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# EFFECT OF TRYPTAMINE AND TRYPTAMINE HOMOLOGUES ON CEREBRAL ELECTRICAL ACTIVITY AND BEHAVIOUR IN THE CAT

BY

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Tryptamine and 5-hydroxytryptamine occur in the brain and in other tissues (Amin, Crawford & Gaddum, 1954; Hess, Redfield & Udenfriend, 1959; Rapport, Green & Page, 1948) and presumably have some function there. Since 5-hydroxytryptamine does not readily enter the central nervous system when injected systemically (Shore, Pletcher, Tomich, Carlsson, Kuntzman & Brodie, 1957; Udenfriend, Weissbach & Bogdanski, 1957), Vane (1959) suggested studying the central actions of related compounds such as $\alpha$- or *N*-alkyltryptamines and their 5-methoxy derivatives, which are able to pass the blood brain barrier and resist attack by monoamine oxidase. We have therefore tested these substances on behaviour and cerebral electrical activity in the cat; the results have been described to the British Pharmacological Society (Bradley & Marley, January 1961).

The effects of intraventricular injections of 5-hydroxytryptamine and chemical antagonists on behaviour in the cat were tested by Feldberg & Sherwood (1954) and by Gaddum & Vogt (1956) and the effects on cerebral electrical activity after systemic or intraventricular injection by Bradley (1958). The action of 5-hydroxytryptamine on evoked responses in the cat brain has been reported by Malcolm (1958) and of a series of indoles on transmission in the cat lateral geniculate nucleus by Evarts (1958). Recently, the effect of a number of tryptamine derivatives applied iontophoretically has been tested on neurones of the lateral geniculate nucleus (Curtis & Davis, 1962), the cerebral cortex (Krnjević & Phillis, 1963) and the brain stem (Bradley & Wolstencroft, 1965) in the cat.

## METHODS

Experiments were made on forty-six adult cats of which forty were *encéphale isolé* (Bremer, 1936), four were *cerveau isolé* (Bremer, 1935) and two were prepontine preparations. Four cats carrying chronically implanted electrodes and two monkeys with implanted electrodes were also studied.

The acute preparations were anaesthetized with ethyl chloride and ether. The cat *encéphale isolé* was prepared as described by Bradley & Key (1958), while for the *cerveau isolé* an approach to the midbrain through a fronto-parietal craniotomy was used (Bradley & Elkes, 1957). The prepontine sections were made by drilling through the occipital bone on either side of the mid-line immediately inferior to the tentorium cerebelli, incising the dura over the superior cerebellar surface, and transecting the brain-stem

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at the junction of the mesen- and metencephalon. After the cord or brain section, the animals were artificially ventilated. Next, eight to sixteen cortical electrodes were inserted through small burr holes in the skull over both cerebral hemispheres (the contralateral hemisphere in animals with a fronto-parietal craniotomy) and a midline earthing electrode was placed in the frontal sinus. Concentric bipolar electrodes with the stimulation or recording points separated by approximately 1 mm were orientated in two of the following sites: brain-stem reticular formation, thalamic nuclei, medial geniculate body, inferior colliculus or hippocampus, using a Bonetti stereotactic instrument, the co-ordinates being taken from an atlas of the cat brain. Once in position, the coaxial electrodes were fixed to the cranium with dental cement and the animal was released from the stereotactic instrument, unless click-evoked responses were to be obtained. In one *encéphale isolé* preparation, a Collison cannula (Feldberg & Sherwood, 1953) was also implanted. The sciatic and femoral nerves were divided, as were the vagi and cervical sympathetic nerves.

The operative procedures completed, wound margins were infiltrated with procaine and the ether stopped. At least 1 hr was allowed to elapse before commencing the experiment. Bipolar recording of electrocortical activity was made with a four-channel Edison Swan portable pen electroencephalograph. Stimuli were delivered from a Grass stimulator.

The thresholds for electrocortical arousal, elicited by stimulation of the brain-stem reticular formation or the midline thalamic nuclei, were determined by increasing the applied voltage in 0.1-V increments, and stimulating for 10 sec at each step. Rectangular pulses of 1 msec duration at a frequency of 300 shocks/sec were used. The threshold for behavioural arousal (opening of the eyes, contraction of the nictitating membranes and twitching of the ears) was also determined. Recruiting responses, elicited by low frequency stimulation of the thalamic intralaminar nuclei, were recorded from the cruciate and supra-sylvian gyri. As differentiation between an augmenting and a recruiting response is often difficult (Hanbery & Jasper, 1953), it was assumed that, when low frequency thalamic stimulation produced effects in several different gyri, these were recruiting responses: if thalamic stimulation produced effects localized to a specific cortical area, then these were augmenting responses. The voltages delivered by the stimulator were calibrated on an oscilloscope at the end of the experiment with the brain electrode *in situ*. Click-evoked responses from the medial geniculate body, the inferior colliculus or the auditory cortex were recorded on an oscilloscope and on the electroencephalograph. Clicks at 30/min and of 1 msec duration were delivered to a crystal ear-piece mounted in the hollow ear bar of the stereotactic instrument.

One of the animals with chronically implanted electrodes was prepared as described by Bradley & Elkes (1953). For the other three, the cortical electrodes were made from small silver spheres soldered to short lengths of 0.012-in. (0.3-mm) diameter " Diamel "-coated silver wire (Johnson, Matthey & Co., Ltd.) sealed with "Araldite " cement (Ciba) into nylon screws inserted through the cranium and dura. The free ends of the silver wires were soldered to the terminals of a microsocket and the entire assembly was attached to the cranial vertex with " Simplex " autopolymerizing acrylic resin (Dental Fillings, Ltd.). Deep electrodes were made from two or three adhering strands of the " Diamel "-coated silver wire with their tips bared.

For recording, the animal was placed in a constant environment chamber fitted with a one-way glass observation window in a relatively sound-proof room. A flexible cable with a microplug at each end led from the microsocket on the cat's cranium to another in the roof of the chamber connected to the electro-encephalograph junction box: this permitted the animal unrestrained movement. The cat was allowed 1 to 2 hr acclimatization before control electrocortical and behavioural recordings were made.

