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MONOAMINE REPLACEMENT AFTER RESERPINE: CATECHOLAMINERGIC AGONISTS RESTORE MOTOR ACTIVITY BUT PHENYLETHYLAMINE RESTORES ATROPINE-RESISTANT NEOCORTICAL LOW VOLTAGE FAST ACTIVITY

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SUMMARY

A large dose of reserpine abolishes an atropine-resistant form of neocortical low voltage fast activity (LVFA) which normally accompanies certain patterns of motor activity in rats. An attempt was made to reverse this effect by replacement of specific monoamines or by injection of suitable agonists in rats pretreated with reserpine (10 mg/kg). The following compounds, alone or in various combinations, failed to restore atropine-resistant LVFA in reserpinized rats even though spontaneous motor activity was restored in many cases: L-DOPA (150–300 mg/kg) after pretreatment with an inhibitor of peripheral L-aromatic amino acid decarboxylase; 5-hydroxytryptophan (100–200 mg/kg); D-amphetamine (1–2 mg/kg); apomorphine (0.25–2.5 mg/kg); lysergic acid diethylamide (100–300 μg/kg); and clonidine (0.5–1.0 mg/kg). In contrast β-phenylethylamine was quite effective in restoring atropine-resistant LVFA and its effects were not diminished by pretreatment with α-methyl-*p*-tyrosine (400 mg/kg), chlorpromazine (15 mg/kg) or trifluoperazine (5–10 mg/kg). It is suggested that a trace amine plays an essential role in the production of atropine-resistant LVFA independent of catecholamines.

INTRODUCTION

Experiments described in a series of previous publications have shown that atropine, atropine sulfate, or scopolamine-HBr abolish neocortical low voltage fast activity (LVFA) occurring during immobility and other Type II behavior but do not abolish the LVFA associated with locomotion and other Type I behavior[25–27]. A

combination of atropine sulfate plus reserpine abolishes all LVFA, both in response to natural stimuli (handling, etc.) and electrical stimulation of the reticular formation. This suggests that reserpine inactivates an atropine-resistant reticulocortical pathway which is normally active if, and only if, Type I movements are in progress.

It is well known that large doses of reserpine produce a severe depletion of catecholamines and 5-hydroxytryptamine (5-HT) in brain and other tissues. This depletion occurs as a result of inhibition of uptake of the amines by intracellular storage granules, thereby increasing exposure to mitochondrial monoamine oxidase[15, 16]. Considering these facts, as well as the fact that the effect of reserpine on atropine-resistant LVFA is blocked by prior treatment with nialamide, an inhibitor of monoamine oxidase, it appears that a substrate of monoamine oxidase (i.e. a monoamine) is essential to the function of the hypothesized atropine-resistant reticulocortical pathway[27].

An important experiment in the development of research on brain monoamines was the demonstration by Carlsson et al.[7] that L-DOPA was capable of reversing the behavioral catalepsy and akinesia which reserpine produces. This provided clear evidence that reserpine induced catalepsy is due primarily to depletion of catecholamines. In the experiments reported here, a similar replacement procedure was used to identify the amine(s) essential to the production of atropine-resistant LVFA. Reserpinized rats were treated with atropine together with a variety of test compounds while records were made of neocortical electrical activity and behavior. Test compounds included L-DOPA as well as a number of other compounds reported to antagonize the behavioral effects of reserpine, including: D-amphetamine[19,20], lysergic acid diethylamide (LSD)[6], β-phenylethylamine (PEA)[11] and apomorphine[2]. These compounds can all be regarded as direct or indirect agonists of dopamine[5,10]. In addition, tests were made using 5-hydroxytryptophan (5-HTP, the immediate precursor of 5-HT) and clonidine, a noradrenergic agonist[1].

Successful restoration of LVFA in rats treated with both reserpine and atropine should be attributable to one of two principal mechanisms: (1) antagonism of reserpine, perhaps by replacing a substance depleted by reserpine; and (2) antagonism of atropine, perhaps by an eserine-like effect. Since most of the replacement substances used are likely to have low anticholinesterase activity, this latter possibility can probably be largely discounted except in the case of LSD[29].

METHODS

The experimental apparatus and methods were the same as described by Vanderwolf and Pappas[27]. Rats prepared with chronically implanted neocortical slow wave recording electrodes were given a preliminary test with atropine sulfate (50 mg/kg) to demonstrate the presence of behavior-correlated slow wave activity. Four or more days later, reserpine (10 mg/kg, i.p.) was administered. After a delay of 12–22 h: (a) a 5-min duration record was taken of neocortical activity and spontaneous behavior; and (b) the response to handling and light pushing of the hindquarters (to induce struggling and walking) was observed. Next, a test drug was administered and

spontaneous behavior and neocortical activity were recorded continuously for 30–60 min. Then atropine sulfate (50 mg/kg) was administered and recording continued. If the rats were not spontaneously active, the response to handling and pushing was observed again. In some experiments, atropine was administered first and a test drug was administered 30 min later when it had been demonstrated that no LVFA could be elicited by handling and pushing to induce walking.

