Psychopharmacologia 4, 354—366 (1963)

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α-Ethyltryptamine (Etryptamine): An Electroencephalographic, Behavioral and Neurochemical Analysis*

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With 3 Figures in the Text

(Received August 8, 1962)

The therapeutic use of hydrazine derivatives in the treatment of mental depression has stimulated considerable interest in agents which inhibit the enzyme system monoamine oxidase (MAO). While the exact

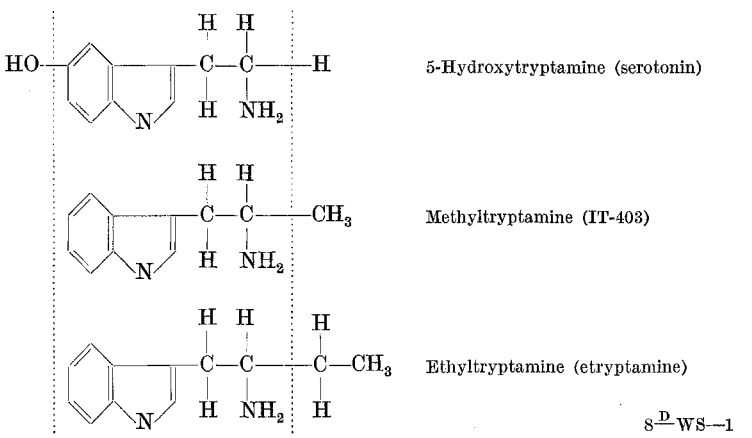

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Fig. 1. Structural relationship between 5-hydroxytryptamine (serotonin), α-ethyltryptamine (etryptamine) and α-methyltryptamine (IT-403). The three tryptamines are identical for that portion of the structure which falls within the dashed lines

mechanism by which these chemical agents achieve a therapeutic effect is unknown, one pharmacological action is an increase in the brain levels of the indole and catechol amines through the inhibition of MAO (AYD; BAILEY et al.). Recently, other compounds of a non-hydrazine nature have been found to exert an inhibitory action on MAO. Previous work

* Etryptamine, registered under the trade name of Monase by the Upjohn Company, has been withdrawn as a clinical therapeutic due to its adverse effect on blood forming elements.

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from this laboratory on one of these agents, α-methyltryptamine, demonstrated that this structure exerts a stimulatory action on the central nervous system in conjunction with singificant increases in the level of brain serotonin (VAN METER et al.). The present investigation is concerned with a closely allied compound, α-ethyltryptamine[1], a competitive, reversible inhibitor of MAO which has no apparent action on 5-HTP decarboxylase (GRIEG et al. 1959, GRIEG et al. 1961). Such an action was reported for α-methyltryptamine (VAN METER et al.). The structural relationships between α-ethyltryptamine, α-methyltryptamine and serotonin (5-HT) are shown in Fig. 1. Experiments were designed to evaluate the activating property of α-ethyltryptamine (etryptamine) in terms of various behavioral, EEG and biochemical correlates and also to modify the action of this compound with various blocking and sensitizing agents in order to more clearly elucidate possible mechanisms of action.

Method

Studies on rabbit

EEG analysis. A total of 120 adult New Zealand male albino rabbits ranging in weight from two to three kilograms were employed in these experiments. Animals were tracheotomized under ether and local pontocaine anesthesia, curarized and artificially respired prior to the administration of etryptamine. Brain wave recordings were made on an 8 channel, Grass Model III D electroencephalograph (EEG). Coaxial electrodes were implanted according to stereotaxic maps (SAWYER et al.) for the rabbit. Coordinates were as follows: anterior cortex (motor), anterior 3, lateral $3^1/_2$, vertical plus 8; posterior cortex (limbic), posterior 4, lateral 4, vertical plus $8^1/_2$; caudate nucleus, anterior 3, lateral $3^1/_2$, vertical plus 4; and hippocampus, posterior 4, lateral 4, vertical plus $5^1/_2$.

The following outline summarizes the major types of experiments employed on the rabbit.