With the acute preparations, drugs were given into the cannulated femoral vein, as was an equal volume of 0.9% saline as control. Blood pressure was recorded from the femoral artery with a pen-writing induction manometer in some animals. With the conscious unrestrained cats in which drug experiments were made once weekly injections were given intraperitoneally, and with monkeys into the pretibial vein. At the end of the acute experiment, or series of experiments with the chronic preparations, the animal was killed, the brain fixed in 5% formol saline with the stimulating electrodes *in situ* and the position of the tips subsequently determined histologically. Sections of the midbrain examined in formol-preserved brains were found to be complete.

*Drugs.* These included hydrochlorides of tryptamine, (+)- and (−)-α-methyltryptamine, (±)-5-methoxy-α-methyltryptamine, (±)-α-ethyltryptamine, *N,N*-dimethyltryptamine, tryptamine and tyramine; (−)-

adrenaline bitartrate, (±)-amphetamine sulphate, bromolysergic acid diethylamide, physostigmine sulphate, chlorpromazine hydrochloride and atropine sulphate were also used. Signs of the optical activity of the drugs are not given subsequently. The doses in all cases refer to the salt.

## RESULTS

### *Conscious chronic preparations*

*Cats.* Nineteen separate experiments were carried out with the four preparations. Within 15 min of injecting α-methyl-, α-ethyl- or *N,N*-dimethyltryptamine (0.5 to 2.0 mg/kg, intraperitoneally) bursts of 6 to 10 cycles/sec high-voltage (250 to 400 μV) electrocortical activity appeared. Initially, the bursts (eight to sixteen spindles) were separated by low-voltage activity and occurred about three times per minute; later they became more frequent (Fig. 1,*b*), and after 60 min were often continuous and of 600 μV amplitude. At first, electrocortical arousal with suppression of high-voltage activity was readily obtained on sensory stimulation but as the burst activity became continuous this was difficult to achieve.

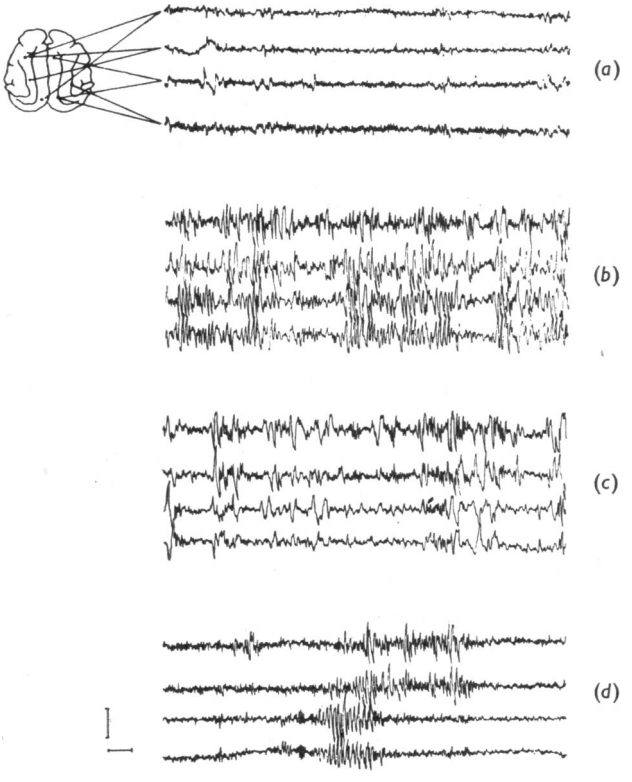


Fig. 1. The effect of α-methyltryptamine on cerebral electrical activity in a chronic cat preparation showing the development of large amplitude rhythms (6 to 10 cycles/sec). (*a*) Control record (alert); (*b*) 40 min after α-methyltryptamine (2.0 mg/kg, intraperitoneally); (*c*) 50 min after the injection of α-methyltryptamine and 10 min after bromolysergic acid (2.0 mg) with partial antagonism of the effect of α-methyltryptamine; (*d*) 110 min after the injection of bromolysergic acid. Calibrations, 500 μV and 1 sec at bottom left.

This inability to elicit arousal was not due to habituation to the stimulus, as electrocortical arousal was unobtainable when the stimulus was changed. An occasional variant of the rhythmic high-voltage activity was a slow wave (2 to 3 cycles/sec) pattern of 100 to 250 $\mu$V amplitude (Fig. 2). Rhythmic phenomena synchronous with those at the cortex were recorded from deep structures (brain-stem reticular formation, dorsomedial and ventromedial nuclei of the thalamus). The effects on electrocortical activity were greater and more protracted with compounds having a methyl group in the $\alpha$-position than with substituents on the terminal amino group of the ethylamine side-chain.

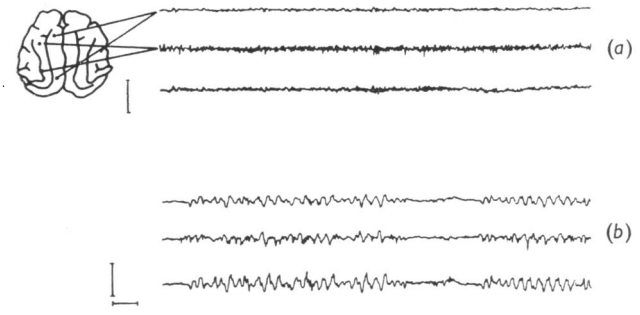


Fig. 2. The effect of $\alpha$-methyltryptamine on cerebral electrical activity in a chronic cat preparation showing the development of slow rhythms (2 to 3 cycles/sec). The lowest of each three records is from left ventromedial thalamic nucleus. (*a*) Control record (alert); (*b*) 85 min after $\alpha$-methyltryptamine (2.0 mg/kg). Calibrations, 250 $\mu$V (top), 500 $\mu$V (bottom) and 1 sec.

