Possible involvement of serotonin receptors in the facilitatory effect of a hallucinogenic phenethylamine on single facial motoneurons

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2,5-Dimethoxy-4-methylamphetamine (DOM, "STP") is a potent hallucinogen, proposed to be a serotonin receptor agonist. Its effects have not previously been tested upon central neurons where serotonin is excitatory and serotonin antagonists are effective. Extracellular single unit recordings were obtained from facial motoneurons in anaesthetized rats, and drugs were applied from five-barrelled micropipettes by iontophoresis. Facial motoneurons were commonly silent. During subthreshold application of glutamate, firing could be induced by dopamine and DOM. As reported by others, serotonin and noradrenaline also excited facial motoneurons under these conditions. Methysergide antagonized responses to serotonin and DOM but not those to noradrenaline; methysergide could not usually discriminate between responses to serotonin and dopamine. Ketanserin reversibly antagonized (but could not discriminate between) responses to serotonin, dopamine, and noradrenaline. Chlorpromazine antagonized responses to dopamine at doses that did not alter serotonin-induced excitation, and responses to DOM were not reduced by doses of chlorpromazine, that had no local anaesthetic effect on action potentials elicited by DOM and serotonin. These results suggest that DOM is an agonist on at least one type of central serotonin receptor. This receptor may also be a ketanserin (5-HT_2) binding site.

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Le 2,5-diméthoxy-4-méthylamphétamine (DOM, «STP») est un puissant hallucinogène et sensé être un agoniste du récepteur de sérotonine. Ses effets n'ont jamais été testés sur les neurones centraux où la sérotonine est excitatrice et où les antagonistes de la sérotonine sont efficaces. On a obtenu des enregistrements monocellulaires extracellulaires de motoneurones faciaux chez des rats anesthésiés et des drogues furent appliquées par iontophorèse avec des micropipettes à cinq branches. Les motoneurones faciaux étaient habituellement silencieux. La dopamine et le DOM purent induire une activité lors de l'application infraliminaire de glutamate. Tel que rapporté dans d'autres études, la sérotonine et la noradrénaline excitèrent aussi les motoneurones faciaux dans ces conditions. Le méthysergide antagonisa les réponses à la sérotonine et au DOM, mais pas celles à la noradrénaline; normalement, le méthysergide ne put distinguer les réponses à la sérotonine des réponses à la dopamine. La kétansérine antagonisa de manière réversible les réponses à la sérotonine, à la dopamine et à la noradrenaline, mais ne put faire de distinction entre elles. La chlorpromazine antagonisa les réponses à la dopamine à des doses qui n'altèrent pas l'excitation induite par la sérotonine, et les réponses au DOM ne furent pas réduites par des doses de chlorpromazine qui n'avaient pas d'effet anesthésique local sur les potentiels d'action induits par le DOM et la sérotonine. Ces résultats suggèrent que le DOM est un agoniste sur au moins un type de récepteur sérotoninergique central. Ce récepteur peut aussi être un site de fixation de la kétansérine (5-HT_2).

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Introduction

The available evidence suggests that the potent phenethylamine hallucinogen 2,5-dimethoxy-4-methylamphetamine (DOM) is not an indirectly acting agent; rather, it has been proposed to be a direct agonist at neuronal receptors in the central nervous system that recognize the putative neurotransmitter serotonin (5-hydroxytryptamine, 5-HT) (Dyer et al. 1973; Nichols et al. 1982; Glennon et al. 1983). In general, however, knowledge of the interaction between phenethylamine hallucinogens and various neurotransmitter receptors in the brain lags behind that for indoleamine type drugs (e.g., lysergic acid diethylamide (LSD) and 5-methyoxy-*N*,*N*-dimethyltryptamine (5-MeODMT)). In common with the effect of low doses of LSD (Freedman 1961), high doses of DOM (Wallach et al. 1972; Leonard 1973; Anden et al. 1974) but not mescaline (Anden et al. 1974) or D-amphetamine (Tonge and Leonard 1971) decrease the turnover of 5-HT in the rat brain.

Many of the behavioural effects of DOM (and indole hallucinogens) are prevented by low doses of 5-HT antagonists, which interact with the ketanserin (5-HT_2) binding site (Colpaert et al. 1982; Glennon et al. 1983). Indeed, an impressive correlation has been recently found between the ability of 15 hallucinogens to prevent the binding of the 5-HT_2 ligand ketanserin to rat cortical membranes and the threshold dose for each drug required for hallucinogenesis (Glennon et al. 1985). It has also been suggested that 5-HT-induced excitation in the central nervous system may be mediated by a 5-HT_2 site (Davies et al. 1985), as usually only this effect of 5-HT is prevented by antagonists that have high affinities for this binding site (Haigler and Aghajanian 1974).