I. Racemic drug form.
  A. Femoral or marginal ear vein route of injection.
    1. Varying dosages of etryptamine from 2—15 mg/kg, 19 animals.
    2. High dosages of etryptamine from 20—170 mg/kg, 6 animals, with accompanying norepinephrine determinations.
    3. Moderate dosage of etryptamine of 5 mg/kg.
      a) Rabbits sacrified at 15, 30, 60, 120, 180 and 360 min for serotonin determinations, 44 animals.
      b) Control rabbits recorded for 60, 180 and 360 min without etryptamine for serotonin determinations, 12 animals.
  B. Intracarotid route of injection.
    1. Moderate dosage of etryptamine of 5 mg/kg, rabbits sacrified at 15, 30, 60, 120 and 360 min for serotonin determinations, 20 animals.

[1] Liberal amounts of α-ethyltryptamine acetate and its steroisomers were supplied by the Upjohn Company, Kalamazoo, Michigan.

II. Stereoisomeric drug forms.
   A. Intracarotid route of injection.
      1. Levorotary form at 5 mg/kg, 9 animals.
      2. Dextrorotary form at 5 mg/kg, 5 animals.
      3. Recombined racemic form at 5 mg/kg, 5 animals.

As can be seen from this outline, the two stereoisomers of etryptamine were studied individually and in an equimolar mixture of the levorotary and dextrorotary forms in addition to the commercially prepared racemic form. In previous work with α-methyltryptamine (VAN METER et al.), variation in pharmacological response was shown to be influenced by site of injection and consequently, both the intracarotid and intravenous routes of injection were studied. In the majority of experiments, etryptamine was administered in single injections ranging from 2 to 15 mg/kg of animal body weight. Etryptamine was also studied in combination with atropine sulfate (1—4 mg/kg), chlorpromazine[1] (4—6 mg/kg), tranylcypromine[2] (1—2 mg/kg) and methyl lysergic acid butanolamide[3] (UML-491, 1—2 mg/kg). In this part of the study, etryptamine was given at a dosage of 10 mg/kg by vein except in four experiments involving atropine sulfate pre-treatment in which etryptamine was given by intracarotid route. All modifying drugs were given by vein.

Biochemical analysis. Brain serotonin determinations were made on 76 of the rabbits under EEG study by a bioassay technique using the rat uterus (GARVEN). Brain norepinephrine determinations were also made on six of the rabbits under EEG study by a method using perchloric acid extracts (BERTLER et al.). These were animals specially selected on the basis of having received the highest total doses of etryptamine ranging from 20—170 mg/kg acting over a six hour period.

Studies on rat

Biochemical analysis. The failure of etryptamine at high dosages to increase brain levels of norepinephrine in the rabbit (see results) prompted the selection of the rat for a more detailed analysis of the action of etryptamine on this brain amine. Brain norepinephrine determinations were conducted as described for the rabbit on 38 adult female rats of the Wistar strain wieghing 230—250 g. Twenty six rats were studied under short term administration (acute) of etryptamine for one day or less at a dosage of from 5—80 mg/kg by intraperitoneal injection. Time intervals were from 1—24 hours. A second group of rats were studied under prolonged administration (chronic) of etryptamine; seven rats received 8 mg/kg intraperitoneally, twice daily, for seven days while five additional saline injected rats served as controls. A

[1] Chlorpromazine: Thorazine (Smith Kline and French Laboratories).
[2] Tranylcypromine: Parnate, SKF-385 (Smith Kline and French Laboratories).
[3] Methyl Lysergic Acid Butanolamide: UML-491 (Sandoz Pharmaceuticals).

further group of three rats received 6 mg/kg of pheniprazine[1] in divided dosages of 2 mg/kg i.p. each for comparison with etryptamine in raising norepinephrine levels in the brain.