If a rat became sedated rather than severely cataleptic following a single 10 mg/kg dose of reserpine, the dose was repeated and further delay of 12–22 h allowed to elapse before an experiment was begun. Occasionally, rats were given reserpine again (after an interval of 1–3 months) and used in a second experiment.

The following drug preparations were used in adddition to those mentioned by Vanderwolf and Pappas[27]. L-DOPA, α-methyl-*p*-tyrosine (αMT) and 5-hydroxytryptophan (5-HTP) were injected as a fine suspension in saline plus 1–2% (w/v) of gum acacia. Clonidine-HCl, D-amphetamine sulfate, β-phenylethylamine-HCl (PEA), and benserazide-HCl (an inhibitor of L-aromatic amino acid decarboxylase[8,9]) were dissolved in 0.9% (w/v) saline. Apomorphine-HCl was dissolved in polyethylene glycol.

RESULTS

Reserpine, catecholaminergic agonists and atropine

Dopamine agonists produced marked increases in spontaneous motor activity in the reserpinized rats. Within 15–20 min following treatment with L-DOPA (300 mg/kg given 30 min after benserazide, 50 mg/kg; n = 8) spontaneous head movements and stepping became frequent. There was also an improved ability to hold up the head and maintain a normal standing posture on 4 or 2 legs. This was succeeded by more vigorous walking, rearing, gnawing, biting and hyperreactivity to auditory and tactile stimuli. Closely similar effects on behavior were produced by D-amphetamine (1–2 mg/kg; n = 3) and apomorphine (2.5 mg/kg; n = 5), while similar but weaker effects were produced by L-DOPA (150 mg/kg; n = 5); apomorphine (0.25 mg/kg; n = 5); apomorphine (1.0 mg/kg; n = 5); and LSD (100–300 μg/kg; n = 2). Administration of atropine generally intensified the motor activity produced by all these drugs. Clonidine-treated rats (0.5–1.0 mg/kg; n = 6) periodically displayed sudden extension movements (kicks) of the limbs without any improvement in postural fixation of the trunk and neck. The head remained slumped on the floor. Clonidine (and LSD to a lesser extent) also produced marked autonomic effects (piloerection, exophthalmos, mydriasis) but L-DOPA and apomorphine failed to do this. The eyes of the reserpinized rats treated with these drugs usually remained closed even during very vigorous motor activity.

L-DOPA and apomorphine produced dose-related increases in LVFA in the reserpinized rats (Figs. 1–3). Amphetamine, LSD and clonidine also produced LVFA. However, when atropine sulfate (50 mg/kg) was subsequently administered all LVFA disappeared. Continuous large amplitude slow waves occurred together with vigorous motor activity. Thus, particularly in rats treated with L-DOPA (300 mg/kg), am-