In view of the finding that DOM has only weak effects on serotonergic cells of the dorsal raphé (Penington and Reiffenstein 1986) and that the three other studies of the action of DOM on central neurons have not applied the drug directly (by iontophoresis) to the cells studied (Aghajanian et al. 1970; Wallach et al. 1972; Trulson et al. 1981), we examined the effect of DOM on facial motoneurons (FMNs) that respond to 5-HT and noradrenaline (NA) with a facilitation of their firing (McCall and Aghajanian 1979, 1980*a*, 1980*b*). In the anaesthetized rat, even large ejections of NA and 5-HT produce no observable effect when FMN firing is recorded extracellularly. In the presence of a low ejection current of glutamate (about one-third of that required to induce firing), small amounts of 5-HT or NA produce large, slow-onset increases of cell firing. Intracellular

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recording *in vivo* from FMN units provided an explanation for the facilitatory effects of 5-HT and NA on excitatory exogenous amino acid and synaptic inputs. Both putative transmitters were found to exert a small slow depolarizing action, which was accompanied by an increase in the input resistance of the cell. The effects of these agents could be selectively antagonized with 5-HT "D-type" antagonists or the α-adrenoceptor antagonist piperoxane (McCall and Aghajanian 1979, 1980*a*). Interestingly 5-MeODMT and mescaline, unlike LSD, were able to mimic the action of 5-HT on FMNs, but the action of DOM or the putative transmitter dopamine (DA) were not tested. We examined the effects of iontophoretically applied DOM and DA on FMN units and attempted to characterize the receptors for these agents by the use of selective antagonists.

Methods

Surgical procedures

A total of 69 male Sprague–Dawley albino rats (200–280 g) were anaesthetized with urethane (1.25 g/kg i.p.). The temperature of the animal was maintained at 37 ± 0.5°C with a battery-operated heating blanket, servo-coupled to a rectal temperature probe. The rat was placed in a stereotaxic apparatus with the incisor bar set at 0 mm elevation over the ear bar zero. A small hole was drilled in the skull over the coordinates of the facial motor nucleus: 2.3 mm posterior to lambda, 2.0 mm lateral to the midline, and 8.0–8.5 mm ventral to the surface of the brain. The dura was cut away, and the hole was plugged with surgical gelatin sponge to facilitate blood clotting. This area was kept moist with cotton wool soaked in physiological saline throughout the experiment.

Electrodes

Extracellular recordings were made with the center barrel of a five-barrel micropipette (tip 10–15 μm). The recording electrode was made from thick-walled borosilicate glass (Hillgenberg outside diam. 2 mm, inside diam. 1 mm) preloaded with glass fibre, which facilitated barrel filling by capillary action. Drug barrels also contained glass fibre but had an outside diam. of 1.2 mm. After filling, the openings were sealed with silicone grease to prevent evaporation and the formation of salt bridges. The center recording barrels contained 2% pontamine sky-blue dye and 0.5 *M* sodium acetate and had resistances of 4–8 MΩ. The other four barrels had resistances of 70–200 MΩ. In most experiments, one barrel was assigned to current balancing purposes and contained 0.15 *M* NaCl. This barrel was also used to test the effects of current and pH when current compensation was not used.

Drugs and chemicals

The iontophoretic electrodes were filled with various combinations of the following compounds made up in distilled deionized water unless otherwise stated: 5-HT (serotonin creatinine sulfate, Sigma, 0.04 *M*, pH 5), GLU (monosodium glutamate, M.C. & B. Chemicals, 0.1 *M*, pH 7.6), ketanserin tartrate (Janssen, 0.02 *M*, pH 4), methysergide bimaleate (Sandoz, 8.5 m*M*, pH 5, in 0.15 *M* NaCl), NA (L-noradrenaline bitartrate, Winthrop, 0.1 *M*, pH 4), chlorpromazine HCl (Sigma, 0.05 *M*, pH 5, in 0.15 *M* NaCl), DA (dopamine HCl, Sigma, 0.1 *M* pH 5), and DOM ((±)-2,5-dimethoxy-4-methylamphetamine HCl, National Bureau of Drug Research, Ottawa, 0.1 *M*, pH 5, with and without 0.15 *M* NaCl). A retaining current of 5 nA was applied to all drug barrels between periods of ejection.

Recording

Single-unit action potentials recorded with the micropipette were passed through a high-input impedance amplifier and displayed on an oscilloscope. The output was fed into a rate meter and the frequency of the unit activity was displayed on a rectilinear pen recorder. Local anaesthetic effects of the antagonist drugs being tested were noted by monitoring the constancy of the action potential amplitude during the experiment.

Protocol and data analysis

As FMNs are silent in the anaesthetized rat, glutamate (≈20 nA) was used to locate the individual cells. Previous investigators (McCall and Aghajanian 1979) have shown *in vivo* that 5-HT and NA facilitate excitatory inputs to FMNs, rather than cause firing themselves. Consequently, the effects of drugs on FMN units were tested, both in the absence but usually in the presence of the ejection of glutamate at a current approximately one-third of that which would induce firing of the cell. Agonists were applied in regular cycles for a period of 30 s, followed by a 99-s pause. Regular responses to the test and control agonists were obtained for a 12-min control period before the antagonist was added. One cell was studied in each animal. Results were measured as the average maximal rate of cell firing during three excitatory responses to agonist in the control (assigned 100%), antagonist, and recovery periods. All trials with each drug combination were averaged for each cell and then means of all cells calculated. The size of the excitatory responses in the different conditons were expressed as mean ± SEM (n = number of cells). To compare the size and shape of action potentials elicited by different putative neurotransmitters and drugs, or if an antagonist caused a local anaesthetic type effect (suggested by a reduction in action potential amplitude (Curtis 1968)), photographic records were made.

