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COMPARISON OF THE ELECTROCORTICAL CHANGES INDUCED BY (+)-AMPHETAMINE AND CHLORPROMAZINE WHEN PERFUSED DIRECTLY INTO THE DORSAL RAPHÉ NUCLEUS OF THE CAT

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1 (+)-Amphetamine mimicked the intermittent and sustained electrocortical desynchronization produced by (−)-noradrenaline (NA) when perfused directly into the dorsal raphé nucleus of cat *encéphale isolé* preparations.

2 The effects of amphetamine or NA were abolished or significantly attenuated by prior application of (−)-propranolol.

3 The effect of amphetamine, but not that of NA, was blocked by prior applications of guanethidine or chlorpromazine (CPZ).

4 Desmethylimipramine (DMI) produced dose-related changes in electrocortical activity which were similar to those induced by NA when applied to the same sites within the dorsal raphé nucleus.

5 DMI potentiated the effects of both amphetamine and NA, but guanethidine only abolished the DMI-induced potentiation of the amphetamine response.

6 (−)-Propranolol, guanethidine and CPZ produced a short period of electrocortical desynchronization at the beginning of the perfusion period before antagonism of the amphetamine response was apparent.

7 The results suggest that CPZ and amphetamine have an action within the dorsal raphé nucleus possibly related to noradrenergic terminals.

Introduction

Noradrenaline (NA) and its synthesizing enzymes have been found within the midline raphé system of the brainstem (Saavedra, Grobecker & Zivin, 1976) and fluorescence studies have shown that the NA is confined principally to terminal varicosities and fibres rather than cell bodies (Chu & Bloom, 1974; Battenberg & Bloom, 1975). There is also evidence to suggest that certain of these terminals represent efferent projections from the NA-containing cells of locus coeruleus and that these projections are capable of influencing the activity of raphé neurones (Chu & Bloom, 1974; Morgane, Stern & Berman, 1974) and thus indirectly the electrical activity of more rostral structures (Lorens & Guldberg, 1974; Bobillier, Seguin, Petitjean, Salvert, Touret & Jouvet, 1976). Indeed, perfusion studies have demonstrated that NA applied directly to neurones within the dorsal raphé nucleus (DRN) results in electrocortical desynchronization and eventually behavioural alerting (Key & Kryzwosinski, 1977). From the results of this study it was suggested that the effects were brought about by the activation of inhibitory β-adrenoceptors which modulate the tonic activity of dorsal raphé neurones.

Studies have shown that amphetamine is capable of mimicking both the inhibitory and excitatory actions of NA on single neurones in the brain stem of rats when these compounds are applied by iontophoresis (Straschill & Perwein, 1971; Boakes, Bradley

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& Candy, 1972). Moreover, certain of the peripheral and central actions of chlorpromazine (CPZ) have also been ascribed to postsynaptic effects at noradrenergic synapses (Bradley, Wolstencroft, Hösli & Avanzino, 1966; Gordon, 1967). This similarity in the locus of action of CPZ and amphetamine is interesting in view of the antipodal and antagonistic effects which these drugs show on certain behavioural and electrocortical parameters of arousal or sleep (Bradley & Hance, 1957; Bradley & Key, 1958; White & Boyajy, 1959). Since the raphé nuclei have been implicated in sleep mechanisms (Kostowski, Giacalonne, Garattini & Valzelli, 1969; Jouvet, 1973) and possess noradrenergic synapses, they may represent one of the neuroanatomical locations where both CPZ and amphetamine may act. These drugs have therefore been applied directly to the DRN by perfusion cannulae and their effects, in relation to the arousal level and to NA-induced electrocortical desynchronization, assessed from changes in the electrocorticogram.

The effect of amphetamine on noradrenergic transmission has been related at the neuronal level to the induced release of NA, NA reuptake blockade, monoamine oxidase (MAO) inhibition, as well as a direct effect on postsynaptic receptors (Blaschko, Richter & Schlossman, 1937, Rossum, Schoot & Hurkmans, 1962; Glowinski & Axelrod, 1965; Boakes *et al.*, 1972; Segal & Bloom, 1974). In an attempt to determine the nature of the amphetamine effect within the DRN and to distinguish between the pre- and postsynaptic actions of amphetamine, a comparison has been made with the effects of the NA reuptake blocker, desmethylimipramine. The effect of amphetamine has also been studied following presynaptic adrenergic blockade induced by guanethidine.

