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Apomorphine-induced blinking and yawning in healthy volunteers

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Yawning and spontaneous blink rate (SBR) are two physiological reflexes which have been incompletely examined but one neurobiological step of these two behaviours seems, at least in part, dopamine-dependent. The reference dopaminergic agonist, apomorphine hydrochloride (0.5, 1, and 2 $\mu g\ kg^{-1}$ s.c.), was compared with a placebo in a double-blind latin-square design, and was shown to induce yawning and increase SBR in a population of eight healthy volunteers. These two behavioural effects were not dose-related. The individual SBR differences were correlated with the individual number of yawns for all the four treatments at the 10–30 min interval. Thus, parallel yawning and SBR behaviour suggests a similar pharmacological mechanism. Apomorphine-induced yawning and blinking may be therefore of use in the evaluation of central dopaminergic pathways in man.

Keywords apomorphine yawning blinking dopamine

Introduction

Blinking is a behaviour which is easy to observe in most vertebrates and in all mammals, and which occurs spontaneously in the absence of any identifiable stimulus. Blinking is centrally correlated with cognitive and visual functions, and spontaneous blinking rate (SBR) varies with the activity of the subject (Stern *et al.*, 1984). Yawning is a reflex which, although not yet completely understood, is known to be physiologically induced by hunger, boredom, and imitation. However, its pathological meaning has been acknowledged since ancient times. At least one neurobiological step of these two behaviours is dopamine-dependent. Variations in SBR (Karson, 1983; Karson *et al.*, 1984) and yawning (Heusner, 1946) have been observed in various pathologies mainly related to dopaminergic system dysfunction: Parkinson's disease, progressive supranuclear palsy (PSP), Huntington disease, schizophrenia, Gilles de la Tourette syndrome. Apomorphine, a dopaminergic reference agonist, induces yawning (Holmgren & Urba-Holmgren, 1980; Mogilnicka & Klimek, 1977; Urba-Holmgren *et al.*, 1982; Yamada & Furukawa, 1980) and increases SBR (Karson, 1983) in animals. Thus, dopaminergic systems may modulate blink rate and yawning. The aim of our study was 1) to determine if low doses of apomorphine devoid of emetic properties could induce yawning and increase SBR in healthy volunteers, and 2) to study dose-ranging in order to determine if yawning and SBR can serve as assessment factors of the central nervous system (CNS) dopaminergic receptors in humans.

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Methods

Healthy volunteers

Eight healthy male volunteers were selected for the study. Their ages ranged from 21 to 27 years (mean 23.4) and their weight, from 58 to 81 kg (mean 70.5). Subjects were asked not to drink alcohol during the period starting 24 h prior to each treatment and up to the end of each session, and to abstain from all CNS drugs. Subjects were advised not to drive on treatment days. Approval was obtained from the Ethics Committee of the Timone Hospital and each subject gave written informed consent before the study.

Drug supply

Apomorphine and a placebo were prepared by a nurse who was not part of the study. Treatments consisted of:

1) Apomorphine (0.5, 1 and 2 $\mu g\ kg^{-1}$)
2) Placebo (saline).

Subcutaneous injections (1 ml) were immediately administered by the experimenter.

Experimental design

Each subject was his own control and was given all four treatments. The treatments were assigned to the eight subjects according to a balanced latin-square design under double-blind conditions. At least 48 h were left between the treatments to ensure wash-out of the study medication.

Assessment

After a 15 min baseline session, the treatment was administered. The test battery assessed side effects, SBR, and yawning. The subjects remained in constant environmental conditions (closed office, constant hydrometry, temperature and luminosity).

- Side effects were assessed through direct observation by two experimenters throughout the entire session.
- SBR was recorded on videotapes, and counted by two observers every 5 min, for a duration of 30 s, over a 1 h period.
- Yawning, i.e. involuntary opening of the mouth followed by at least one deep inhalation before mouth closing, was monitored continuously on videotapes by two observers.