Histology

Each site from which recordings were made was afterwards stained by the passage of a cathodal current out of the recording pipette (10 μA for 10 min). This resulted in the deposition of a discrete blue spot. Animals were then perfused through the heart with 10% buffered formaldehyde solution. Serial sections (50 μm) of the brain were then cut, counterstained, and examined with a microscope for the presence of the blue spot.

Results

Forty-nine of 69 recording sites were stained successfully and histological examination demonstrated that all of them were located within the facial motor nucleus. As reported by McCall and Aghajanian (1979), FMNs in the presence of small amounts of glutamate showed slowly developing, large increases in firing, in response to the ejection of low currents (10–25 nA) of 5-HT and NA. This did not occur in response to the routine ejection of current carried by sodium ions from the current balance barrel (at the same pH as the 5-HT). Under these conditions, the application of 5-HT increased the firing rate of all 51 cells to which it was applied. It took 20–30 s for firing to be initiated, which usually occurred before the termination of the ejection of 5-HT; the period of firing normally outlasted the 5-HT application by a factor of at least two (Fig. 1*a*). If the ejection of glutamate was terminated, then the responses to 5-HT did not occur. NA was applied to 13 cells and in each case it produced a similar response to that of 5-HT application (Figs. 1*b*, 2*b*). DA had not previously been tested on FMN units; it was found when DA was ejected under the same conditions that 27 of 28 cells responded with excitation. It was possible to elicit regular responses to 5-HT and DA, or 5-HT and NA, in an alternating fashion. However, some difficulty was encountered in alternating applications of NA and DA: there was a tendency to quickly lose the response to one or the other monoamine. The application of the phenethylamine DOM, with pulses of the same duration (30 s), also facilitated the firing of FMN units on 35 of 37 cells (Figs. 1, 2*a*, 3, and 4). The duration of the DOM-induced firing was similar to that caused by NA, DA, and 5-HT; also a similar maximal frequency of firing was attained (10–15 Hz). The size of the excitatory response of FMNs to alternating DOM and DA applications was usually not as well maintained; this was similar to the effects noted with responses to NA and DA; however, two successful experiments were performed. If the firing of the FMNs was maintained by suprathreshold glutamate ejection, then the application of 5-HT or