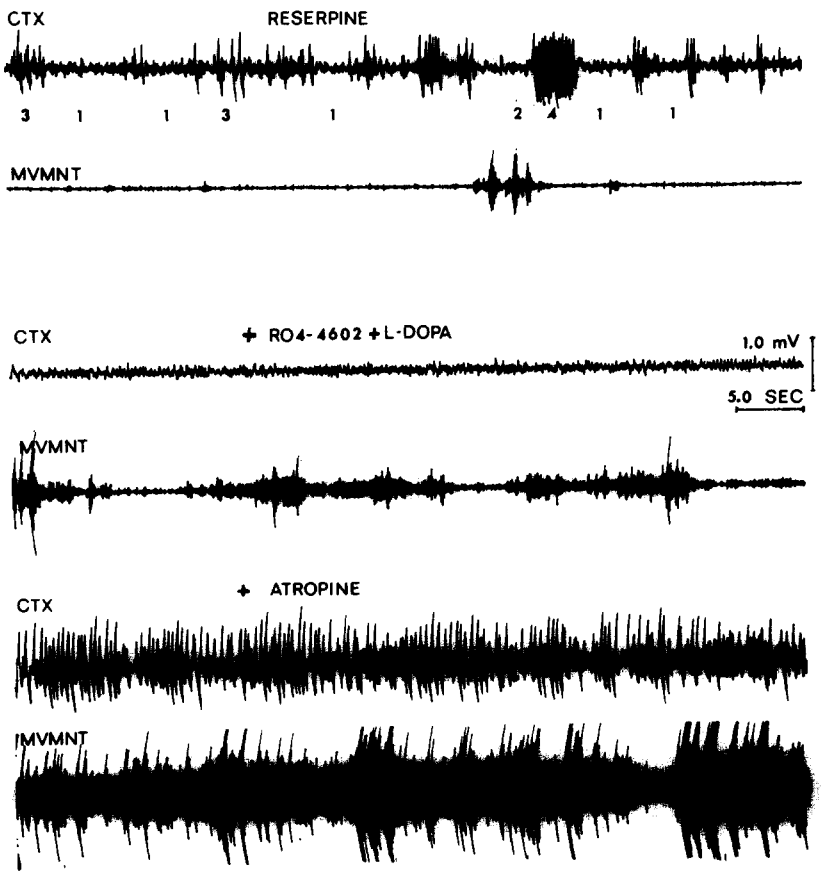

Fig. 1. Effects of reserpine, L-DOPA and atropine on neocortical electrical activity and behavior. CTX, neocortex; MVMNT, movement sensor output. Top traces: after treatment with reserpine (10 mg/kg/day × 2). Note: 1, low voltage fast activity (LVFA) during immobility; 2, LVFA during spontaneous movement; 3, irregular slow waves during immobility; 4, rhythmical spindle activity during immobility. Middle traces: 60 min after injection of Ro-4-4602 (benserazide) (50 mg/kg) and 30 min after L-DOPA (300 mg/kg), LVFA is nearly continuous. The rat moves its head, rears and walks. Bottom traces: 10 min after injection of atropine (50 mg/kg), all LVFA is abolished although rat is very active, walking and gnawing at the apparatus.

phetamine (1–2 mg/kg) or apomorphine (2.5 mg/kg) vigorous Type I behavior (walking, rearing, and head movements) was restored but atropine-resistant LVFA was totally absent.

If the catecholaminergic agonists were given following pretreatment with reserpine and atropine they produced vigorous motor activity but no LVFA at all. This lack of effect was seen in rats treated with reserpine and atropine followed by: (a) benserazide plus L-DOPA ($n = 6$); (b) apomorphine ($n = 5$); and (c) D-amphetamine ($n = 3$). Combinations of apomorphine plus clonidine ($n = 2$) or L-DOPA plus clonidine ($n = 4$) were also ineffective in restoring LVFA in rats pretreated with reserpine and atropine.

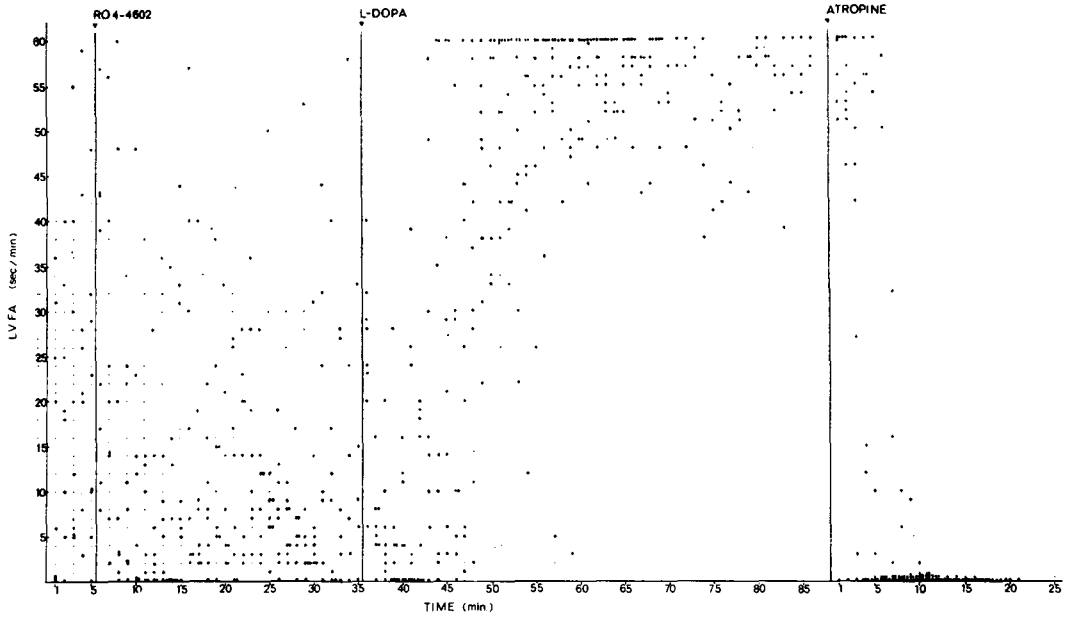

Fig. 2. Effect of L-DOPA and atropine on the occurrence of LVFA in 8 reserpinized rats (reserpine, 10 mg/kg). Each dot represents the number of seconds that LVFA was present in a 60-sec period in the record from a single rat. RO-4-4602, injection of an inhibitor (benserazide) of peripheral L-aromatic amino acid decarboxylase (50 mg/kg); L-DOPA, injection of L-DOPA (300 mg/kg); atropine, injection of atropine (50 mg/kg). Atropine sulfate was administered when LVFA was continuously present during at least 55 sec/min in 5 successive min. Seven of the 8 rats reached this criterion after a delay of 25.6 min (range 7–50 min). The eighth rat was given atropine 51 min after L-DOPA treatment even though its LVFA production was not sufficiently stable to reach the criterion level. Note that L-DOPA increases the occurrence of LVFA but that atropine eliminates it.