Methods

A total of 32 cat *encéphale isolé* preparations were used. The operative procedure, carried out under halothane/oxygen anaesthesia, the type and position of the electrocortical recording electrodes (Figure 1), the concentric two-tube perfusion cannula, as well as the implantation technique and experimental procedure have all been described previously (Bradley & Elkes, 1957; Key & Kryzwosinski, 1977). The area of perfusion at the tip of the cannula was 0.53 mm^2 and the cannula was angled at 45° and implanted stereotactically so that the tip of the outer cannula lay 0.5 to 0.75 mm below the ventricular surface in the dorsal aspect of nucleus raphé dorsalis (DRN). The stereotactic coordinates, taken from the cat brain atlas of Berman (1968), were P1, sagittal plane 0.0, horizontal plane 1.0. The drugs were dissolved in artificial cerebro-spinal fluid (CSF) and perfused at 120 µl/min by means of a Watson-Marlow H.R. Flow Inducer. The CSF was perfused continuously throughout the experiment and the drugs solutions switched in for the required period of time. In these experiments the temperature of the perfusate was maintained at 38 ± 0.5°C and the pH between 6.5–6.8.

Systemic blood pressure was monitored by means of a mercury manometer connected to the femoral artery. Wound edges and pressure points were infiltrated with 1% w/v lignocaine hydrochloride solution upon completion of the operative procedure and subsequently at intervals during the experiment. A period of 1 h was allowed for recovery from the anaesthetic. Control recordings of the electrocorticogram (ECoG) were taken over a further hour before perfusion of the artificial CSF was started. The ECoG was monitored throughout the experiment on an 8-channel Mingograph EEG and for descriptive purposes reference has been made to four basic patterns representing the alert, relaxed, drowsy and sleeping behavioural states, according to the schema described by Bradley & Elkes (1957). Paradoxical (REM) sleep was not observed in these preparations. A more quantitative assessment of the changes produced by the perfusion of the drugs was obtained by integrating the electrocortical waveform recorded from the association cortex of the right or left middle suprasylvian gyrus. The output of the integrator was in the form of pulses which represented fixed increments of electrical energy (Figure 1, int). The pulses were counted over successive 20 s periods and expressed graphically to reflect the degree of desynchronization of the ECoG (Figure 1a) as previously illustrated (Key & Kryzwosinski, 1977). Thus an increase in electrocortical desynchronization, which occurred as the animal progressed from slow wave sleep to the fully alert behavioural state (cf Figure 1b and 1c), was indicated by a marked and often abrupt decrease in the integral counts. Intermediate alterations in the degree of desynchronization accompanying, for example, a change from slow wave sleep to the drowsy or relaxed behavioural state were reflected by smaller decreases in the integral counts (Figures 3c and 4d).

Upon completion of the experiment the brain was removed from the skull, fixed in 10% formal saline solution and later examined histologically to determine the precise position of the cannula tip. In all the experiments described the cannula was in the midline and within the dorsal aspect of the DRN.

The drugs tested were guanethidine sulphate (Ciba), desmethylimipramine (Geigy), (+)-amphetamine sulphate (Menley and James), and the hydrochlorides of (−)-noradrenaline (Sigma), (−)-propranolol (ICI) and chlorpromazine (May and Baker). The concentrations of the solutions have been expressed in molarity calculated in terms of the salt.