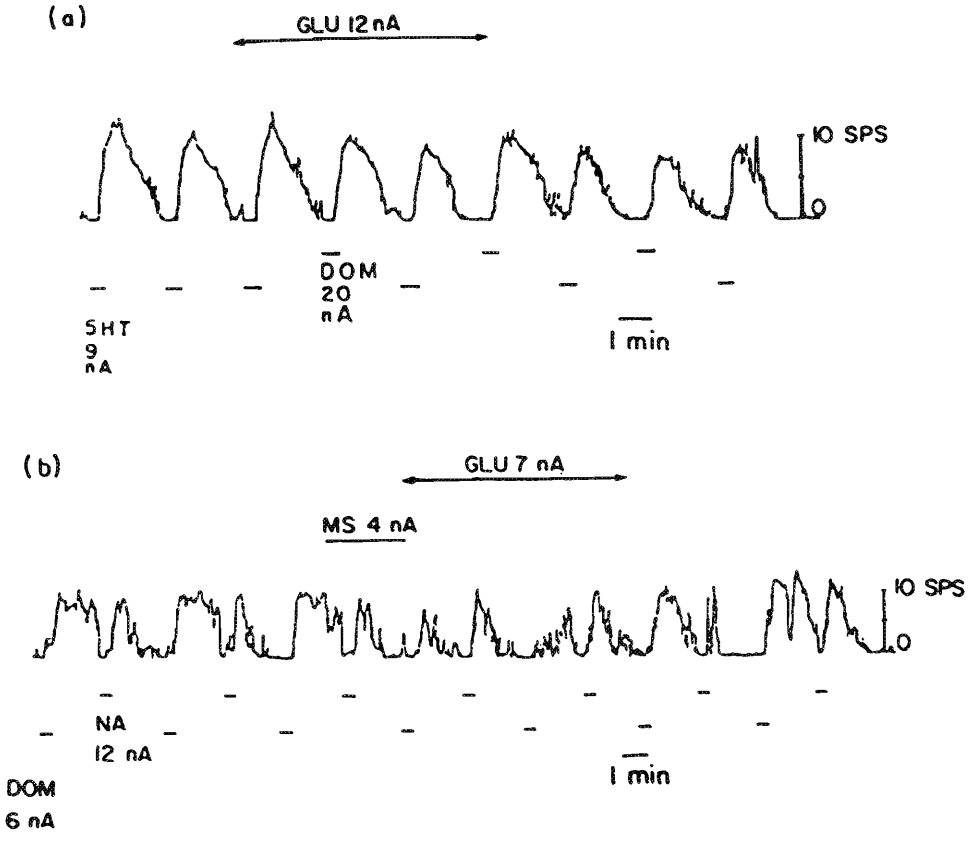

FIG. 1. The facilitatory effect of DOM, 5-HT, and NA on the firing rate (in spikes per second, SPS) of two facial motoneurons. (*a*) Long-lasting 5-HT-elicited firing which commenced before the termination of an iontophoretically applied pulse of 5-HT. The application of similar currents of DOM produced an activation of this cell, the form of which is difficult to distinguish from that caused by 5-HT. Note that the double headed arrows in all figures indicate that the application of glutamate (GLU) lasted throughout the trace. (*b*) Ejection of a small current from the methysergide (MS) containing barrel reduced the size of the DOM-induced excitation by at least 50%. This amoung of MS had no effect upon the control response to NA.

DOM caused a further increment in cell firing rate. The application of DOM always elicited action potentials of a similar amplitude and shape to those elicited by the application of 5-HT.

The effect of 5-HT antagonists

Small currents of methysergide (average 8 nA applied for 5 min or less) completely prevented the excitatory response of FMNs to 5-HT without altering the size or the shape of the action potential (Figs. 2*a*, 2*b* and Table 1). For all four cells where responses to NA were alternately elicited with those to 5-HT (Fig. 2*b*), the responses to 5-HT were antagonized but those to NA were completely unaffected (Table 1). Similarly, responses to DOM were antagonized by methysergide on all five cells tested. On three of these cells the specificity of the antagonism of DOM was assessed by comparing the antagonist effect on responses to NA; the latter responses were unaffected (Fig. 1*b*). Records from two cells, were the ejection of DOM and 5-HT were alternated showed that methysergide antagonized the effect of both compounds; in addition, the recovery of the responses to both DOM and 5-HT had the same time course (Fig. 2*a*). On four cells methysergide antagonized the effect of 5-HT, but on three of the four cells the reference agonist effect of DA was also reduced by a similar amount; this can be seen in Table 1. On the remaining cell methysergide selectively prevented the response to 5-HT and left responses to DA relatively unaffected.

The 5-HT_2-selective antagonist ketanserin reversibly antagonized the response of FMNs to 5-HT with no effect upon the action potential size or shape ($n = 3$ cells). However, ketanserin was also effective at reversibly antagonizing responses to DA (Fig. 2*c* and Table 1) and NA. Results depicted in Fig. 2*c* suggest that the response to DA may take a little longer to recover from antagonism by ketanserin than does the response to 5-HT.

The effect of chlorpromazine

The neuroleptic chlorpromazine antagonized the response of 10 cells to DA (Fig. 3*a* and Table 1) with no effect upon the action potential size or shape. On all five of these cells where the control agonist 5-HT (alternated with the pulses of DA) was tested, chlorpromazine had no effect on 5-HT-elicited firing or action potentials. Chlorpromazine did not reduce the effect of 5-HT on a further three cells where the 5-HT was alternated with pulses of DOM. However, the effects of chlorpromazine on responses of FMNs to DOM appeared to be quite complex. When responses to DA were obtained alternately with responses to DOM, the response to DA was completely antagonized by chlorpromazine; however, a reduction in the size of the response to DOM was also apparent (Fig. 3*b*, $n = 2$ cells). The responses to DOM showed poor recovery, and what recovery there was, occurred some time after full recovery of the responses to DA. Where the application of DOM was alternated with 5-HT (three cells), it was clear that amounts of chlorpromazine, which had no effect upon the responses to 5-HT, did not affect the response