Behavioural changes, which did not develop until 30 min after drug application, appeared in a certain sequence. If the animal was restless, it became subdued and there was licking of the lips and occasional retching. Recurrent alternating flexor and extensor movements affecting individual limbs were next seen. There was mydriasis with preservation of the pupillary reflex response to light, dilatation of the palpebral fissures, and retraction of the nictitating membranes. The animal seemed reluctant to move but, if forced to do so, walked with an ataxic wide-based gait. Animals, formerly affectionate, were no longer demonstrative and seemed apathetic and bewildered. Salivation, so prominent after the intravenous injection of these compounds (Vane, Collier, Corne, Marley & Bradley, 1961), occurred in only one cat. These behavioural changes persisted for 6 hr or more with the long-acting tryptamines, and disappeared before the changes in electrocortical activity. Occasionally, electrocortical effects appeared without the behavioural changes.

The animals had fully recovered 24 hr after the drug injection. However, one cat given 5-methoxy-$\alpha$-methyltryptamine (2.0 mg/kg) died within 12 hr. In this animal, although the rhythmic electrocortical activity appeared, there was miosis, tachypnoea, salivation, sweating of the paws, tremor, involuntary limb movements and assumption of a crouching position. Unlike experiments with the other tryptamine compounds this cat was excited rather than subdued throughout the 6-hr observation.

The electrocortical and behavioural effects elicited by $\alpha$-methyltryptamine were reduced or abolished by the prior or subsequent injection of bromolysergic acid (2.0 mg, intraperi-

toneally). If bromolysergic acid was given first, the electrocortical effects did not appear for 30 min, and then remained minimal, while the behavioural effects never developed. If bromolysergic acid was given after α-methyltryptamine, the amplitude, frequency and number of spindles in each burst were reduced (Fig. 1,*c* and *d*); occasionally there was slowing of the 6- to 10-cycles/sec spindles to 4 to 6 cycles/sec. The rhythmic electrocortical potentials were also more easily blocked by sensory stimuli, and the animal was more attentive although still ataxic.

The electrocortical, but not the behavioural, changes usually elicited by α-methyltryptamine (1.0 mg/kg) could be obtained 60 min after amphetamine (1.5 mg/kg), although the amplitude of the spindle bursts was diminished.

*Monkeys.* Two rhesus monkeys were injected intravenously with 0.5 and 1.0 mg/kg respectively of α-methyltryptamine. No changes in behaviour or electrocortical activity were observed during the subsequent 2 hr.

### *Acute preparations (cat)*

Encéphale isolé

*Behaviour and neocortical activity.* Tryptamine (0.25 to 1.0 mg/kg, intravenously) produced behavioural and electrocortical arousal lasting for 20 sec, associated with a rapid rise in blood pressure. Immediately after the peak pressor effect, the alert electrocortical pattern was replaced by 2 to 4 cycles/sec activity of 250 to 500 μV amplitude, lasting for approximately 1 min and accompanied by alert behaviour. The behavioural effects produced by tryptamine will be described with those of α-methyltryptamine. The electrocortical changes were independent of the pressor action of tryptamine, as equipressor doses of tyramine elicited only electrocortical arousal. Doses up to 1.0 mg of tryptamine injected into the cerebral ventricles had equivocal actions on behaviour and electrocortical activity.

Within 1 min of giving α-methyltryptamine intravenously (0.5 to 2.0 mg/kg) to drowsy cats, there was electrocortical alerting for 1 min accompanying the steep rise in blood pressure. Occasionally electrocortical activation persisted for 10 min but the electrical activity always returned to the drowsy state with the blood pressure still 10 to 20 mm Hg above the pre-injection level. Behavioural excitation was invariable and rarely occurred without electrocortical arousal; the behavioural changes, which were maximal initially, only gradually abated. They included head retraction, facial myoclonus with rhythmic jaw opening and closure, tremor of the vibrissae, conjugate eye movements and ear twitching. There was mydriasis, dilatation of the palpebral fissures and contraction of the nictitating membranes. The contracture of the chest muscles was sometimes sufficiently powerful to render the animal asphyxic in spite of artificial ventilation unless intermittent positive pressure was applied to the chest. The limbs went into extensor spasm remitting to alternating vigorous flexion-extension movements of all, but most marked in the hind-limbs. Although the spasm of the chest muscles waned within 2 to 10 min there were recurrences. Electrocortical arousal was not secondary to the movements elicited by the action of α-methyltryptamine on the spinal cord since it occurred after elimination of movement by section of the femoral and sciatic nerves; if spasm of the chest muscles was prolonged there was temporary disappearance of electrocortical activity. The excitant action of the (+)-isomer of α-methyl-

tryptamine was about twice as marked as that of the (−)-isomer. The behavioural changes produced by tryptamine were similar, but rarely lasted more than 5 min. These behavioural affects evoked by tryptamine or α-methyltryptamine were abolished almost immediately by administration of chlorpromazine (2 mg/kg).

In half the experiments, within 30 min of giving α-methyltryptamine bursts of 250- to 350-μV electrocortical slow waves appeared similar to those observed in the minority of chronic preparations (Fig. 3,*d*). These bursts became continuous, ultimately slowing to 2 to 4 cycles/sec with disappearance of the " spindling " seen in the normal drowsy or sleepy cat. The slow waves were not due to asphyxic brain damage, as they were observed in cats in which the injection of α-methyltryptamine did not produce spasm of the chest muscles. In one-third of the experiments, groups of 6- to 8-cycles/sec high-amplitude electrocortical spindles appeared similar to those found in most of the chronic preparations (Fig. 3,*b*). As with the chronic preparations the bursts of activity (eight to twelve spindles) occurred initially at three per minute, increasing within 60 min to 12 bursts/min. The peak amplitude often reached 350 to 500 μV but was rarely of the amplitude seen in the chronic