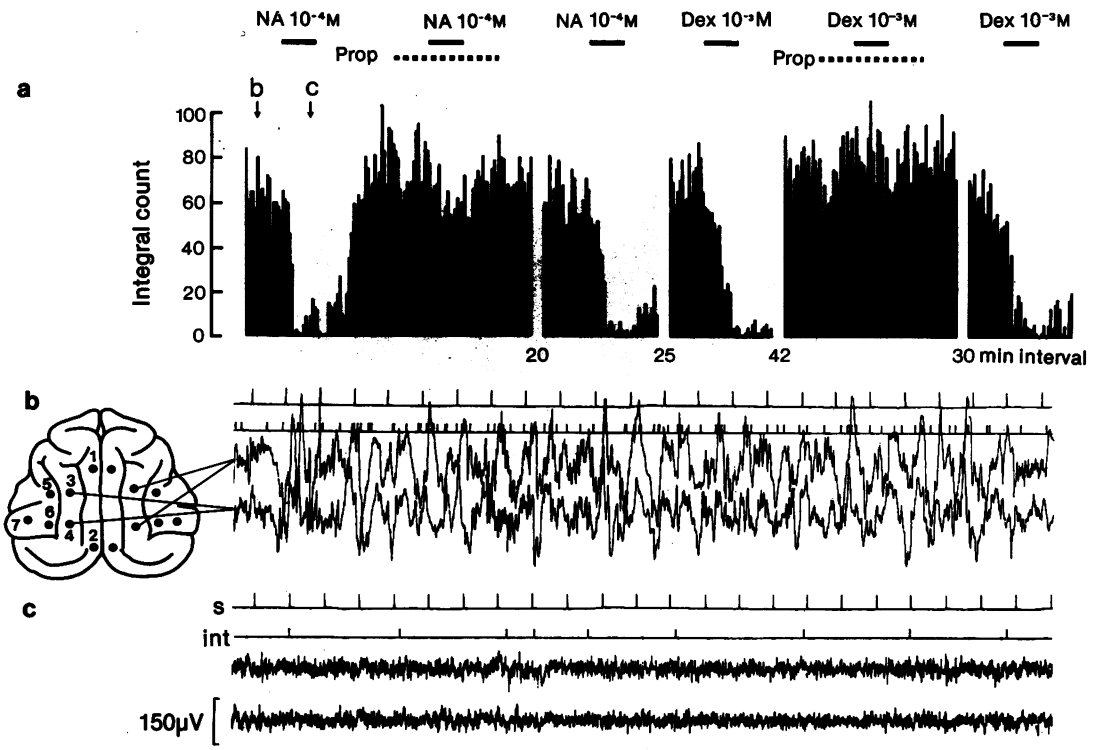

Figure 1 The effects of noradrenaline (NA) and (+)-amphetamine (Dex) on the pattern of electrocortical activity when perfused into the same site within the dorsal raphé nucleus of the cat. (a) Histogram depicting the integral counts over successive 20 s periods. Solid bars show 5 min perfusion periods of NA and amphetamine. Perfusion of (−)-propranolol (10^{-4} M) is indicated by the interrupted bars (Prop). Desynchronization of the electrocorticogram recorded from the left middle suprasylvian gyrus is reflected by a decrease in the integral counts. Note that a prior perfusion of (−)-propranolol markedly attenuates or completely abolishes the response to NA and amphetamine. Recovery occurred after 20 and 30 min respectively. (b) An example of the pattern of electrocortical activity recorded during the sleeping behavioural state. The standard positions for the placement of cortical recording electrodes are given by the numbers: (1) anterior lateral gyrus; (2) posterior lateral gyrus; (3) middle suprasylvian gyrus; (4) middle suprasylvian gyrus; (5) middle ectosylvian gyrus; (6) middle ectosylvian gyrus; (7) posterior ectosylvian gyrus. (c) An example of the pattern of electrocortical activity recorded during the alert behavioural state with corresponding integral pulses (int) and time marker (s).

Results

Noradrenaline and amphetamine

The perfusion of NA into the DRN of the sleeping animal (32 expts) produced changes in the pattern of electrocortical activity within 1 to 2 min of the start of the application. These changes, which were reflected by alterations in the integral counts (Figures 1 and 2), were dose-related and similar to those reported previously (Key & Krzywosinski, 1977). Basically, the effects ranged from the introduction of slightly faster frequencies in the electrocorticogram (ECoG) when low concentrations (10^{-5} to 5×10^{-5} M) were applied, the appearance of intermittent (phasic), or even sustained (tonic) electrocortical desynchronization with higher concentrations (5×10^{-5} to 5×10^{-4} M), to the complex three phase desynchronization: synchronization: desynchronization response (Figure 2), which characterized the effect of NA applied in still higher concentrations (10^{-4} to 10^{-3} M).

(+)-Amphetamine, perfused at the same sites as NA within the DRN (29 expts) mimicked the electrocortical changes induced by NA (Figure 1). However, minimal effective concentrations were higher