Behavioral analysis. Behavioral observations were made on the 41 rats under biochemical analysis. Additional observations were made on 24 other rats who had received etryptamine in combination with atropine sulfate or tranylcypromine in an attempt to modify behavioral effects of etryptamine. These last 24 rats were studied in four groups of six animals each. One group received 1 mg/kg of atropine sulfate as a pre-treatment two hours before receiving 25 mg/kg of etryptamine, a second group received 2 mg/kg of tranylcypromine as the pre-treatment under the same experimental conditions and a third group received the 25 mg/kg of etryptamine two hours before 2 mg/kg of tranylcypromine. A fourth group of rats received etryptamine alone for both time periods as a control; half under each condition. All drugs were prepared in saline solution and injected intraperitoneally.

Results

Studies on rabbit

EEG analysis. EEG alerting invariably accompanied the administration of etryptamine irrespective of the dosage studied. As in the case with the closely allied compound, α-methyltryptamine, these stimulatory effects were of two types, depending on the time of their occurrence. (The actual difference in type may reflect nothing more than route of drug administration.) Activation of the EEG was normally apparent by 30—40 min (delayed arousal) following a single intravenous injection of from 2—15 mg/kg of etryptamine with effects persisting unabated, until the sacrifice of the animal (1—6 hours). Amplitude reductions were usually apparent within 15 min of the administration of the drug. Single intravenous injections in excess of 10 mg/kg were generally found to be deleterious as evidenced by the flattening of the EEG rhythms but by spaced multiple injections of etryptamine, animals were brought to extremely high drug levels of up to 170 mg/kg without succumbing. EEG arousal of satisfactory intensity for experimental study of drug effects was always obtained at a value of 5 mg/kg by intravenous injection (roughly equivalent to 3 mg/kg of d-amphetamine).

An initial EEG alerting was also encountered with the administration of etryptamine. This arousal was noted within two to three minutes after intracarotid injections but was rarely obtained when the drug was given by vein. While the incidence of occurrence of this initial effect was less than one-half of that for the delayed arousal, it occurred

[1] Pheniprazine: Catron, JB-516 (Lakeside Laboratories).

sufficiently often, as can be seen from the five minute post-injection section of Fig. 2, to be considered a characteristic effect of etryptamine.

The duration of EEG alerting induced by etryptamine, whether initial or delayed, was found to be dependent upon the experimental procedure. In rabbits who had received etryptamine after being prepared for EEG recording, i.e., following tracheotomy, electrode implantment,

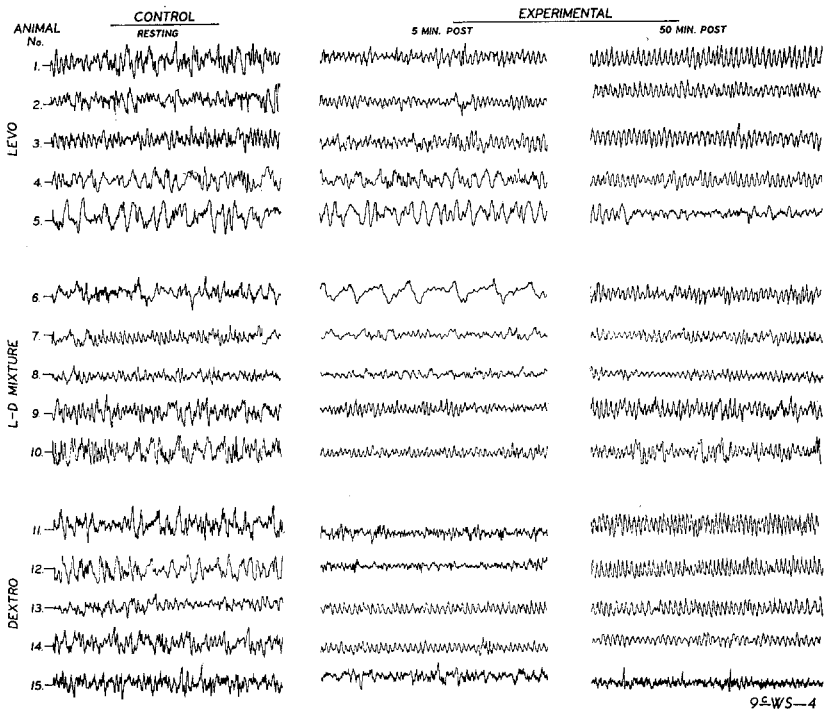

Fig. 2. Comparative effects of stereoisomers of α-ethyltryptamine on hippocampal EEG patterns of fifteen rabbits at a dosage of 5.0 mg/kg administered by way of the intracarotid route of injection. Activation is apparent in thirteen of the animals at 50 min post-injection irrespective of isomeric form of the drug