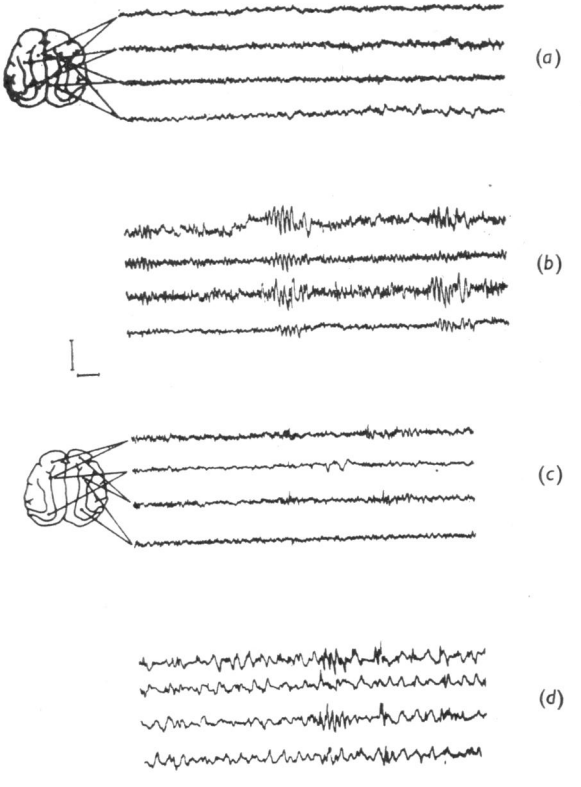


Fig. 3. Electrocortical records from two *encéphale isolé* preparations. (*a*) Control record of first preparation (alert); (*b*) 150 min after α-methyltryptamine (0.5 mg/kg), with large amplitude 6 to 10 cycles/sec electrocortical activity; (*c*) control record of the second preparation (alert); (*d*) 90 min after α-methyltryptamine (1.5 mg/kg), with large amplitude 2 to 3 cycles/sec electrocortical activity. Calibrations, 500 μV and 1 sec.

preparations. Ultimately, the 6- to 8-cycles/sec activity slowed to 4 to 6 cycles/sec, each burst containing as many as sixteen spindles; in only one animal did the intermittent burst activity develop into 2- to 4-cycles/sec waves. The rhythmic 6- to 8-cycles/sec electrocortical discharges were best seen over the gyrus interlateralis and suprasylvius, but this could have been related to the interelectrode distance which was maximal at these sites. Similar changes were seen over the motor and auditory cortex. The 2- to 4-cycles/sec or 6- to 8-cycles/sec rhythmic activity, synchronous with that at the cortex, was also recorded from deep structures (ventromedial thalamic nucleus, medial geniculate body, brain-stem reticular formation). As in the chronic preparations, electrocortical arousal with suppression of the drug-induced activity was at first easily obtained, but was later difficult to achieve whatever sensory modality was used.

The injection of 1.0 mg of α-methyltryptamine into the cerebral ventricle elicited electrocortical arousal lasting for 1 min and behavioural changes similar to those with intravenous administration: these were abolished within 5 min of injecting intravenously 4 mg of chlorpromazine.

The adrenal glands were removed in two cats to exclude arousal due to direct or indirect release of catechol amines from the adrenal medulla. Behavioural and electrocortical arousal appeared as before after α-methyltryptamine.

*Hippocampal activity.* The injury discharge evoked when the electrode was first placed in the hippocampus had usually abated when the drug was given. Initially there was a reciprocal relationship between the changes produced by α-methyltryptamine in hippo-

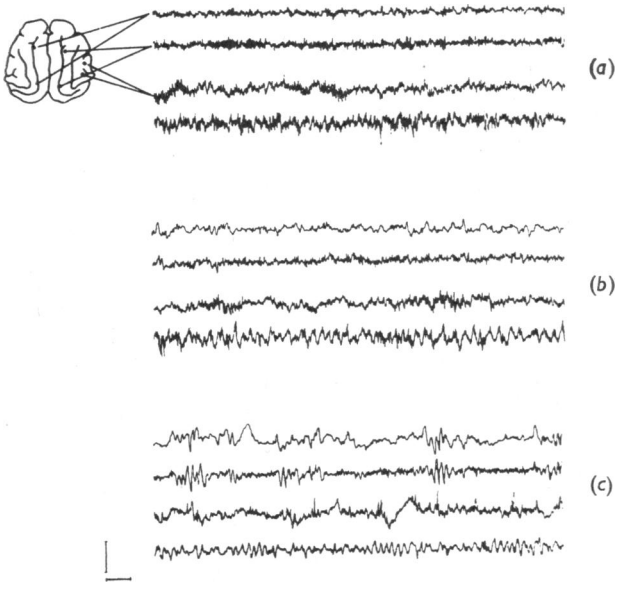


Fig. 4. Neocortical and hippocampal (lowest of each four traces) records from an *encéphale isolé* preparation. (*a*) Control (alert); (*b*) 5 min after α-methyltryptamine (1.0 mg/kg), showing intensified slow waves in the hippocampus whilst the preparation remained alert; (*c*) 140 min after (*b*), showing the time relationship between burst activity in the neocortex and hippocampus. Calibrations, 500 μV and 1 sec.

campal and neocortical electrical activity. Thus, after α-methyltryptamine (1.0 mg/kg) the behavioural and electrocortical arousal was associated with a decrease in fast and an increased amplitude of slow wave activity (3 to 4 cycles/sec) in the hippocampogram (Fig. 4,*b*). Later, the reciprocal relationship was not so evident, for the 2- to 4- or 6- to 8-cycles/sec rhythmic neocortical patterns were accompanied by hippocampal slow waves with superimposed fast activity. There was a variety of changes in the hippocampogram synchronous with the bursts of 6- to 8-cycles/sec high-voltage neocortical activity. These included low-amplitude hippocampal potentials preceding or coincident with the bursts (Fig. 4,*c*), or a large hippocampal wave preceded and followed by low-amplitude hippocampal activity.