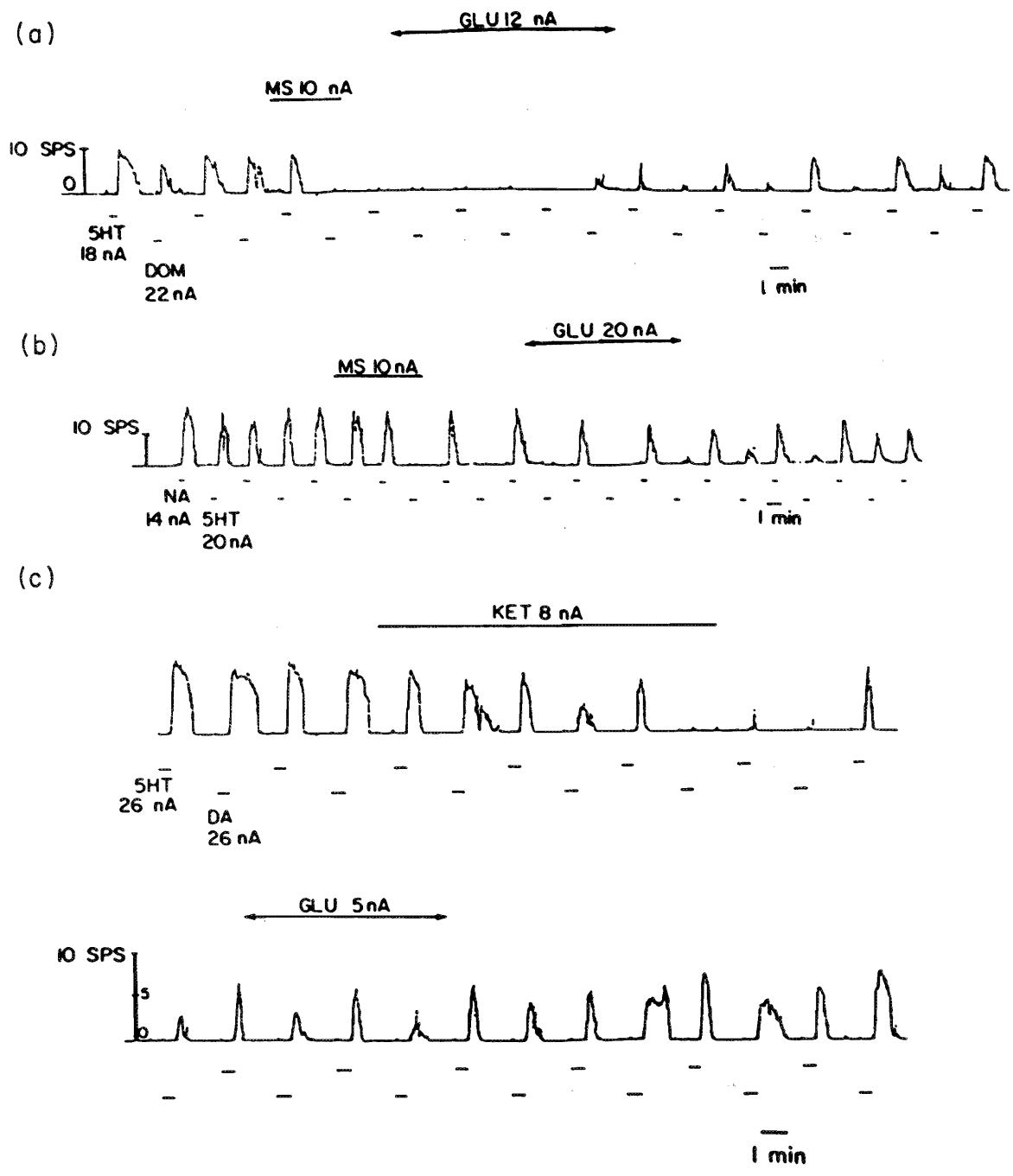

FIG. 2. The effect of the 5-HT antagonists methysergide (MS) and ketanserin (KET) upon responses (measured in spikes per second, SPS) of three facial motoneurons to DOM, 5-HT, NA, and DA. (*a*) The application of MS (10 nA) completely antagonized responses of this cell to 5-HT and DOM. The responses start to recover together, but in this particular experiment recovery of the response to 5-HT appeared sooner than did the response to DOM. Recovery of the response to DOM did not quite reach control levels, but when measured over all experiments recovery was usually complete. (*b*) Typical example of the reversible selective antagonistic action of MS on responses to 5-HT; note responses to NA are unaffected. Half-way through the trace there was a small decrement in the responses to both monoamines, this may have been due to a change in the excitability of the cell with time. (*c*) On another cell the application of KET reversibly reduced the size of responses to DA and 5-HT. The response to DA appeared to take a little longer to recover than did the response to 5-HT. The two traces of Fig. 2*c* are continuous.

to DOM. Higher currents of chlorpromazine produced a local anaesthetic effect on the 5-HT-elicited action potential and also upon the action potential elicited by DOM (Fig. 3*c*); this may have contributed to the chlorpromazine-induced reduction of the response to DOM when it was alternated with DA. It is noteworthy that the local anaesthetic effect on the 5-HT-elicited action potentials wore off quicker than did the effect on the DOM-elicited action potential. Where enough chlorpromazine had been ejected to produce a reduction in the action potential amplitude elicited by 5-HT, the recovery of the response to DOM (but not 5-HT) was always poor (Fig. 4, Table 1).

Discussion

In the present investigation it was found that ejection of DA and the phenethylamine hallucinogen DOM, in the presence of an amount of glutamate that is considerably subthreshold for the