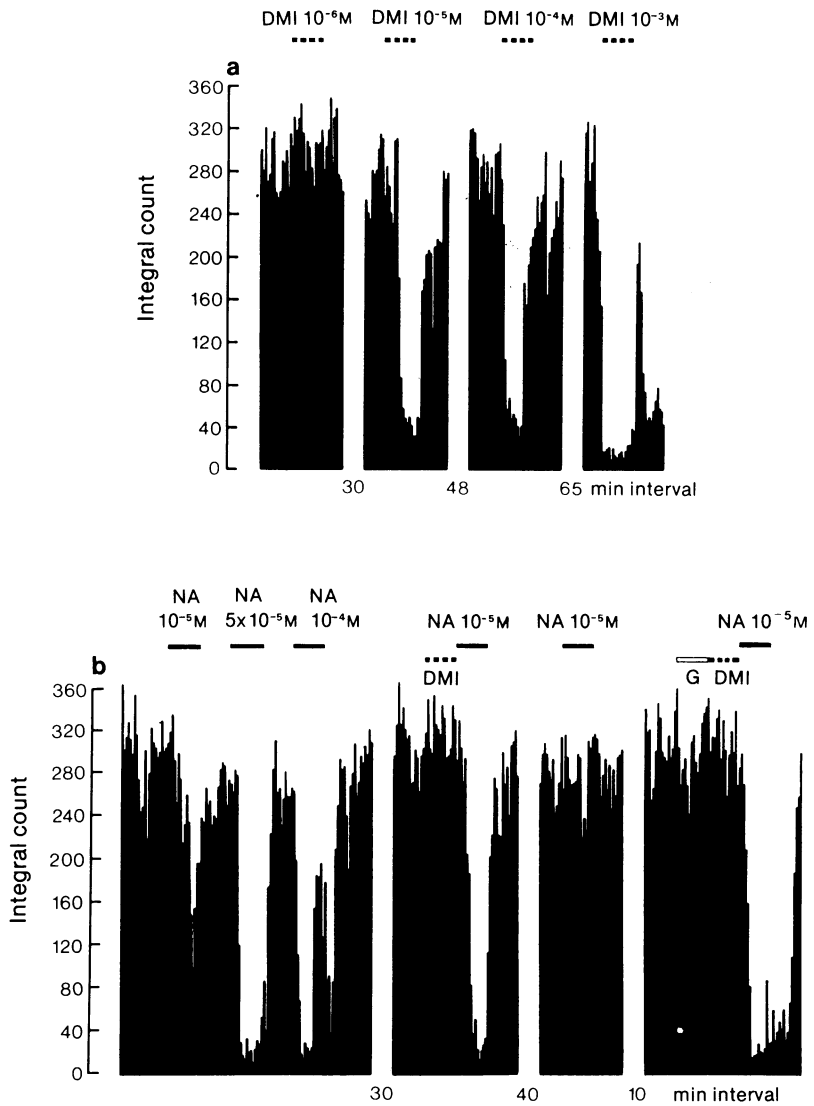

Figure 2 (a) Histograms showing the effect of desmethylimipramine (DMI) on the pattern of electrocortical activity when perfused in different concentrations into the dorsal raphé nucleus of the cat. Integral counts were taken over successive 20 s periods using the electrocortical activity of the right middle suprasylvian gyrus. Interrupted bars indicate 5 min perfusion periods of desmethylimipramine. Note that high concentrations of desmethylimipramine (10^{-4} and 10^{-3} M) induce the three phase desynchronization: synchronization: desynchronization response. (b) Histograms showing the effect of desmethylimipramine (DMI) on the electrocortical response induced by the perfusion of noradrenaline (NA) at the same site within the dorsal raphé nucleus of the cat. The results are taken from the same experiment as in (a). Note that the lower concentration of NA (10^{-5} M) did not produce tonic electrocortical desynchronization and that the higher concentration induced the three phase desynchronization: synchronization: desynchronization response. The concentration of NA (10^{-5} M) which was without effect or produced only intermittent (phasic) bursts of electrocortical desynchronization, initiated prolonged (tonic) desynchronization when perfused subsequent to an application of desmethylimipramine (10^{-6} M-interrupted bar). This potentiation was not influenced by a prior perfusion of guanethidine (G, 5×10^{-6} M, open bar).

(5×10^{-4} to 10^{-3} M), the latency to the onset of the response was longer (2 to 4 min), and this drug did not elicit the three phase response seen following high concentrations of NA, at least, not during a 5 min perfusion period. Application for 10 or more min at 10^{-3} or 10^{-2} M concentrations would occasionally induce such changes, in which case the secondary desynchronization phase was usually very prolonged (20 to 60 min).

The electrocortical desynchronization induced by NA or (+)-amphetamine, especially when used in minimal effective concentrations, could be completely antagonized by (−)-propranolol, or the degree of desynchronization markedly reduced such that the only effect observed was the introduction of slightly faster frequencies in the ECoG corresponding to a change from the sleeping to the drowsy behavioural state (Figure 1). These antagonistic effects were observed, providing the (−)-propranolol was perfused during, and at least 5 min before, the application of the NA (14 expts) or (+)-amphetamine (14 expts). However, an increase in the concentration of NA or (+)-amphetamine would restore the responses to control levels.

It was noticeable that (−)-propranolol, at the concentrations employed (5×10^{-5} or 10^{-4} M), also induced a change in the pattern of electrocortical activity. However, this change was transient and only occurred in the first 1 to 3 min of the perfusion. It consisted of either a reduction in the amplitude of the slow wave activity or the introduction of 1 to 5 s bursts of desynchronization. Both of these effects were reflected in the integral counts by a small but noticeable reduction (Figure 1).