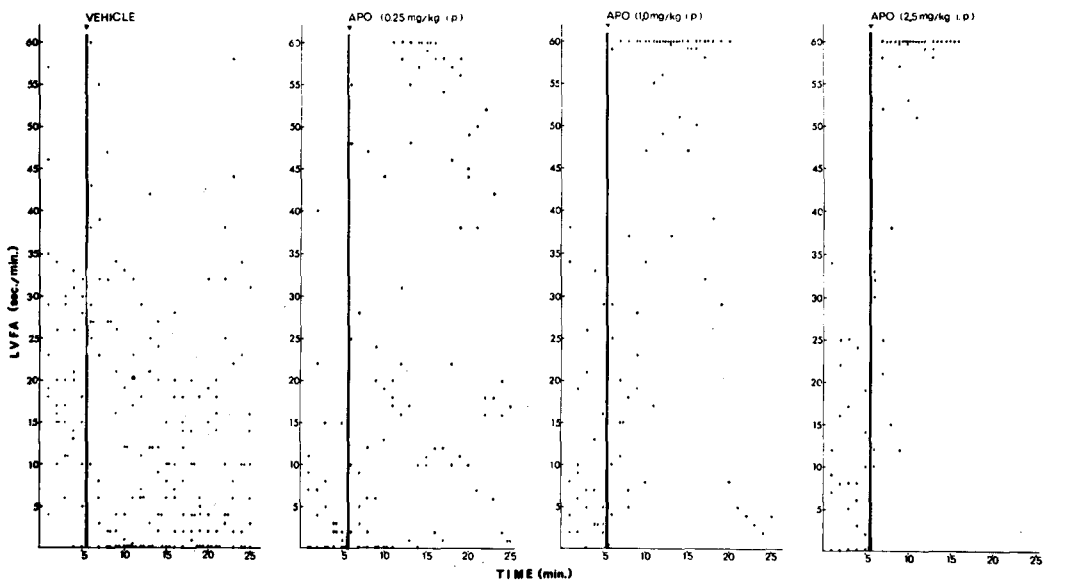

Fig. 3. Effect of various doses of apomorphine on the occurrence of LVFA in rats pretreated with reserpine (10 mg/kg). Dots as in Fig. 1; n = 5–7 rats/group.