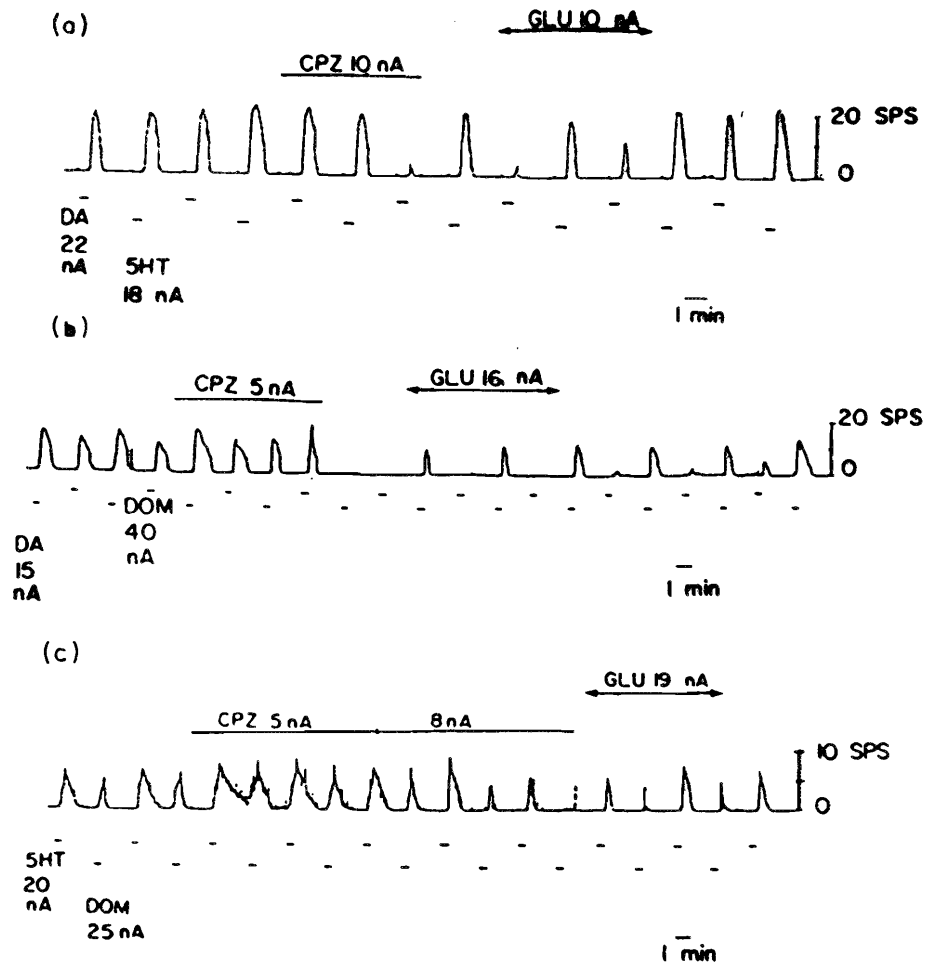

FIG. 3. The effect of chlorpromazine (CPZ) on responses (measured in spikes per second, SPS) of three facial motoneurons to DA, 5-HT, and DOM. (*a*) This illustrates the excitatory effect of alternately applied 5-HT and DA producing increases in cell firing rate which are regular in amplitude and duration. Application of the neuroleptic CPZ reversibly antagonized the excitatory response to DA, while the response to 5-HT was unaffected. (*b*) CPZ completely antagonized the response to DA (without changes in the shape or form of the action potential), which started to recover about 3 min after the termination of the ejection of CPZ. The response to DOM was also reduced, but it did not start to recover until about 14 min after the termination of the current of CPZ. The response to DOM did not recover by more than 40% of control. When the cell started to fire again in response to DOM, a local anaesthetic action was observed which was not evident in spikes elicited by DA. (*c*) Low currents of CPZ (which had no effect upon the response to 5-HT) also did not affect the response to DOM. However, just after the break in the bar, where the CPZ current was increased from 5 to 8 nA, a local anaesthetic effect on the 5-HT-elicited action potential was noted. At this point a similar effect on the DOM-elicited spike was also seen; this may have contributed to the reduction in DOM-elicited firing by CPZ. The local anaesthetic effect on the 5-HT-elicited spike wore off quicker than did the effect on the DOM-elicited spike.

initiation of action potentials, was able to cause excitation of FMNs. These effects were similar to those reported by other investigators who have studied the actions of 5-HT and NA on FMNs under the same conditions, effects which they termed "facilitation of excitatory input" (McCall and Aghajanian 1979; Vandermaelen and Aghajanian 1982). These effects are neuromodulatory, in the sense that they are often quite long lasting and increase the action of any other excitatory input to the cell. This action of the three monoamines is deserving of further study, as the effect of 5-HT and NA was shown to be mediated by separate receptors (McCall and Aghajanian 1980*a*). The present study demonstrates that the effect of another agonist (DA) on at least one other distinct receptor is capable of producing a similar excitation of FMNs. The finding that it was usually difficult to elicit responses to NA and DA when they are applied alternately is puzzling, because it suggests that cross-desensitization may occur. The implication is that the two compounds were activating the same receptor, although McCall and Aghajanian (1980*a*) showed that chlorpromazine does not block responses to NA, while we have shown it does antagonize DA. Boakes et al. (1979) also reported that chlorpromazine would not prevent the excitatory action of NA on randomly encountered brainstem neurons. In the periphery, DA can activate α-adrenoceptors, but DA is 1/40 as potent as NA (Goldberg 1972). On spinal motoneurons *in vivo* (a preparation that has yielded results analogous to those of this study (White and Neuman 1980)) other groups have noted a similar difficulty when attempts were made to elicit responses to NA and DA in an alternating fashion (Barasi and Roberts 1977). Despite this difficulty, these investigators concluded that DA activated a DA receptor and NA a separate receptor, as α-flupenthixol antagonized responses to DA but potentiated responses to NA. As in