*Effects of other drugs on neocortical activity.* The intermittent 6- to 8- or the 2- to 4-cycles/sec electrocortical activity seen after α-methyltryptamine (0.5 to 2.0 mg/kg) was converted to an alert electrocortical pattern after physostigmine (0.4 to 0.5 mg/kg). The rhythmic activity associated with α-methyltryptamine was replaced by 1- to 3-cycles/sec large-amplitude potentials after atropine (3.0 mg/kg). The dose required for these two drugs, which act on cholinergic mechanisms but not primarily on the brain-stem arousal system (Bradley & Elkes, 1957), was the same as that needed to elicit similar effects when given on their own. However, for substances which elicit arousal through adrenergic mechanisms or receptors in the brain-stem, the dose for electrocortical arousal was substantially raised after the appearance of rhythmic or slow potentials produced by α-methyltryptamine. Thus, amphetamine (5 mg/kg) reduced the amplitude of the slow wave electrocortical activity produced by α-methyltryptamine (1.5 mg/kg); 15.0 mg/kg of amphetamine (instead of the usual 1 to 3 mg/kg) was required to elicit sustained electrocortical arousal. In another cat, 13.3 μg/kg of adrenaline (normal dose 2.5 μg/kg) was needed to produce electrocortical arousal when the rhythmic or slow wave changes due to α-methyltryptamine (1.0 mg/kg) were established.

Rhythmic 4- to 6-cycles/sec high-voltage electrocortical potentials lasting 2 min could be obtained with tryptamine (1 mg/kg) in an animal behaviourally and electrocortically alert after amphetamine (1.5 mg/kg).

*Evoked electrocortical activity: electrocortical arousal elicited by electrical stimulation of the brain-stem reticular formation.* Because of the long-lasting behavioural arousal produced by α-methyltryptamine, brain-stem stimulation was restricted to eliciting the thresholds for electrocortical arousal. The tips of the stimulating electrodes were disposed either medially in the reticular formation (Fig. 5) with control thresholds of 0.4 to 0.7 V for electrocortical arousal and 0.5 to 0.7 V for behavioural arousal; or laterally among the vestibular nuclei (Fig. 5), with control thresholds of 0.8 to 2.7 V for electrocortical, and 1.0 to 3.0 V for behavioural arousal. After α-methyltryptamine (0.5, 1.0, 1.5 and 2.0 mg/kg) arousal thresholds were increased by 150 to 350% for stimulation at the medial site (Fig. 6) and 6 to 500% for the lateral site. Increase in threshold occurred within 5 to 15 min of giving the drug. Whereas electrocortical arousal persisted after cessation of the stimulus in the control, this did not occur after α-methyltryptamine (Fig. 6). With smaller doses (0.5 mg/kg) the maximal increase in threshold occurred about 90 min after giving the drug, with return to control values in the ensuing 60 min (Table 1). After larger doses (2.0 mg/kg) the maximal increase in threshold was found in 60 min and the threshold remained elevated until the end of the experiment (Table 1). In one cat (expt. 43), although there was an initial

TABLE 1

ELECTROCORTICAL AND BEHAVIOURAL AROUSAL THRESHOLDS IN CAT ENCÉPHALE ISOLÉ PREPARATIONS, BEFORE AND AFTER INTRAVENOUS INJECTION OF α-METHYL-TRYPTAMINE

E=Threshold for electrocortical arousal; B=threshold for behavioural arousal

| Expt. No. | Weight (kg) | Dose (mg/kg) | Threshold type | Control threshold (V) | Threshold (V) at time (min) after drug | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 5 | 15 | 20 | 30 | 60 | 75 | 90 | 120 | 150 | 180 | 240 |
| 64 | 3·0 | 0·5 | E | 0·4 | | | | 0·5 | 1·2 | | 1·4 | 0·88 | 0·55 | | |
| | | | B | 0·5 | | | | 0 | 0 | | 0 | 0 | 0 | | |
| 38 | 3·2 | 1·0 | E | 2·7 | | | 3·0 | | 5·0 | | 5·9 | 5·9 | | | |
| | | | B | 3·0 | | | 0 | | 0 | | 0 | 0 | | | |
| 59 | 2·4 | 1·0 | E | 1·0 | | | | 1·0 | 0·9 | | | 1·3 | | | |
| | | | B | 1·1 | | | | 0 | 0 | | | 0 | | | |
| 60 | 2·4 | 1·0 | E | 0·8 | | 1·2 | | 1·4 | 1·4 | | 1·25 | 1·3 | | | |
| | | | B | 1·0 | | 0 | | 0 | 0 | | 0 | 0 | | | |
| 61 | 2·4 | 1·0 | E | 0·5 | | | | 0·7 | 0·75 | | | 0·75 | 0·75 | | |
| | | | B | 0·65 | | | | 0 | 0 | | | 0 | 0 | | |
| 62 | 2·5 | 1·0 | E | 1·3 | | | | 2·5 | 2·5 | | | 3·5 | 3·0 | | |
| | | | B | 1·4 | | | | 0 | 0 | | | 0 | 0 | | |
| 43 | 2·2 | 1·5 | E | 1·8 | 1·9 | | | 1·9 | 1·4 | | | 0·9 | 0·9 | 0·9 | |
| | | | B | 1·9 | 0 | | | 0 | 0 | | | 0 | 0 | 0 | |
| 46 | 2·0 | 1·5 | E | 0·7 | | 0·8 | | 1·15 | | 1·15 | | 1·4 | | 1·4 | 1·15 |
| | | | B | 0·7 | | 0 | | 0 | | 0 | | 0 | | 0 | 0 |
| 51 | 3·0 | 1·5 | E | 0·5 | | | | 0·9 | 1·0 | | 1·1 | 1·1 | | 1·0 | |
| | | | B | 0·7 | | | | 0 | 0 | | 0 | 0 | | 0 | |
| 26 | 3·0 | 2·0 | E | 0·5 | | | | 0·9 | 0·9 | | | 0·9 | | 0·9 | 0·9 |
| | | | B | 0·6 | | | | 0 | 0 | | | 0 | | 0 | 0 |
| 36 | 2·3 | 2·0 | E | 1·4 | | | | 1·4 | | | 4·4 | | 4·4 | 5·4 | 6·9 |
| | | | B | 1·5 | | | | 0 | | | 0 | | 0 | 0 | 0 |

small increase in threshold, at 60 min the threshold was lower than for the control and continued to decrease. The decline in thresholds for electrocortical arousal after an initial decrease in some of the experiments precludes the possibility that the elevated thresholds were generally due to deterioration of the preparation.