etc., the etryptamine induced arousal persisted until the sacrifice of the animal; a period of six hours in some experiments. By injecting the etryptamine prior to the preparation of the animal for recording, however, it was determined that the drug induced alerting usually subsided three to four hours after injection.

Fig. 2 presents the hippocampal tracing from each of fifteen rabbits injected by intracarotid route with 5 mg/kg of the stereoisomers of etryptamine; the hippocampal rhythms being selected on the basis of the sensitivity of this brain structure to changes in central nervous system activity. As can be seen from these tracings, considerable varia-

tion is noted from one animal to the next at the five minute post-injection point but at the 50 min post-injection point, arousal is apparent, without qualification in 13 of 15 animals. From this EEG data, both stereoisomers of etryptamine are equally active with little differentiation between the levorotary and dextrorotary forms.

Etryptamine antagonism. The intravenous injection of 10 mg/kg of etryptamine failed to induce EEG arousal, either initial or delayed, in rabbits pre-treated with 1—2 mg/kg of atropine sulfate five minutes prior to the experiment. In animals receiving the etryptamine first, this same dosage of atropine sulfate reversed the arousal pattern when given after the drug induced alerting had sustained itself but an additional 1—2 mg/kg of atropine sulfate was required to maintain the reversal. Experiments employing chlorpromazine as the antagonist produced identical results. Animals pre-treated with 4—6 mg/kg of chlorpromazine 16—24 min prior to the experiment failed to alert in response to the intravenous injection of 10 mg/kg of etryptamine. EEG arousal patterns previously induced by etryptamine in a second set of animals were quickly reversed by 2 mg/kg of chlorpromazine with additional amounts of chlorpromazine being required to maintain the reversal of activating effects.

Etryptamine induced EEG arousal was enhanced by the serotonin antagonist UML 491. Rabbits pre-treated with 1—2 mg/kg of UML 491 for one hour became unusually responsive to peripheral stimulation such as touch. The subsequent intravenous administration of 10 mg/kg of etryptamine produced an EEG arousal pattern more intense than patterns normally obtained from this dosage of etryptamine alone. Pronounced spike-like wave forms occurred in the hippocampal tracings and one of eight animals had a subcortical EEG seizure after the combination of UML 491 and etryptamine. Rabbits pre-treated with 1 mg/kg of UML 491 each day for four days rather than just one hour before etryptamine were found to be more similar to untreated control animals in terms of responsiveness to peripheral stimulation but both the four day and the one hour pre-treatment animals displayed markedly enhanced delayed arousal patterns in response to the combination of UML 491 and etryptamine.

Equivocal EEG effects were noted in animals receiving 10 mg/kg of etryptamine after pre-treatment with 1—2 mg/kg of tranylcypromine. Brief, sharp periods of EEG arousal occurred but were intermixed with periods of "sleep-like" EEG activity. The EEG record alternated between the two states, both appearing equally often.

Biochemical changes. The Table presents brain serotonin determinations for the cortex and mid-brain at varying time periods following the intravenous administration of 5 mg/kg of etryptamine in the rabbit.

Table. *Effect of etryptamine (5.0 mg/kg iv) on rabbit brain serotonin**

Drug time until sacrifice**	Cortex			Mid-brain		
	N	Mean	SD	N	Mean	SD
Control — 1, 3, and 6 hour combined . .	10	0.200	0.055	10	0.416	0.110
15 min	8	0.263	0.087	7	0.417	0.094
30 min	7	0.217	0.043	8	0.456	0.083
60 min	8	0.220	0.079	8	0.472	0.095
120 min	6	0.211	0.021	6	0.429	0.108
180 min	4	0.181	0.080	4	0.402	0.110
360 min	9	0.175	0.041	8	0.402	0.050

* Values expressed as micrograms per gram of brain tissue.