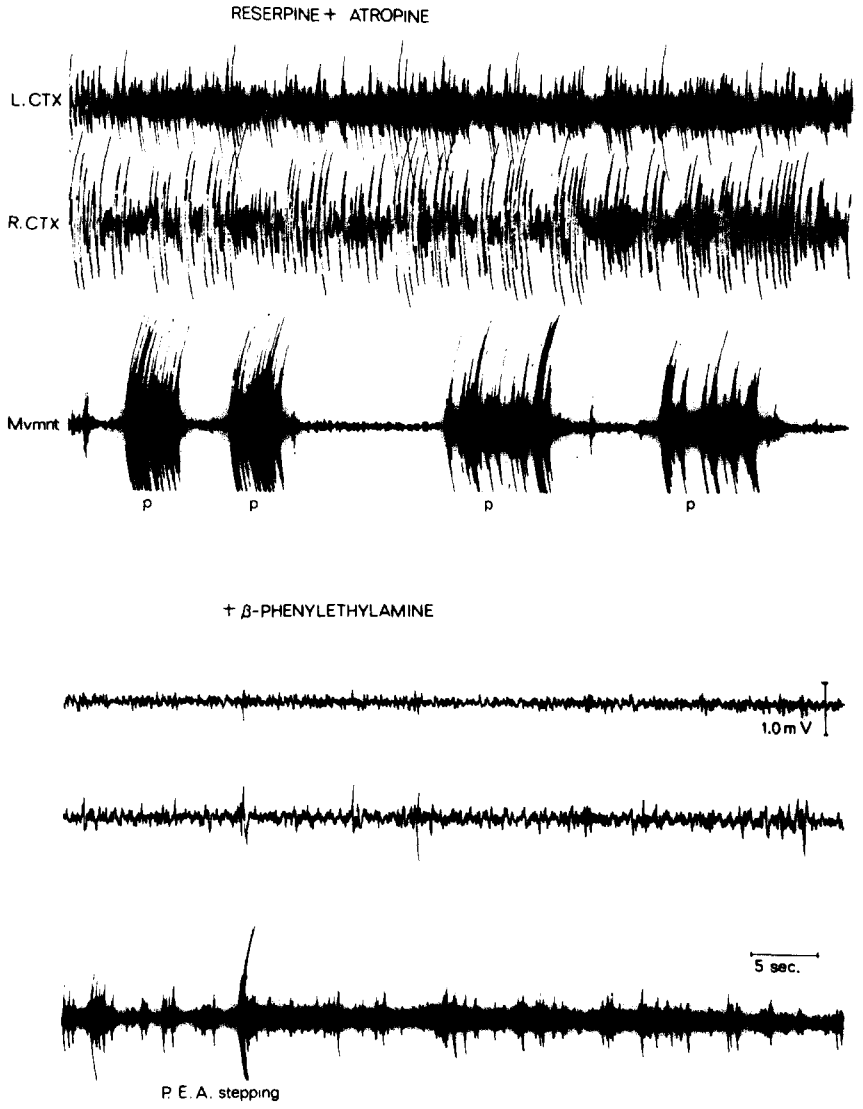

Fig. 4. Effect of β-phenylethylamine (80 mg/kg) on neocortical electrical activity in a rat pretreated with reserpine (10 mg/kg) and atropine (50 mg/kg). Abbreviations as in Fig. 1 except that L and R refer to left and right parietal cortex. Top traces: 16 h after reserpine and 0.5 h after atropine. At times marked 'p' rat is induced to struggle by being picked up. LVFA is absent. Lower traces: 9 min after injection of phenylethylamine (PEA) nearly continuous LVFA is present together with spontaneous stepping movements of the forelimbs (P.E.A. stepping, see text).

Reserpine, 5-hydroxytryptophan and atropine

Seven reserpinized rats were given 5-HTP (100 mg/kg, n = 2; 200 mg/kg, n = 5). In one rat atropine sulfate (50 mg/kg) was given 30 min prior to the 5-HTP, while 6 rats received atropine 30–60 min after 5-HTP treatment. 5-HTP alone had no obvious effect on behavior or on the electrocortical activity characteristic of heavily reserpinized rats. Prior to atropine administration LVFA occurred spontaneously in some

rats, or could be elicited by tactile stimuli or by urging the rat to walk, but after atropine was administered such LVFA was abolished. In 3 rats apomorphine (2.0 mg/kg) and clonidine (0.5–1.0 mg/kg) were added after treatment with 5-HTP and atropine. This increased motor activity but did not produce LVFA.

Reserpine, β-phenylethylamine and atropine

Administration of PEA (80 mg/kg; n = 10) to rats pretreated with reserpine and atropine produced head movements, stepping, walking or rearing within 2–3 min. Gnawing occurred in 6 of these rats after a delay of 7–51 min (mean = 34.3 min). PEA also elicited peculiar stepping movements in the forelimbs, of a type never observed following administration of L-DOPA, D-amphetamine, apomorphine, clonidine, or LSD. While the rats lay in a prone position, the forepaws were alternately raised, protracted with digits extended, lowered to the floor, and retracted. Frequently, one