*Evoked electrocortical activity : electrocortical arousal by stimulation of the intralaminar thalamic nuclei.* Electrical stimulation of the intralaminar thalamic nuclei failed to elicit

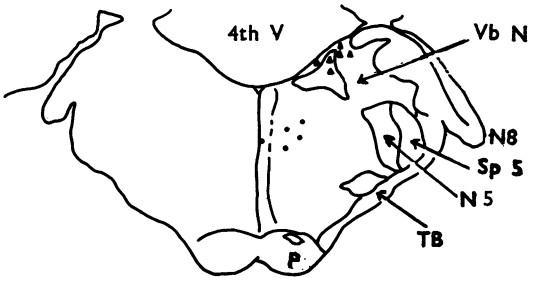


Fig. 5. Section of cat brain-stem in Horsley-Clarke frontal plane −6.0 showing stimulation points. ●, Points at which control thresholds for electrocortical arousal were between 0.4 and 0.7 V; ▲, points at which thresholds were between 0.8 and 2.7 V (4th V=4th ventricle; VbN=vestibular nuclei; N5, Sp 5=nucleus and spinal tract of trigeminal nerve; N.8=8th nerve; TB=trapezoid body; P=pyramidal tract).

behavioural arousal but produced electrocortical arousal restricted to the period of stimulation. Control thresholds (1.4 to 4.5 V, mean 2.7 V) for electrocortical arousal were higher in the five cats tested than those for stimulation of the brain-stem reticular formation and were raised 20 to 290% (1.8 to 5.5 V, mean 3.9 V) within 30 min of giving α-methyltryptamine. Subsequent histological examination showed the electrode tips to have been disposed in either the dorsomedial or the intralaminar thalamic nuclei.

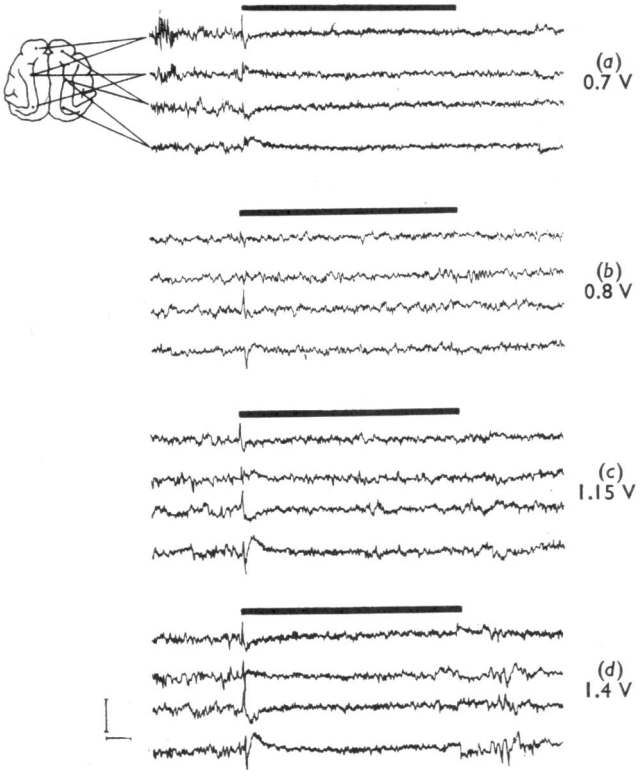


Fig. 6. Progressive increase in threshold for electrocortical arousal elicited by electrical stimulation of the brain-stem reticular formation and produced by α-methyltryptamine. (*a*) Control (drowsy); electrocortical arousal persists after ceasing stimulation; (*b*) 15 min after α-methyltryptamine (1.5 mg/kg); (*c*) 75 min after the injection; (*d*) 120 min after the injection, electrocortical arousal does not persist after ceasing stimulation. Stimulation was during black bars, at voltages shown on right. Calibrations, 500 μV and 1 sec.

*Evoked electrocortical activity : recruiting responses.* The voltages necessary to elicit threshold (0.9 to 3.0 V, mean 1.5 V) or maximal (2.7 to 3.5 V, mean 2.4 V) recruiting responses in five drowsy or alert cat *encéphale isolé* preparations were increased within 30 min of giving α-methyltryptamine, those for the recruiting threshold being raised 20 to 180% (1.2 to 3.5 V, mean 2.1 V). This increase was not due to deterioration of the preparation, since in one cat while the threshold for the recruiting response was elevated that for

electrocortical arousal on brain-stem stimulation was decreased; furthermore, the recruiting response remains stable for 2 to 3 hr in the cat *encéphale isolé* preparation (Key, 1958). Recruiting responses from the contralateral cerebral hemisphere were more easily reduced than those on the side of stimulation (Fig. 7). This is in line with Domino's (1955) suggestion that a more direct pathway exists from the diffusely projecting thalamic nuclei to the homolateral than to the contralateral cortex. Subsequent histological examination showed the electrode tips to lie in the nucleus centralis lateralis or the nucleus paracentralis. The thresholds for augmenting responses were also raised by α-methyltryptamine.

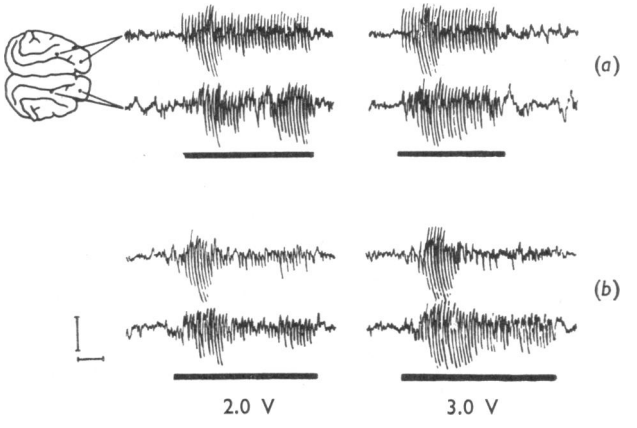


Fig. 7. Diminished recruiting response in an *encéphale isolé* preparation produced by α-methyltryptamine. Stimulation of right nucleus centralis lateralis at 8 shocks/sec. (*a*) Control records; (*b*) 120 min after α-methyltryptamine (1.5 mg/kg). Calibrations, 500 μV and 1 sec. Stimulation was during black bars, 2.0 V on left and 3.0 V on right.