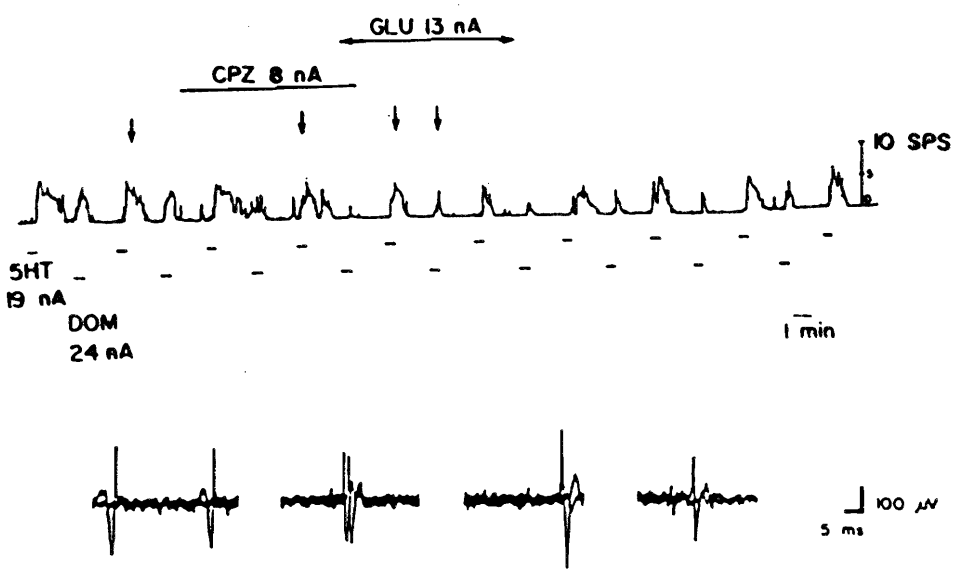

FIG. 4. The effect of chlorpromazine (CPZ) on the amplitude of action potentials elicited by 5-HT and DOM applied to single facial motoneurons. As in Fig. 3*c*, low currents of CPZ had no effect upon the excitatory responses (measured in spikes per second, SPS). However, near the end of the CPZ application local anaesthetic effects were noted. The four downward pointing vertical arrows from left to right indicate the times at which the respective photographs of the action potentials were taken. The first photograph shows two control spikes elicited by 5-HT (DOM-elicited spikes were identical). The second photograph shows a depression of the amplitude of the action potential elicited by 5-HT. This had recovered by the third arrow to a supra-control level. The photograph corresponding to the fourth arrow demonstrates that the local anaesthetic effect of CPZ on DOM-elicited spikes was considerably longer lasting than was its effect upon the 5-HT-elicited action potentials.

TABLE 1. Facial motoneuron firing during antagonism and recovery as a percentage of control

Antagonist	Agonist	*n* (cells)	During antagonism	Recovery	Median (range) antagonist current (nA)
Methysergide	5-HT	11	23±7	87±3	8 (3–13.5)
	NA	7	101±3	100±5	8 (4.5–11)
	DA	4	39±21	74±20	6 (5–8)
	DOM	5	18±7	89±13	8 (4.5–15)
Chlorpromazine	5-HT	8	98±1	100±1	8 (5–10)
	DA	10	25±7	96±3	6 (4–10)
	DOM	5*	60±19	38±11	7 (5–8)
Ketanserin	5-HT	3	12	100	10 (6–16)
	DA	1	0	100	8
	NA	1	50	100	16

NOTE: Values are expressed as mean ± SEM.

*Effects of chlorpromazine on responses to DOM were measured at a time either just prior to the depression of the amplitude of action potentials elicited by 5-HT or at the time when the control response to DA was antagonized. Currents cited are those required to produce the antagonist data (not all currents used).

the present study, a neuroleptic clearly differentiated between responses to 5-HT and those to DA; only the response to DA was antagonized.

That DOM caused only excitation of FMNs is interesting, in view of the spectrum of actions noted with other hallucinogens on these cells (McCall and Aghajanian 1980*b*). At low currents, LSD sensitizes FMNs to the effects of both NA and 5-HT, while larger amounts have an antagonist action. Similarly, small amounts of mescaline have a sensitizing effect, but unlike the action of LSD, larger amounts of mescaline cause excitation of FMNs. The indoleamine hallucinogen 5-MeODMT caused only excitation.

The effect of methysergide

It is not surprising that responses of FMNs to 5-HT but not those to NA were antagonized by methysergide, as this compound has perhaps the lowest affinity for α_1-adrenoceptors of all the "D" type (smooth muscle) 5-HT antagonists (Janssen 1983; Humphrey 1984). As the excitatory effect of DOM was prevented by methysergide, when that induced by NA was unaffected, this indicates that the effect of DOM was not mediated by an action on α_1-adrenoceptors. By contrast, methysergide has seldom, if ever, been tested for its ability to discriminate between the neuronal excitatory effects of 5-HT and DA. Both Whitaker and Seeman (1977) and Janssen (1983) have reported

that the ability of methysergide to prevent the binding of ligands to DA and 5-HT binding sites shows only a narrow margin of selectivity. This is reflected in the present results as methysergide usually antagonized responses to both DA and 5-HT (but not NA). This can be considered as further evidence that receptors for NA and DA on FMNs are not identical.