** Brains were removed rapidly, frozen on solid carbon dioxide and stored at —20° C prior to chemical analysis.

As can be seen from the Table, the degree of serotonin elevation is insignificant. Higher levels were obtained when etryptamine was given by the intracarotid route but the increase of 5-HT never exceeded 100% of control levels. The difference in serotonin level produced by the differing routes of drug administration for the cortex are portrayed in Fig. 3. In general, peak values occurred 15—60 min after injection depending on the route and restoration to control values occurred by two to four hours.

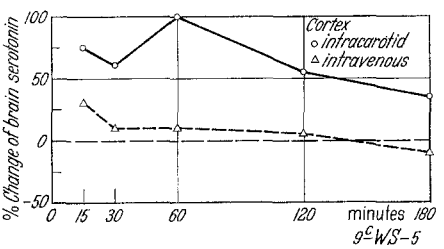

Fig. 3. Effect of α-ethyltryptamine on cortical serotonin level at varying time periods following either the intravenous or intracarotid injection of 5.0 mg/kg of the drug. The table gives number of animals per time period for intravenous route. Groups of four rabbits were used per time period for intracarotid route

The relatively high dosages of etryptamine failed to increase norepinephrine levels in the brains of rabbits. Further norepinephrine determinations on the rabbit were not undertaken since these particular animals had received maximal dosages from 20—170 mg/kg of etryptamine acting over a period of six hours.

Studies on rat

Biochemical changes. None of the etryptamine dosages of from 5—80 mg/kg by intraperitoneal injection increased norepinephrine levels in the brains of the rats within a period of from 1—24 hours (acute). The rats under chronic study who had received etryptamine over a period of seven days showed a 68% increase in norepinephrine on the 7th day when the brains were taken; control animals yielding average values of 0.383 ± 0.038 μg/g of brain tissue and drug injected animals 0.644 ± 0.085 μg/g of brain tissue (p less than 0.01).

Animal behavior. Little or no observable changes in behavior was noted in the rats at a dosage of 5 mg/kg of etryptamine acting over a one hour period.

Pronounced behavioral effects were noted in rats injected with 20—30 mg/kg of etryptamine acting over a three to four hour period. When unstimulated, the rats tended to remain stationary in their cages or to move with slow "stalking-like" movements with their abdomens dragging on the cage floor much like a cat after its prey. Preening and cleaning movements ceased. The rats were hypersensitive to audiogenic stimuli such as hissing air jets or jangling keys. These stimuli produced rapid walking mouvements or backing and turning movements which started and stopped abruptly with the onset or cessation of the stimulus. When handled, the rats displayed a tense musculature and vocalized much more than untreated animals. They also failed to locate and attack the source of moderate pain stimuli applied to the tail. Motor weakness and incoordination were also apparent at this stage. The rats performed poorly when placed on a horizontal bar, slipping, falling off, and were unable to regain their position after their rear legs were removed from the bar. In contrast, rats treated with 6 mg/kg of pheniprazine were indistinguishable from control animals in motor activity and behavior. This comparison between pheniprazine and etryptamine becomes even more striking when it is considered that 6 mg/kg of pheniprazine produces a great elevation of amines while 20—30 mg/kg of etryptamine is without effect (COSTA and PSCHEIDT, COSTA et al.).

Etryptamine was found to be toxic at 68—80 mg/kg acting over a 10—24 hour period. The six rats receiving this dosage showed adverse effects, breathing shallowly, one-third were prostrated with one death being recorded. The seven rats who had received 8 mg/kg of etryptamine, twice daily, for seven days (chronic group) displayed less gross behavioral changes than the rats injected for one day or less at a dosage of 20 to 30 mg/kg. In particular, the musculature was not as tense and movements were less stylized in the chronic group.