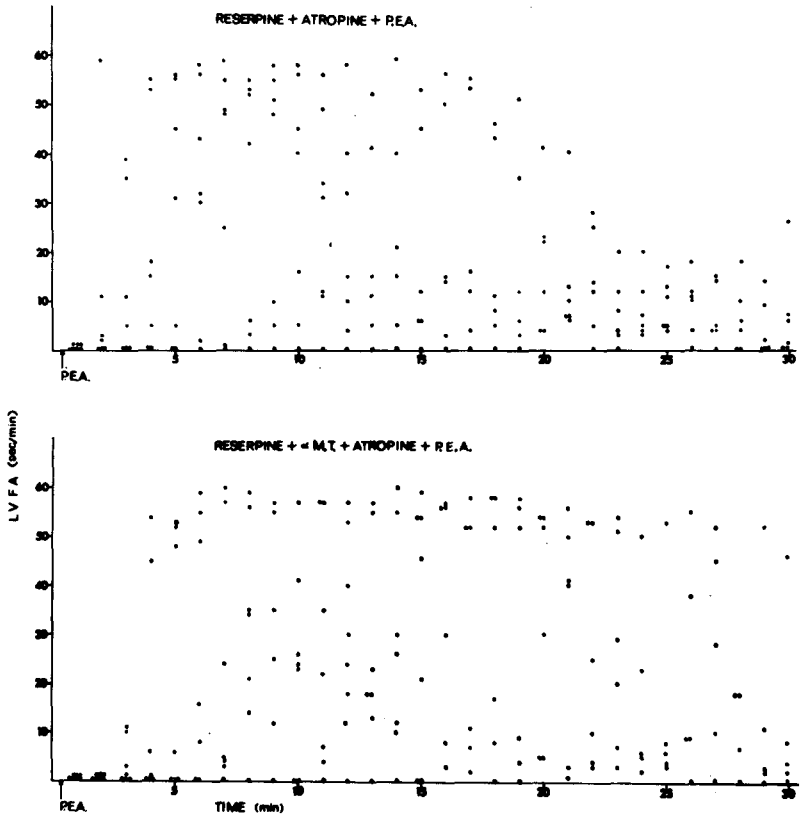

Fig. 5. Effect of α-methyl-*p*-tyrosine on duration of LVFA produced by phenylethylamine (PEA) in rats pretreated with reserpine and atropine. Dots as in Fig. 2. Top panel: effect of PEA (80 mg/kg) in 7 rats pretreated with reserpine (10 mg/kg) and atropine (50 mg/kg). Bottom panel: effect of PEA (80 mg/kg) in an additional 7 rats pretreated with reserpine (10 mg/kg), α-methyl-*p*-tyrosine (αM.T., 400 mg/kg) and atropine (50 mg/kg). In both groups PEA was injected 12–18 h after reserpine, 3–5 h after α-methyl-*p*-tyrosine (when given) and 0.5 h after atropine. Note that LVFA appears at least as prominently in rats pretreated with αM.T. as in those receiving only reserpine and atropine.

paw would repeat this step cycle 2–3 times, then the other paw would do the same and so on, for minutes at a time. Side-to-side movements of the head were usually associated with the stepping, but the hind legs often remained motionless.

Smaller doses of PEA (40 mg/kg, n = 6; 20 mg/kg, n = 4) produced similar but less pronounced effects on behavior.

PEA produced some peripheral autonomic effects, including the secretion of a viscous saliva. In some rats this was very profuse, occasionally resulting in suffocation and death.

Within 2–6 min after PEA injection (80 mg/kg) clear LVFA appeared in both frontal and parietal cortex of rats pretreated with reserpine and atropine (Figs. 4 and 5). This LVFA sometimes preceded, sometimes accompanied and sometimes followed the appearance of motor activity. Usually the LVFA was interspersed with occasional large amplitude slow waves. Within 30 min LVFA had largely disappeared and continuous large amplitude slow wave activity had returned (Fig. 5) even though the rats continued to walk about and gnaw very actively.

At a dose of 40 mg/kg, PEA produced only poorly developed LVFA which disappeared in a few minutes in most cases. At a dose of 20 mg/kg of PEA only 1 of the 4 rats tested developed LVFA.

Nine rats, pretreated with reserpine 12–18 h earlier, were given α-methyl-*p*-tyrosine (400 mg/kg) 3–5 h prior to recording and treatment with atropine. The combination of reserpine and α-methyl-*p*-tyrosine reduced muscle tone to a level comparable to that of surgical anesthesia. Nonetheless, the rats were capable of feeble struggling when handled and the electrocorticogram contained periods of LVFA (present 47.5 % of the time in a 5-min test) alternating with periods of large amplitude slow waves, a pattern very similar to what was seen after reserpine alone. Atropine abolished all LFVA but when PEA (80 mg/kg) was administered 30 min later, LVFA returned, apparently undiminished by the presence of α-methyl-*p*-tyrosine (Fig. 5).

In contrast to its lack of effect on the LVFA produced by PEA, α-methyl-*p*-tyrosine pretreatment sharply reduced the occurrence of active behavior produced by PEA. Walking, rearing and gnawing did not occur following treatment with PEA (80 mg/kg) in any of the 9 rats pretreated with α-methyl-*p*-tyrosine in addition to reserpine and atropine. One or more of these behaviors occurred in every one of the 10 rats that received PEA (80 mg/kg) following treatment with only reserpine and atropine. However, the peculiar stepping behavior induced by PEA in reserpinized rats was not entirely abolished by α-methyl-*p*-tyrosine.

Chlorpromazine (15 mg/kg, n = 8) or trifluoperazine (5–10 mg/kg, n = 5) also blocked most PEA-induced motor activity without affecting PEA-induced atropine-resistant LVFA. Following a combination of reserpine plus chlorpromazine or trifluoperazine, rats were very inactive but could struggle feebly and displayed LVFA to much the same degree as rats treated with reserpine alone. Atropine abolished all LVFA but it reappeared when PEA was administered even though the rats remained largely inactive and were frequently immobile. Some stepping movements of the forepaws and minor head movements were observed but walking, rearing and gnawing did not occur. As the PEA effect diminished and large slow waves returned, it was

