely synchronized throughout the class. It was difficult to discount the impression that the yawning and stretching occurred as part of a more complex change in the students' behaviour, which was initiated by the end of a distressing experience. Formal observations of the behaviour of people, alone or in large groups, during and following the imposition of stress would be extremely interesting. We suggest that the occurrence of yawning and stretching, in people, may form part of a range of behavioural responses indicative of recovery from stressful events. The animal data which we discuss imply that in people, too, yawning and stretching may follow from neurochemical changes in the brain, which include an inhibition of central dopaminergic activity. In rats it is clear that spontaneous yawning; can be significantly altered by environmental manipulation. In animals and man changes in brain dopamine metabolism and yawning frequency may be closely associated with recovery from acute stress.

During the past decade experiments on drug-induced yawning; in animals have facilitated that construction of a model of the neuronal circuity which subserves yawning. Furthermore, yawning in animals has proved to be a useful pharmacological tool for studying neurotransmitter receptors and receptor subtypes. The challenge remains to discover the physiological trigger for yawning and to fully understand the behavioural and social significance of the response.

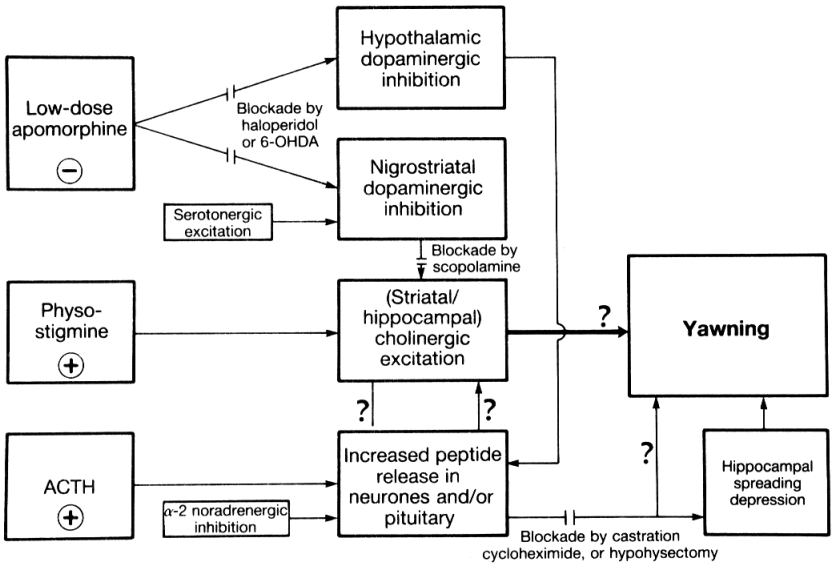

Fig. 4.7. Schematic diagram illustrating control of yawning behaviour by interacting excitatory cholinergic, peptidergic, and serotonergic neurotransmitter systems and inhibitory dopaminergic and noradrenergic mechanisms.

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