Desmethylimipramine

The dose-related electrocortical changes induced by 5 min perfusions of desmethylimipramine (DMI) were strikingly similar to those produced by NA when applied at the same site within the DRN (6 expts). Phasic followed by tonic electrocortical desynchronization was evoked by a concentration of 10^{-5} M following a latency of 2 to 3 min (Figure 2a). The complex, three phase response similar to that induced by high concentrations of NA, characterized the effect of 10^{-4} M concentrations of DMI, while at higher concentrations (10^{-3} M) the intervening period of synchronization was drastically reduced and the secondary alerting phase significantly extended by 10–30 min (Figure 2a). It is likely that the sequence of electrocortical changes seen when using the higher concentrations of DMI reflect not only NA reuptake blockade but also the membrane stabilizing effect which has also been attributed to this drug. It is for this reason that potentiation studies were carried out with concentrations of DMI which were just below

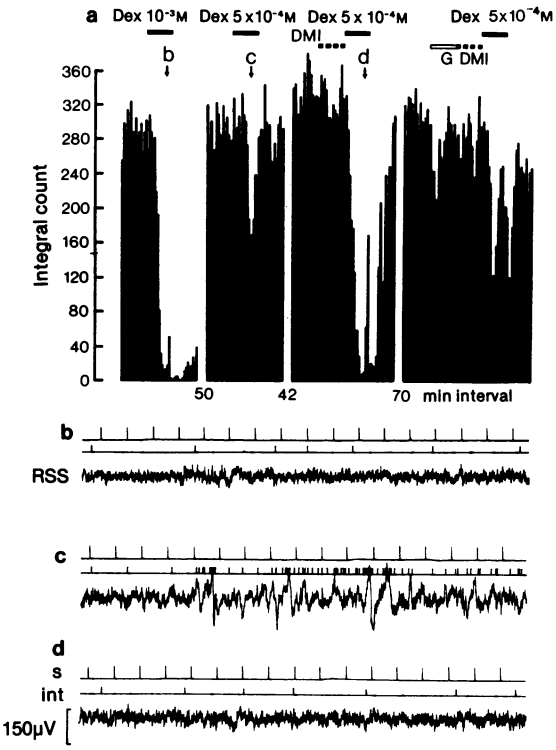

Figure 3 The effect of desmethylimipramine (DMI) on the electrocortical response to (+)-amphetamine (Dex) when perfused into the same site within the dorsal raphé nucleus of the cat. The results are taken from the same experiment as depicted in Figure 2. (a) Histogram showing the integral counts over successive 20 s periods. Solid bars represent 5 min perfusions of amphetamine. Interrupted bar shows 5 min perfusion of desmethylimipramine (DMI) and open bar is guanethidine (G). Note that tonic electrocortical desynchronization is produced by amphetamine 10^{-3} M, but only intermittent, phasic desynchronization is induced by 5×10^{-4} M. Following a perfusion of desmethylimipramine (10^{-6} M) a concentration of 5×10^{-4} M amphetamine now induces tonic electrocortical desynchronization during the perfusion period. The desmethylimipramine-induced potentiation of the response however may be abolished by a 5 min perfusion of guanethidine (5×10^{-6} M). (b) An example of the pattern of electrocortical activity recorded during the perfusion of 10^{-3} M amphetamine (tonic response). (c) Phasic, intermittent periods of desynchronization induced by a 5×10^{-4} M concentration of amphetamine. (d) Tonic electrocortical desynchronization induced by 5×10^{-4} M amphetamine as a result of the potentiation produced by a prior perfusion of desmethylimipramine (10^{-6} M). RSS = right middle suprasylvian gyrus; int = integral pulses.