All rats receiving etryptamine in combination with 1 mg/kg of atropine sulfate or 2 mg/kg of tranylcypromine became hypersensitive, displaying the signs described for etryptamine administered alone. In particular, atropine sulfate failed to modify the behavioral effects of 25 mg/kg of etryptamine. Tranylcypromine, on the other hand, appeared to intensify the effects of this dosage of etryptamine and to shorten the time of their development.

Discussion

Central nervous system stimulation was found to be a characteristic action of etryptamine. Pronounced behavioral effects were in evidence

in the rat and an EEG alerting, either initial or delayed, invariably accompanied the administration of etryptamine in the rabbit. In this respect, then α-ethyltryptamine produced stimulatory effects similar to those reported for the closely allied compound α-methyltryptamine (VAN METER et al.). Serotonin levels were less elevated and the EEG activation was less intense with α-ethyltryptamine as compared to α-methyltryptamine but these differences are a matter of degree rather than of kind. Both compounds act as central nervous system stimulants; a property shared by other and stronger MAO inhibitors.

The biochemical findings of this study raise several problems. With the larger effective doeses of etryptamine, the parallelism between EEG and biochemical changes suggest that serotonin was involved in producing the central nervous system stimulation reflected in the delayed EEG arousal. Amplitude reductions were usually apparent in the EEG within 15 min of drug administration when serotonin levels were found to be on the increase, the actual occurrence of the delayed arousal required from 30—40 min which was a point in time when peak serotonin values were being obtained and the restoration of both processes to a pre-drug control state was usually complete by two to four hours. The difficulty with the above conclusion, however, is that the same time course was noted for the delayed EEG alerting which consistently accompanied the intravenous injections of etryptamine at low dose levels where the changes in serotonin level were found to be insignificant. It appears, then, that the EEG arousal is not directly related to changes in level of brain serotonin.

Biochemical data on changes in brain norepinephrine levels in the rat also present a similar problem. The significant increases of norepinephrine studied over a seven day period of etryptamine administration is in agreement with the findings of GRIEG (GRIEG et al. 1962) that significant increases in norepinephrine level occur after about the fourth day of etryptamine. The gross behavioral changes, however, which took place in the group of rats injected for one day or less were found to be independent of changes in norepinephrine level since it was found that none of the dosages of etryptamine increased norepinephrine levels within 24 hours in the rat. High doses of up to 170 mg/kg of etryptamine acting over a six hour period were also without effect on the norepinephrine levels in the rabbit. Thus again, there appears to be no direct causal relationship between the stimulatory effects of etryptamine and changes in the level of brain amines.

In regard, then, to the overall problem of mechanism of action of compounds which possess monoamine oxidase inhibition, the failure of etryptamine to induce elevated serotonin levels at a time when it is

effective in activating the EEG, strongly suggests that the induced stimulation of the central nervous system is not related to the level of the biogenic amines under study or, for that matter, to the inhibition of monoamine oxidase. We therefore must seek alternate explanations for the stimulatory activity of this drug. The simplest explanation would be that etryptamine possesses direct CNS stimulatory activity *per se*. The initial EEG alerting in the rabbit which accompanied the intracarotid injection of etryptamine substantiates this view. The two to three minute latency of this effect appears unusually long when considering the rapid action of an agent such as acetylcholine chloride but this type of latency is quite characteristic for stimulatory agents such as d-amphetamine sulfate and pentylenetetrazol (Metrazol) in the rabbit. A second possibility which is always present, is that other amines such as dopamine may have been involved in the mode of action of etryptamine. Finally, etryptamine may induce two mutually antagonistic actions; the elevation of amines to a small extent may be obscured by a depression of amines caused by nervous system stimulation accompanying etryptamine. VOGT (1954) has shown an action such as this in dogs for drugs which stimulate central sympathetic centers.