*Evoked electrocortical activity: click-evoked potentials at the auditory cortex, inferior colliculus and medial geniculate body.* Care was taken to ensure the absence of extraneous stimuli when recording click-evoked potentials, as Hernandez-Peon, Scherrer & Jouvet (1956) found that the prominent click-evoked potential recorded in the cochlear nucleus of the drowsy cat is markedly attenuated if the animal's attention is diverted by other forms of sensory stimuli. As α-methyltryptamine produced prolonged behavioural arousal, the click-evoked potentials were recorded in six cats behaviourally alert before drug administra-

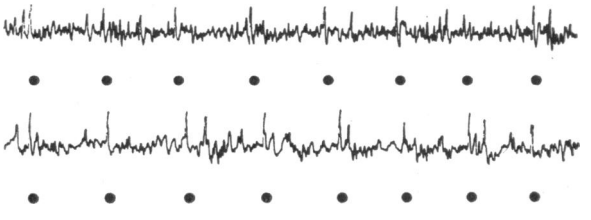

Fig. 8. Evoked click potentials recorded from right medial geniculate body in an *encéphale isolé* cat preparation. Upper trace: control record; lower trace: augmented response 60 min after α-methyltryptamine (2.0 mg/kg).

tion. However, although the amplitude of the evoked potential was usually increased (Fig. 8), the results were difficult to assess because the initial electrocortical alerting produced by α-methyltryptamine was replaced by slow wave electrocortical activity with immense variability of baseline potential.

Cerveau isolé

This preparation remains behaviourally and electrocortically asleep, unlike the *encéphale isolé* preparation which alternates between behavioural and electrocortical sleep and alertness. After α-methyltryptamine (1.0 to 2.0 mg/kg) behavioural and electrocortical arousal did not occur, but there was a further and delayed increase in the amplitude and quantity of the slow wave electrocortical activity with disappearance of spindling, suggesting that, although behavioural effects depend on the continuity of the brain-stem with the cerebrum, the drug may also act on receptors above the midbrain. Contracture of the chest muscles and limb movements occurred as in the *encéphale isolé* cats. For abolition of the immediate behavioural and electrocortical arousal after tryptamines, as after amphetamine, the midbrain lesion must extend dorsally through the posterior third of the thalamus to the base of the brain just caudal to the mammillary bodies. The completeness of the lesion was tested at the end of the experiment by giving amphetamine (up to 25 mg/kg) and confirming the absence of behavioural and electrocortical arousal.

*Prepontine section*

Two cats were prepared. Behavioural and electrocortical arousal were elicited by tryptamine and α-methyltryptamine, together with the body and limb movements as in other preparations. Slow wave electrocortical activity was now very conspicuous after tryptamine, and the rhythmic spindle bursts appeared after α-methyltryptamine as in the *encéphale isolé* cats. Receptors for the mediation of the electrocortical and behavioural effects of these drugs must therefore lie between the planes of section for the prepontine and *cerveau isolé* preparations.

## DISCUSSION

The actions of tryptamines on the central nervous system seem to be complex. In the experiments described here an *intravenous* injection of tryptamine in the feline *encéphale isolé* resulted in a brief behavioural and electrocortical activation which was followed by the appearance of slow waves in the electrocorticogram. Laidlaw (1912) described transient central stimulation, convulsions, tonic limb extension, snarling, piloerection and mydriasis after intravenous administration of tryptamine into the intact cat. In addition, and not reported by Laidlaw, is the prolonged subdued state which succeeds the excitement (Vane *et al.*, 1961). Tryptamine therefore appears to have a central excitant action which is very short-lived and central depressant properties which have a slower onset. The brief action of tryptamine is presumably due to its rapid oxidative deamination (Weissbach, Lovenberg, Redfield & Udenfriend, 1961). Tryptamine derivatives with an α-alkyl substituent are resistant to deamination by monoamine oxidase and, assuming that the substitution does not radically modify the central effects of or potency of the molecule, it should, by enabling the extended effect of tryptamine to be studied, give a clearer picture of its action.

Thus, prolonged behavioural arousal was elicited by intravenous administration of α-methyltryptamine in the *encéphale isolé*. The effects of this substance on cerebral electrical activity did not agree with the behavioural effects, however. There was electrocortical activation lasting for not more than 10 min; this was followed by slow wave or rhythmic cerebral electrical activity similar to spindling, and an increase in the threshold for electrocortical arousal to electrical stimulation of the brain-stem or thalamic activating systems similar to the elevation in threshold produced by central depressant drugs. This was accompanied by a loss of the tonic arousal response. Recruiting responses were diminished and click-evoked potentials recorded from the auditory pathway were enhanced. High-amplitude electrocortical waves, either in sleep or due to administration of drugs, are generally associated with enhanced evoked responses in sensory pathways (Killam & Killam, 1957).

The reciprocal relationship between the electrical activity of the neocortex and that of the paleocortex (hippocampus) which is normally present in the cat was ultimately lost after administration of tryptamine homologues. The neocortical slow waves or spindles were associated with either diminished or heightened hippocampal potentials, suggesting that the action of the drug might be related to the neurophysiological pacemaker linking the activities of the neocortex and hippocampus. It is difficult to reconcile these results with the startling behavioural effects of α-methyltryptamine, however, as it is substances which do not primarily affect wakefulness or sleep, for example atropine and physostigmine, which have been found to be most potent in abolishing the inverse relationship between hippocampal and neocortical patterns and behaviour (Bradley & Nicholson, 1962).