Statistical analysis

The effects of the drugs studied (individual movements) were evaluated by an analysis of variance with three between-subject factors (subjects, days, and drugs) and one within-subject factor (time) as the main source of variation. Comparison of the doses was performed according to the Newman-Keuls (1 factor) method. The existence of a correlation within individuals between SBR and yawning was tested using the Spearman rank correlation coefficient.

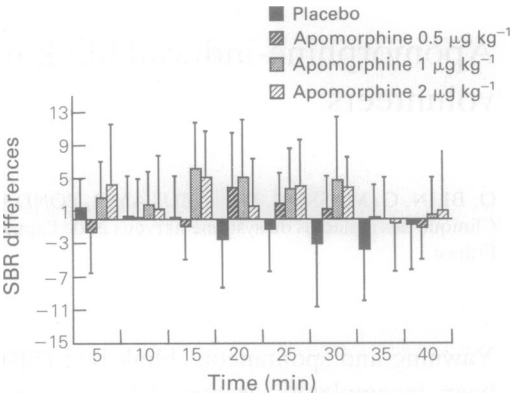

Figure 1 Mean spontaneous blink rate variation (± s.d.) observed in eight healthy volunteers following subcutaneous apomorphine injection.

Results

Side effects

All treatments were well tolerated. None of the subjects exhibited nausea or vomiting.

SBR

There was marked inter-individual variation. Depending on the volunteer, SBR varied from 4 to 32 min^{-1} (mean: 16.12 ± 7.4). The variance analysis yielded a subject effect (F = 7.79 d.f. (7, 105) $P < 0.001$).

Apomorphine, as compared with the placebo, increased SBR (Figure 1). The analysis of variance indicated a statistically significant treatment-related response (F = 13.64 d.f. (3, 105), $P < 0.001$).

The time analysis revealed a significant difference between treatments at 25 min ($F = 3.09$, d.f. (3, 21), $P < 0.05$). The one-factor Newman-Keuls test did not yield any significant difference between doses.

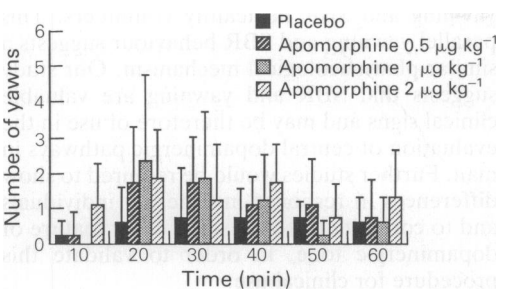

Figure 2 Mean number of yawns (± s.d.) observed in eight healthy volunteers following subcutaneous apomorphine injection.

Yawning

All subjects yawned. Apomorphine, as compared with the placebo, induced yawning in healthy volunteers (Figure 2). The variance analysis yielded a time effect ($F = 6.53$, df (5, 105) $P < 0.001$). Thus, the time interval between yawns was not an equilibrium process. When yawns were compared at each 10 min interval, differences were located at the 10–20 min interval. After checking to see that the distribution was normal, contrast analysis (Winer, 1971) showed a significant difference between apomorphine and the placebo ($F(1, 21) = 4.58$, $P < 0.05$). Conversely, there was no significant difference between the doses.

SBR and yawning

The individual SBR differences were correlated with the individual number of yawns for all the four treatments at the 10–30 min interval ($r_s = 0.429$, $P < 0.01$).

Discussion

Various studies suggest that CNS dopaminergic systems play a major role in SBR and yawning.

In rats, apomorphine induces ptosis (Puech *et al.*, 1974). In monkeys, apomorphine increases SBR (Casey *et al.*, 1980; Karson *et al.*, 1981) as does bromocriptine (Karson, 1983). Treatment with the dopamine D_2-receptor blocker, sulpiride, antagonizes apomorphine-induced SBR (Karson, 1983). Dopamine, which does not penetrate the blood-brain barrier, does not change SBR. Thus, SBR is related to CNS dopamine activity (Karson, 1983).