The concept that excitatory effects of 5-HT in the central nervous system may be mediated by 5-HT_2 type receptors (ketanserin binding sites, Davies et al. 1985) is strengthened by the finding of this study that ketanserin was able to reversibly antagonize the response of FMNs to 5-HT. Ketanserin was also an effective antagonist of responses to DA and NA; this is in keeping with the finding of Janssen (1983) that the high degree of selectivity of ketanserin is mainly between 5-HT binding site subtypes.

The effects of chlorpromazine

5-HT antagonists were found not to have the required selectivity to demonstrate that the responses of FMNs to 5-HT and DOM are due to an action on 5-HT and not on DA receptors. Thus, a selective DA antagonist was sought. In the facial motor nucleus, chlorpromazine proved to be such an agent, which selectively antagonized responses to DA but not 5-HT.

The finding that DA activites FMNs, probably by an interaction with its own specific receptors, may not only provide a valuable model of sites where DA is excitatory but also an explanation of one of the most prevalent side effects of chronic treatment with neuroleptics: involuntary contractions of the facial muscles, called the "buccolingual masticatory syndrome," one of the tardive dyskinesias (Simpson et al. 1981). To provide an explanation for this effect, one has to propose that (*a*) receptors for DA and FMNs become supersensitive after chronic blockade with chlorpromazine, and (*b*) DA normally plays a role in modulating the excitability of FMNs. No immunohistochemical assessment of the presence of DA-containing terminals in the facial motor nucleus has yet been undertaken.

To rule out a possible agonist action of DOM on receptors for DA (Trulson et al. 1977), it is necessary to show that the response to DOM is not reduced by sub-local anaesthetic amounts of chlorpromazine (which antagonized responses to DA). This is what occurred when responses to DOM were alternated with those to 5-HT or DA as control agonists. Higher ejection currents of chlorpromazine produced only transient local anaesthetic type effects on action potentials elicited by 5-HT or DA. In contrast, the local anaesthetic type effect observed on action potentials elicited by DOM was more severe, longer lasting, and often did not recover at all. A speculative explanation of this observation can be based on the fact that both chlorpromazine and DOM are lipophilic compounds (Seeman 1977; Nichols et al. 1977), whereas 5-HT and DA are quite polar and are thus excluded from cell membranes (Handschumacher and Vane 1967). Although chlorpromazine and DOM act at sub-local anaesthetic concentrations (Seeman 1977; this study), when applied together their membrane disordering actions may summate. Provided some recovery occurs between periods of agonist application, this would account for an apparent selective local anaesthetic action on action potentials elicited by DOM. A clearer resolution of this point requires knowledge of absolute drug concentrations, which cannot be achieved *in vivo*. It is most likely that the actions of DOM on FMNs are directly mediated, as unlike D-amphetamine or *para*-chloroamphetamine; there is considerable evidence that DOM is a directly acting agonist (Wallach et al. 1972; Anden et al. 1974; Cheng et al. 1974, Nichols et al. 1982). Indeed, amphetamine derivatives that are methoxylated in the *ortho* and *meta* positions lose their ability to release neurotransmitters (Iversen 1971; Paton 1975). This is consistent with the finding that DOM, like mescaline but unlike D-amphetamine, is not an effective inhibitor of serotonergic neurons in the dorsal raphé nucleus (Penington and Reiffenstein 1986).

It appears also that responses observed in this study have physiological relevance, as cells of the facial motor nucleus are innervated by serotonergic terminals. In addition, the effects observed are probably postsynaptically generated and not complicated by effects on local interneurons (Aghajanian and McCall 1980; Vandermaelen and Aghajanian 1982), since interneurons cannot be detected in the facial motor nucleus (Courville 1966).

In conclusion, results of this study indicate that the phenethylamine hallucinogen DOM has an agonist action on receptors for 5-HT that facilitate the firing of FMNs. The receptor type activated by both 5-HT and DOM has characteristics of the 5-HT_2 receptor and binding site (Fozard 1984; Leysen et al. 1984; Davies et al. 1985), as the effects of 5-HT are antagonized by "D" type 5-HT antagonists and ketanserin. In this regard, it is interesting that phenethylamine hallucinogens exhibit a high potency for the inhibiton of the binding of ketanserin to the 5-HT_2 binding site of rat cortical membranes (Glennon et al. 1985). In addition, behavioural effects of hallucinogenic drugs in animals are selectively prevented by small doses of antagonists that have a high affinity for the 5-HT_2 binding site (Colpaert et al. 1982; Glennon et al. 1983). Finally, 5-HT_2 binding predominates over non-ketanserin-sensitive (5-HT_1) binding, in facial motor nuclei (Pazos and Palacios 1985; Pazos et al. 1985). Taken together with results of the present study, it appears that an interaction with the 5-HT_2-type receptors may underlie or contribute to the mechanism of action of hallucinogenic drugs.

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