Experiments designed to modify the EEG action of etryptamine by other chemical agents produced results in accord with the usual finding for CNS stimulants. EEG alerting induced by etryptamine was either substantially modified or prevented by chlorpromazine and atropine sulfate. Both of these blocking agents have been found to be effective antagonists to a variety of substances. COSTA et al. (1960) have shown that atropine is capable of antagonizing the EEG arousal induced by 5-HTP, pheniprazine and tranylcypromine. As for other types of agents, BRADLEY and HANCE (1957) have demonstrated the effectiveness of chlorpromazine in blocking the action of amphetamine, our own work (STEINER and HIMWICH) has indicated a similar action of chlorpromazine against cholinergic agents while the blocking action of atropine against cholinergic substances (RINALDI and HIMWICH) is well known. From the studies just cited, it would appear that the very low dosage at which atropine sulfate (1—2 mg/kg) and chlorpromazine (2 mg/kg) antagonized the stimulatory action of etryptamine indicates either that there was very little 5-HT action, that etryptamine is a very weak cholinergic agent or, that its action is direct in nature like that of amphetamine. While our type of experiment does not permit a choice between these alternatives, a direct action appears to be the most probable. As for a 5-HT action, this could have been a factor in the delayed EEG alerting but it would not apply to the initial EEG

arousal. It is not likely, either, that etryptamine is a weak cholinergic agent since there is always some value at which an atropine-like blockade of EEG alerting can be reversed by cholinergic agents and etryptamine was found to be incapable of inducing such an effect against atropine or chlorpromazine. Furthermore, chlorpromazine is considerably more effective in antagonizing adrenergic agents such as amphetamine than cholinergic agents such as physostigmine (WHITE and DAIGNEAULT) and the low chlorpromazine dosage which was found effective against etryptamine is more consistent with an adrenergic type of antagonism. In any event, some type of direct action remains a distinct possibility.

Little can be said concerning the remaining data from the etryptamine antagonism experiments. It was expected that pre-treatment with methyl lysergic acid butanolamide as a serotonin antagonist would prevent the stimulatory action of etryptamine. Instead, this pre-treatment appeared to contribute to the stimulatory action of etryptamine but it was also found that the pre-treatment rendered the animals more hyperexcitable even without the addition of etryptamine. The failure of atropine sulfate to block the behavioral changes in rats can be explained on the basis of a dissociation between behavior and EEG; an action noted many years ago by WIKLER (1952) in his work with atropine. Experiments on rabbits with tranylcypromine in combination with etryptamine produced the expected enhancement of EEG alerting but the alternating periods of sleep-like EEG activity rendered the results too equivocal to be interpreted.

Summary

EEG recordings were taken from 120 rabbits receiving α-ethyltryptamine by way of the intravenous and intracarotid routes of injection. Central nervous system stimulation invariably accompanied the drug irrespective of dosage, isomeric form of the drug or route of injection. EEG arousal was either of an immediate or a delayed type depending on the route of drug administration; the intracarotid route evoking an initial alerting while the intravenous route produced a delayed alerting. Both types of arousal were substantially modified or reversed by chlorpromazine and atropine sulfate.

Brain serotonin determinations were made on 76 of the rabbits under EEG study with the cortex manifesting approximately a 100% increase under the relatively high effective dose of the intracarotid route of injection. Norepinephrine levels remained unchanged in six rabbits receiving high intravenous dosages of etryptamine. A total of thirty eight rats were injected on a seven day basis or on a one day or less basis for changes in level of brain norepinephrine. The seven day

group showed a 68% increase over control values while the one day or less group of rats reflected no significant increase.

Behavioral observations were made on 66 rats receiving etryptamine. Pronounced behavioral stimulation was in evidence. These effects were not directly related to changes in the biogenic amines under study and may reflect a direct drug action.

It was concluded that the CNS stimulation reflected in the EEG alerting of rabbits and the behavioral changes of rats was not necessarily related to a change in the brain levels of serotonin or norepinephrine even though both amines were found to be affected by α-ethyltryptamine. While experiments designed to modify the action of α-ethyltryptamine were not conclusive, a direct stimulatory drug action remained a distinct possibility in view of the fact that an immediate EEG alerting was obtained from the intracarotid administration of etryptamine.

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