Apomorphine induces yawning as well (Holmgren & Urba-Holmgren, 1980; Mogilnicka & Klimek, 1977; Urba-Holmgren *et al.*, 1982; Yamada & Furukawa, 1980). Apomorphine-induced yawning is antagonized by both typical (Protais *et al.*, 1983) and atypical neuroleptics (Dubuc *et al.*, 1982), but not by domperidone, a peripheral dopamine receptor blocker (Corsini *et al.*, 1981). Thus, yawning is related to the activation of CNS dopaminergic receptors.

In Parkinsonism (Hall, 1945; Karson *et al.*, 1984) as well as in PSP (Karson *et al.*, 1984), SBR is low. This reduction is related to the severity of the clinical signs. Moreover, there is a difference between non-dyskinetic and dyskinetic patients, SBR being higher in the latter (Karson, 1983; Karson *et al.*, 1982). Yawning seems to be infrequent in Parkinson patients (Boudouresques *et al.*, 1965).

In Huntington's disease, SBR is greater in some patients. Unfortunately, this study deals with patients who have been previously treated with neuroleptics (Karson *et al.*, 1984). In this disease, yawning seems to be frequent (Boudouresques *et al.*, 1965).

In schizophrenia, SBR seems to increase (Karson, 1983; Karson *et al.*, 1986; Ostow & Ostow, 1945; Stevens, 1978). Although there were no details, these studies probably dealt with patients with positive symptoms. In the last two studies, patients had been treated previously.

Few pharmacological studies have been carried out on man. In Parkinsonism, the reduction of SBR is corrected by levodopa administration (Karson *et al.*, 1982). In schizophrenia, the higher SBR is modified by neuroleptics (Karson *et al.*, 1982; Mueser *et al.*, 1984). Methylphenidate, a dopamine reuptake inhibitor, increases SBR in schizophrenia, and this response can be considered as a prediction of relapse after the withdrawal of neuroleptics (Lieberman *et al.*, 1987).

In healthy volunteers, low doses of apomorphine (less than 5 $\mu g\ kg^{-1}$) were shown to induce yawning (Blin *et al.*, 1988; Corsini *et al.*, 1981; Lal *et al.*, 1987; Szechtman *et al.*, 1988). Higher doses (more than 7 $\mu g\ kg^{-1}$) do not lead to the same effect (Lal *et al.*, 1989) probably on account of mutually exclusive reactions to these doses (vomiting). Physiological data on sex (Lal *et al.*, 1987) or chronobiological variations (Anias *et al.*, 1984) indicate that these seem able to modulate the apomorphine-induced yawning, and therefore require further experiment.

The pharmacological mechanism underlying yawning and SBR remains unexplained. According to recent studies on yawning, it seems that more than being simply related to the isolated stimulation of pre- or post-synaptic dopamine D_2-receptors, apomorphine-induced yawning is related to the combined action of the dopamine

D_1- and D_2-receptors (for a review, see Aubin & Garma, 1988).

In our study, apomorphine (0.5, 1 and 2 $\mu g\ kg^{-1}$) induced yawning and increased SBR in healthy volunteers. In the 20–30 min interval, there was a significant correlation between individual SBR differences and individual number of yawns. Thus, in our study, this result suggests a parallel individual evolution between the two behaviours. These behavioural effects were not dose-related. Moreover at lower doses there is a danger that the pharmacological response would be concealed by behavioural variability, triggered by non-specific physiological factors.

In conclusion, low doses of apomorphine, a reference dopaminergic agonist, increased yawning and SBR in healthy volunteers. This parallel yawning and SBR behaviour suggests a similar pharmacological mechanism. Our study suggests that SBR and yawning are valuable clinical signs and may be therefore of use in the evaluation of central dopaminergic pathways in man. Further studies would be required to show differences in response in different individuals and to correlate this with some other feature of dopaminergic tone, in order to validate this procedure for clinical use.

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