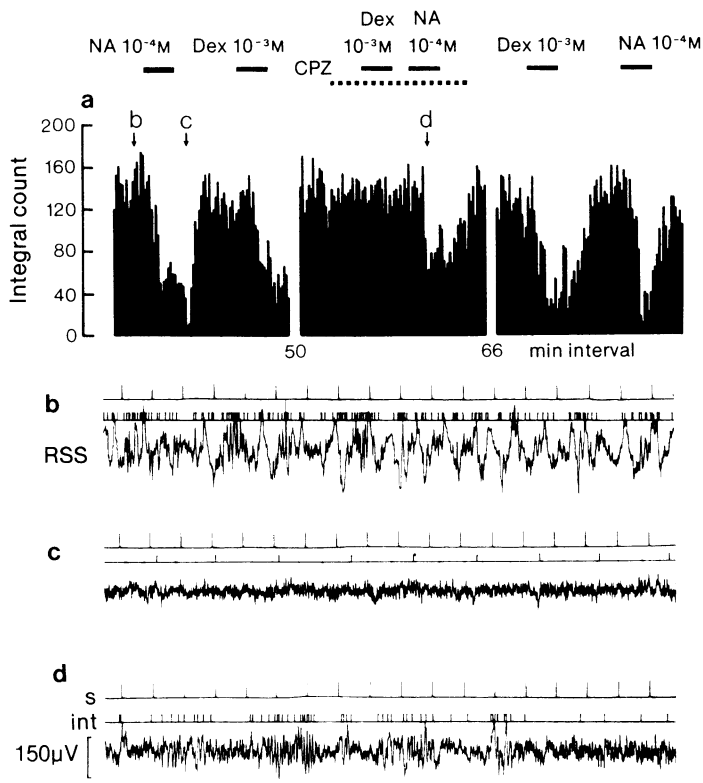

Figure 4 Comparison between the effect of chlorpromazine (CPZ) on the electrocortical changes induced by the perfusion of noradrenaline (NA) and that produced by (+)-amphetamine (Dex) when perfused into the same site within the dorsal raphé nucleus of the cat. (a) Histogram showing the integral counts over successive 20 s periods. Electrical activity recorded from the right middle suprasylvian gyrus. Solid bars show 5 min perfusions of NA or amphetamine. Perfusion of CPZ (10^{-4} M) shown by the interrupted bar. Note that the effect induced by amphetamine (10^{-3} M) is blocked by CPZ but not the response to NA (10^{-4} M). (b) and (c) The patterns of electrocortical activity before and after the perfusion of NA into the dorsal raphé nucleus. (d) The pattern of electrocortical activity induced by NA after a prior perfusion of CPZ (10^{-4} M). RSS = right suprasylvian gyrus; int = integral pulses.

those required to produce noticeable changes in electrocortical activity, that is between 10^{-6} to 5×10^{-6} M.

Prior perfusion of DMI potentiated the effect of exogenously applied NA (6 expts) or (+)-amphetamine (4 expts). Concentrations of NA (Figure 2b), or (+)-amphetamine (Figure 3), which produced either a reduction in the amount of slow wave activity in the ECoG, or introduced phasic bursts of desynchronization in the sleeping animal, initiated prolonged tonic desynchronization when perfused subsequent to an application of DMI.

Chlorpromazine

The perfusion of chlorpromazine (CPZ) produced changes in the patterns of electrocortical activity which were also dose-related. In 8 of the 12 preparations in which this drug was tested, CPZ induced a brief period of desynchronization, 1 to 3 min after the beginning of the perfusion, similar to that seen after (−)-propranolol. However, slow wave activity returned to the electrical record and this pattern then persisted if only low concentrations (5×10^{-5} to 10^{-4} M) were used, providing the perfusion periods were not greater than 30 min. Higher perfusate concentrations, in excess of 5×10^{-4} M, still yielded a short period of desynchronization with a subsequent return of slow wave activity, but this pattern was then followed in sequential fashion by a progressive reduction in the amplitude of the slow waves, the introduction of phasic alerting periods and finally prolonged electrocortical desynchronization accompanied by behavioural alerting. The latency of this latter response

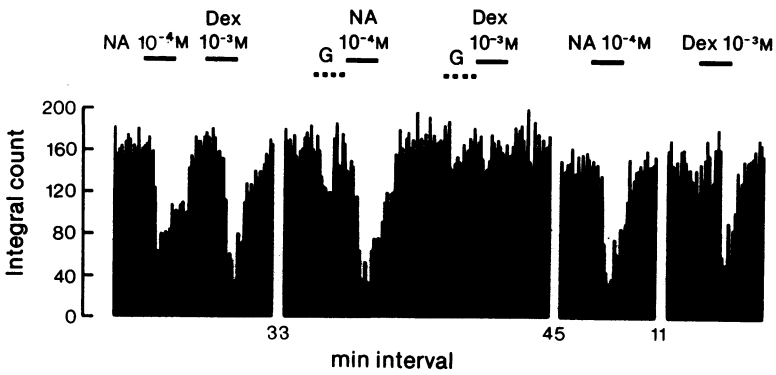

Figure 5 Histograms of integral counts over successive 20 s periods showing that guanethidine blocks the electrocortical desynchronization induced by amphetamine (Dex) but not that induced by noradrenaline (NA). Recovery of the amphetamine response occurred within 40 min. Electrical activity recorded from the left middle suprasylvian gyrus. Black bars show 5 min perfusions of NA or amphetamine. Interrupted bars show 5 min perfusions of guanethidine (G, 5×10^{-6} M).

varied from 12 min with concentrations of 5×10^{-4} or 10^{-3} M, to as little as 5 min with higher concentrations (10^{-3} to 10^{-2} M). In view of the complex nature of the response to CPZ and the possibility that the secondary alerting effects may represent non-specific or local anaesthetic activity, drug antagonism studies using CPZ were always carried out with concentrations of 10^{-4} M, or below, and the length of the perfusion periods was limited to a maximum of 25 min.