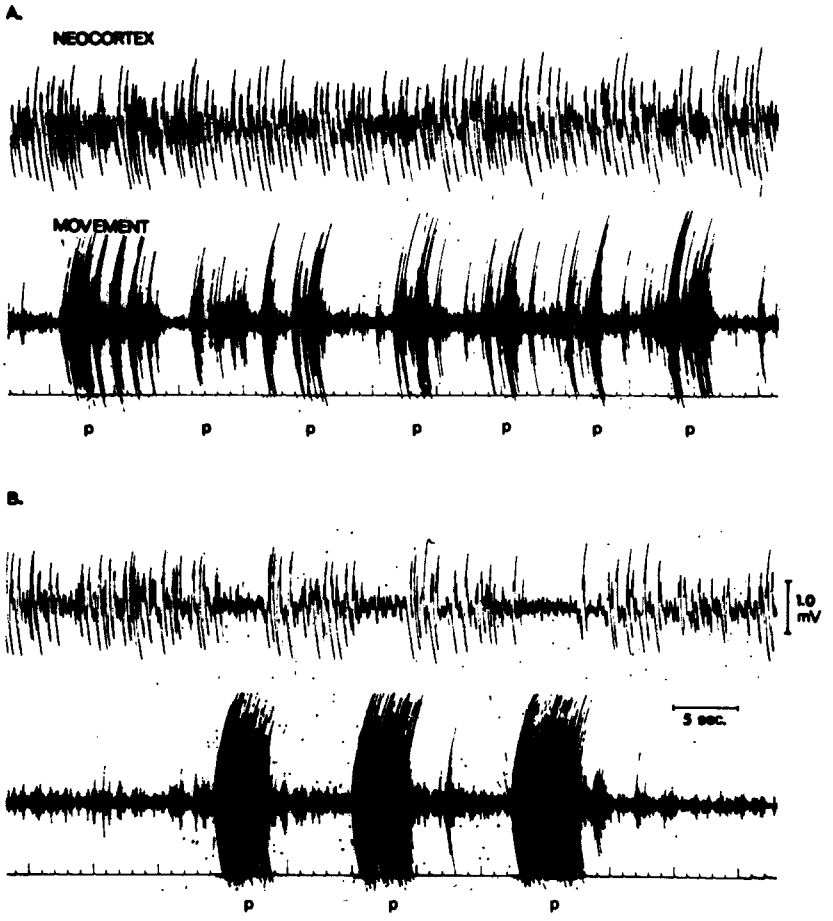

Fig. 6. Effect of phenylethylamine (80 mg/kg) on neocortical electrical activity in a rat pretreated with reserpine (10 mg/kg), chlorpromazine (15 mg/kg) and atropine (50 mg/kg). Upper traces: after a combination of reserpine, chlorpromazine and atropine picking the rat up to induce struggling (P) does not produce LVFA. Lower traces: about 20 min after the injection of PEA, picking the rat up yields good LVFA.

usually possible to restore LVFA briefly by eliciting struggling behavior (Fig. 6). A similar result (though less clear cut) was observed in rats treated with reserpine, α-methyl-*p*-tyrosine, atropine, and PEA. Thus, under some conditions in which the continuous motor activity usually elicited by PEA is largely suppressed, this compound appears to be capable of restoring movement-related atropine-resistant LVFA in reserpinized rats.

The possibility that methysergide or propranolol might block the atropine-resistant LVFA produced by PEA was examined in several rats. Rats were pretreated with reserpine, then given methysergide bimaleate (10 mg/kg, n = 2) or D,L-propranolol-HCl (10–20 mg/kg, n = 2) followed by atropine sulfate (50 mg/kg) 30 min later. When all LVFA had disappeared (15–30 min later) PEA (80 mg/kg) was given. In all cases the development of LVFA appeared to be unaffected by the presence of the test drugs.

Chemical assays

Six unoperated rats were injected with reserpine (10 mg/kg) followed by α-methyl-*p*-tyrosine (400 mg/kg) 13 h later. Between 3 and 5 h after this the rats were decapitated and the brains removed for assay. Whole-brain catecholamine levels were very low. Norepinephrine averaged 8.1% (S.D. = 3.0) of control levels; dopamine averaged 2.6% (S.D. = 3.8). In 3 rats no dopamine could be detected.

Six other unoperated rats received reserpine (10 mg/kg) followed by benserazide (50 mg/kg) 14 h later. After a 30-min delay, L-DOPA (300 mg/kg) was administered. The rats were decapitated 1–2 h later, at a time when they were all very active. Assays indicated that norepinephrine levels had risen to 179.6% (S.D. = 37.9) of the control level established previously[27] while dopamine levels had risen to 5381.3% (S.D. = 701.1) of the control level. Thus, as shown previously[13], L-DOPA produces a large increase in dopamine and a much smaller increase in norepinephrine.