Tryptamine homologues administered *intraperitoneally* to intact cats were found to have only central depressant actions of behaviour and cerebral electrical activity. The animals seemed to be bewildered: they were ataxic and involuntary flexion-extension movements of the limbs appeared. Electrocortical activation was not observed and, although the bursts of high-voltage rhythmic activity developed, slow waves were uncommon.

There is no simple explanation for the differences between the effects of tryptamine homologues given intravenously to cat *encéphale isolé* preparations and intraperitoneally to intact cats. The rate of drug association and dissociation depends upon mass action laws (Paton, 1961); if it is assumed that α-methyltryptamine is a fundamentally excitant molecule, then the behavioural and electrocortical arousal which occurred with intravenous injections might be a reflexion of the sudden maximal drug concentration achieved at the central receptors. The lack of central excitation with intraperitoneal injections would then be due to the gradual development of equilibrium concentrations. This can be at best only a partial explanation as it does not account for the central depressant effects. Moreover, most central excitants produce similar effects whether given intravenously or intraperitoneally, for example amphetamine.

An alternative explanation was made by Dewhurst & Marley (communication to the British Pharmacological Society, January 1964), who suggested, from the results of experiments with different species, that α-methyltryptamine was a central excitant molecule but that the rhythmic electrocortical activity and stuporous behaviour which appeared in some species 15 to 30 min after injection might be due to the formation of a metabolite with central depressant properties. The preferred route for tryptamine metabolism is oxidative deamination, and only those indolealkylamines which are resistant to monoamine

oxidase are dealt with by 6-hydroxylation (Jepson, Zaltman & Udenfriend, 1962). Substituents in the 6-position modify the pharmacological properties of the molecule. Thus, in the cat and other species treated with monoamine oxidase inhibitors, 6-hydroxytryptamine has marked central depressant actions, while 6-methoxy or 6-chloro substitution of α-methyltryptamine converted an excitant molecule to a central depressant or substantially diminished its excitant properties (Dewhurst & Marley, communication to the British Pharmacological Society, January 1964). The explanation applies only to administered indolealkylamines, since their endogenous metabolism may be different and certainly in the cat tryptophan metabolism is anomalous (Brown & Price, 1956). Other indolealkylamines with ring substituents also have central depressant properties. Thus, 5-hydroxytryptamine injected into the cerebral ventricles of the cat produced lethargy (Feldberg & Sherwood, 1954; Gaddum & Vogt, 1956) although electrocortical activity was unaltered (Bradley, 1958).

A number of tryptamines are hallucinogenic in man (Böszörményi, Dér & Nagy, 1959). Rhythmic electrocortical activity similar to that produced by the tryptamine homologues has been observed in cats after intraperitoneal injections of lysergic acid diethylamide or mescaline (Bradley & Elkes, 1957). The resemblance between their actions may be apparent rather than real. Thus, lysergic acid diethylamide has been shown to have an action related to afferent collateral pathways entering the reticular formation and no direct action on the brain-stem reticular formation (Bradley & Key, 1958, 1963), unless very large doses are used. Tryptamine homologues (or their metabolites), on the other hand, appear to have direct depressant actions on the brain-stem reticular formation. Mescaline does have central depressant properties, for it behaves similarly to the phenylethylamines with ring hydroxyl groups by producing sleep and slow waves in the electrocorticogram of young chickens (Key & Marley, 1962).

The phenylethylamines, including amphetamine, can act on peripheral and may also act on central tryptamine receptors (Vane, 1960). From the results of these experiments there seems to be little ground for advocating an action of amphetamine on central tryptamine receptors in the cat. The initial excitant effects of α-methyltryptamine given intravenously, their dependence on intact mesencephalic connexions with the cerebrum and abolition by chlorpromazine resembled the action of amphetamine; the long-lasting effects were quite unlike those of amphetamine. However, because of the atypical tryptophan metabolism in the cat and likely 6-hydroxylation of α-methyltryptamine, it may be relevant to test their actions in other species. In the rat the behavioural effects of amphetamine and α-methyltryptamine are identical (Randrup, Munkvad & Udsen, 1963). Similarly, in the chicken, these amines appear to act on common central receptors, since in equimolar dosage, they have identical effects on electrocortical activity and behaviour and these are abolished by the specific tryptamine antagonist, methysergide (Dewhurst & Marley, 1964).

Too few molecules were studied to allow rigorous testing of structure-activity relations. If the predominant activity was due to a metabolite this would anyway vitiate any conclusions. It was nevertheless important to establish that the behavioural and cerebral changes produced by the tryptamines could be abolished by bromolysergic acid. The receptors mediating the effects of the tryptamines appear to be widespread for, in addition to the changes in electrical activity recorded at the cortex, thalamus, and brain-stem, the tryptamine homologues act on reflexes and evoked potentials in the spinal cord (Marley & Vane, 1963).

SUMMARY

1. Tryptamine and α-methyltryptamine, injected intravenously into cat *encéphale isolé* preparations, produced an initial brief electrocortical alerting and behavioural arousal, the latter being much longer-lasting with α-methyltryptamine. Behavioural and electrocortical alerting were dependent upon intact mesencephalic connections and were abolished by chlorpromazine.

2. α-Methyltryptamine caused the appearance of large-amplitude 2- to 4- or 6- to 8-cycles/sec electrical potentials, which were recorded both at the cortex and from deep structures, within 30 min of the injection. Corresponding changes occurred in the activity of the hippocampus.

3. The development of this activity was associated with an increase in the threshold for electrocortical arousal produced by stimulating the brain-stem or thalamic activating systems, and of the threshold for eliciting the recruiting response; click-evoked potentials, recorded in the auditory pathway, were enhanced. These effects were antagonized by substantial doses of amphetamine or adrenaline.

4. In intact cats, *N*- or α-alkyltryptamines, injected intraperitoneally, produced 8- to 10-cycles/sec large-amplitude neocortical potentials; the animals seemed bewildered and were ataxic, and slow flexor-extensor limb movements occurred. These behavioural and cerebral electrical changes were abolished by bromolysergic acid.

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