Figure 4 illustrates the effect of a prior perfusion of CPZ (10^{-4} M) on the electrocortical desynchronization induced by NA (10^{-4} M) and (+)-amphetamine (10^{-3} M). The response to (+)-amphetamine was either antagonized (7 expts) as in Figure 4, or the degree of desynchronization markedly reduced (5 expts), but could be restored to control levels by the use of higher concentrations (5×10^{-3} M) or a longer perfusion period (10 min). In contrast, the response to NA, was never abolished. In 3 of the 12 experiments, CPZ elicited a reduction in the degree of NA-induced desynchronization, that is phasic alerting responses occurred rather than the tonic desynchronization seen in the control. When this change did occur the response to NA, as well as that to (+)-amphetamine, could not be restored to control levels by increasing the perfusate concentrations of these drugs.

Since it was likely that the concentration of CPZ was too high and that in these situations the drug also was producing a partial membrane stabilizing effect on the postsynaptic cells (see Gordon 1967), the perfusate concentration was reduced to 5×10^{-5} M and the experiment repeated 30 to 40 min later. With the lower concentration the response to NA was not affected whereas that to amphetamine, although not abolished, was still greatly reduced.

Guanethidine

The electrocortical changes induced by guanethidine (5 expts) were qualitatively similar to those of CPZ. Perfusion was characterized by an initial brief change in activity, with the introduction of faster frequencies in the ECoG, or the appearance of short, 1 to 5 s bursts of desynchronization. The effect was transient but could still be observed at the lower concentration level (5×10^{-6} M), by a small but noticeable reduction in the integral counts over the first 1 to 2 min of the perfusion period (Figures 3 and 5). Higher concentrations of 10^{-4} M or above, especially if perfused for periods longer than 10 min, invariably induced tonic electrocortical desynchronization with behavioural arousal.

A prior perfusion of guanethidine (5×10^{-6} M) for 5 min (5 expts), did not abolish the desynchronization induced by exogenously applied NA (Figure 5). On the other hand, the same concentration of guanethidine blocked (Figure 5) or greatly reduced the desynchronizing effects of (+)-amphetamine to such an extent that the only observable change in the ECoG was a 10 to 20% reduction in the amplitude of the slow waves and the introduction of 0.5 to 2.0 s bursts of faster activity (6 to 15 Hz) during the period of perfusion. Blockade by guanethidine could be overcome since increasing the perfusion concentration of (+)-amphetamine (at least $\times 5$) would restore the response to control levels. However, it was noticeable that even at higher concentrations the response latency to (+)-amphetamine was still relatively long (3 to 5 min).

Guanethidine also showed an interesting interaction with DMI, since it was possible to suppress the DMI-induced potentiation of the amphetamine re-

sponse with a prior 5 min perfusion of guanethidine (Figure 3, 5×10^{-6} M). However, the DMI-induced potentiation of the response to exogenously applied NA was not noticeably influenced (Figure 2b).

Discussion

NA and (+)-amphetamine produced phasic or tonic electrocortical desynchronization when perfused into the DRN. This similarity in their effects and the ability of (−)-propranolol to antagonize the responses of both drugs, would suggest the involvement of common β-noradrenergic receptors. This conclusion would be in keeping with earlier observations that isoprenaline also mimics the electrocortical desynchronization induced by NA and that the effect of NA and isoprenaline within the DRN may be blocked by (−)-propranolol or sotalol but not by (+)-propranolol or phenoxybenzamine (Key & Krzywosinski, 1977). However, whereas the action of NA may be explained by a direct action on postsynaptic receptor sites, the results obtained with guanethidine indicate that the mode of action of amphetamine is indirect, possibly related to presynaptic mechanisms. Guanethidine proved ineffective in antagonizing the response to exogenously applied NA, but in contrast, antagonized the effect of amphetamine and eliminated the DMI-induced potentiation of the amphetamine response. Adrenergic blocking agents such as guanethidine have been shown to inhibit synaptic transmission by an action at extra-vesicular NA storage sites within the presynaptic terminals (Shand, Morgan & Oates, 1973; Abbs & Dodd, 1974; Giachetti & Hollenbeck, 1976). It has also been suggested that the reversal of guanethidine-induced neuronal blockade by amphetamine is due to displacement of the blocker from these sites and that both drugs therefore have a common or related intraneuronal site of action (Day & Rand, 1963; Giachetti & Hollenbeck, 1976). On the other hand, cocaine, an inhibitor of NA uptake mechanisms, also reverses the neuronal blockade induced by guanethidine, albeit, not as consistently or as quickly as amphetamine (Day, 1962; Gerkins, McCulloch & Wilson, 1969; Kirpekar, Wakade, Dixon & Prat, 1969). Taken together, these observations would suggest that although selective displacement of NA from intraneuronal storage sites may be regarded as a principle presynaptic action of amphetamine, the ability of amphetamine to block NA reuptake (Glowinski & Axelrod, 1965) cannot be disregarded as a contributing factor in the total amphetamine response.