DISCUSSION

The experiments reported here were an attempt to identify the monoamine(s) involved in the production of atropine-resistant LVFA by a replacement procedure in which specific monoamines, their agonists, or precursors were administered to reserpinized rats.

The results were clear. A precursor and agonists of the catecholamines, dopamine and norepinephrine, (L-DOPA, apomorphine, amphetamine, clonidine, LSD) were all ineffective in restoring atropine-resistant LVFA. 5-Hydroxytryptophan, the immediate precursor of 5-HT and capable of restoring brain 5-HT levels after reserpine treatment[12], was also ineffective. This indicates that the unknown transmitter or modulator, which is essential for the production of atropine-resistant LVFA in association with Type I movement in atropinized rats, is not a catecholamine: nor is it 5-HT. This conclusion is supported by other evidence. Atropine-resistant LFVA is not abolished by: (a) depletion of catecholamines by neonatal systemic injection of 6-OH-dopamine[22] or by intraventricular injection of 6-OH-dopamine[28]; (b) blockade of the synthesis of catecholamines by means of α-methyl-*p*-tyrosine or FLA-63[22]; (c) catecholamine receptor blockers such as chlorpromazine, trifluoperazine, haloperidol, phenoxybenzamine, pimozide and propranolol[26,27]; (d) blockade of the synthesis of 5-HT by means of *p*-chlorphenylalanine[26]; and (e) blockade of activity in central 5-HT neurons by means of LSD[27].

PEA was the only compound found capable of restoring LVFA in rats pretreated with reserpine and atropine. Under some circumstances it also appeared to restore the normal correlation of atropine-resistant LVFA with Type I behavior. Thus PEA might be a natural transmitter in an aminergic reticulocortical system or might be a precursor or agonist of the natural transmitter or modulator.

PEA is an indirect agonist of dopamine and norepinephrine, capable of releasing both amines from presynaptic sites[11]. The motor activity produced by PEA in reserpinized rats is probably largely due to release of residual dopamine. Such motor activity is largely abolished by pretreatment with α-methyl-*p*-tyrosine in addition to

reserpine, a drug combination which virtually eliminates brain dopamine[5,14]. These results were confirmed here. However, it is unlikely that the production of atropine-resistant LVFA by PEA is mediated by dopamine or norepinephrine. First, L-DOPA, shown to produce normal or supranormal levels of dopamine and norepinephrine in reserpinized rats, did not restore atropine-resistant LVFA. Apomorphine, amphetamine and clonidine, direct or indirect agonists of dopamine and norepinephrine, respectively, were also ineffective. Second, the PEA effect was not abolished by virtual elimination of dopamine by treatment with α-methyl-*p*-tyrosine or by blockade of dopamine and norepinephrine receptors by chlorpromazine, phenoxybenzamine, propranolol or trifluoperazine. Therefore, it is likely that PEA produces atropine-resistant LFVA in reserpinized rats by interaction with an unknown type of monoamine receptor which is distinct from the norepinephrine and dopamine receptors.

The nature of this hypothetical receptor and its natural ligand remain unclear. A possible candidate, PEA is a normal constituent of brain tissue and has been suggested as a possible central modulator or activator[3,23]. However, since PEA does not appear to be depleted by reserpine[4] it is unlikely to be the monoamine normally involved in the production of atropine-resistant LVFA. Perhaps PEA acts as an agonist of some other naturally occurring trace amine such as octopamine, *p*-tyramine or *m*-tyramine.

Although PEA restored atropine-resistant LVFA it did not always restore the normal correlation of atropine-resistant LVFA and Type I behavior. This was especially clear in the early phase of PEA action in rats pretreated with reserpine and atropine plus one of α-methyl-*p*-tyrosine, chlorpromazine or trifluoperazine. Under these conditions PEA restored LVFA during behavioral immobility. Conversely, in reserpinized rats dopamine agonists restored spontaneous head movement and locomotion but did not restore atropine-resistant LVFA. These facts suggest that in a rat treated with atropine alone, trace aminergic and dopaminergic mechanisms collaborate to produce the normal correlation between Type I behavior and LVFA. The fact that stimulation of the region of the nucleus of the posterior commissure can produce LVFA during immobility in atropinized rats may suggest that a trace aminergic pathway can be activated independent of dopaminergic pathways and of motor activity.

The behavioral function of the trace amine-dependent reticulocortical pathway proposed here requires further investigation. It is of interest in this connection that trace amine activity appears to be abnormal in paranoid schizophrenia and depression[18,24].

Dopamine agonists increased neocortical LVFA in reserpinized rats but such LVFA could be abolished by atropine. This finding is consistent with data showing that release of acetylcholine from the neocortex is increased by dopamine agonists[17] and suggests that dopaminergic mechanisms normally influence activity in cholinergic reticulocortical fibres.

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