Reuptake blockade rather than increased NA release is probably the most likely explanation for the DMI-induced potentiation of the amphetamine response. While it is known that DMI does not affect the accumulation of amphetamine in the CNS or peripheral tissues (Ross & Renyi, 1964; Thoenen, Huerlimann & Haefely, 1968), it does significantly reduce the NA releasing effect of amphetamine from rat heart slices (Giachetti & Hollenbeck, 1976). Such an action in the DRN would not be compatible with a potentiation of the electrocortical response to amphetamine if the effect was mediated solely through NA release. However, an amphetamine inhibition of the NA transport system could influence the accumulation of NA simply by adding to the partial uptake blockade already induced by the relatively low concentration of DMI.

Whichever mechanism predominates in the neural response to amphetamine, the presynaptic nature of the amphetamine effect raises an interesting speculation with regard to the site of action of CPZ. At the periphery CPZ is a competitive antagonist of NA at α-receptors (Gordon, 1967) and has also been reported to affect NA reuptake mechanisms (Axelrod, Whitby & Hertting, 1961). Even so, these effects are unlikely to account for the competitive blockade of amphetamine-induced electrocortical desynchronization, especially as blockade occurred at a time when the response to exogenous NA was unimpaired. The electrocortical changes induced by the perfusion of CPZ and the differential effect of this drug on amphetamine and NA responses is strikingly similar to those of guanethidine. Whether or not CPZ and guanethidine possess a similar intraneuronal locus of action is open to speculation, but the results of the present study raise the possibility that the primary effect of CPZ in blocking the action of amphetamine within the DRN is presynaptic.

When used in relatively high concentrations or perfused for long periods of time, CPZ, guanethidine, DMI and (−)-propranolol, all produced a sequence of electrocortical changes, the final result of which was tonic desynchronization coupled with behavioural alerting. These latter effects can also be produced by xylocaine and (+)-propranolol (Key & Krzywosinski, 1977) and thus may represent a non-specific local anaesthetic action, a property which has been ascribed to all of these drugs (see Goodman & Gilman, 1975). It is obvious that effects related more specifically to noradrenergic transmission must be sought for using the lowest effective concentrations of these drugs, or short periods of perfusion. In this respect the initial, brief period of electrocortical desynchronization observed after the application of guanethidine, CPZ or (−)-propranolol is probably significant and it may well be that all these drugs produce the effect through a common mechanism. Accumulation of guanethidine within the presynaptic terminal is essential for its effect (Giachetti & Hollenbeck, (1976) and on the basis of its interaction with amphetamine, a similar intraneuronal locus of action

could be postulated for CPZ. Since penetration into the terminal would appear necessary in both cases, CPZ and guanethidine could compete with NA for sites on the membrane transport system. By doing so, a transient increase in extraneuronal NA could occur and result in an initial sympathomimetic effect before neuronal blockade. The brief period of electrocortical desynchronization induced by (−)-propranolol is more difficult to explain. In the peripheral nervous system (−)-propranolol does not cause an initial β-adrenoceptor stimulation (Fitzgerald, 1972). Nevertheless, Myers, Lewis, Reid & Dollery (1975) have demonstrated that intracerebroventricular (−)-propranolol may induce an initial hypertensive effect before the more prolonged hypotensive changes characteristic of the drug and that the effect may be abolished by pretreatment with either 6-hydroxydopamine, desimipramine or yohimbine. On this evidence it would be reasonable to assume that (−)-propranolol is taken up into the central noradrenergic nerve terminals. Thus, in common with CPZ and guanethidine, (−)-propranolol could also produce a transient increase in extraneuronal levels of NA by competing with NA for sites on the transport mechanism.

The results of the present study indicate that amphetamine, CPZ, DMI, guanethidine and (−)-propranolol may affect noradrenergic tranmission in the DRN. It is interesting that some of these drugs have been reported to interfere with normal sleep/wakefulness patterns (Bradley & Elkes, 1957; Bradley & Hance, 1957; Murman, Almirante & Saccani-Guelfi, 1966). Such effects could be, in part, the result of an action within the raphé system, whereby the level of tonic noradrenergic inhibitory influences are altered and thus the balance between sleep and wakefulness disturbed.

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