Br. J. Pharmac. (1981), **73**, 485–493

In vivo PHARMACOLOGICAL STUDIES ON THE INTERACTIONS BETWEEN TRYPTAMINE AND 5-HYDROXYTRYPTAMINE

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1 Three methods have been used in an attempt to study the interactions of tryptamine with central 5-hydroxytryptamine (5-HT) systems.

2 In groups of mice pretreated with tranylcypromine, tryptamine reduced the number of mice showing head twitches following the 5-HT precursor, 5-hydroxytryptophan. This effect was not seen in mice pretreated with saline and tryptamine itself did not induce head twitches in either group.

3 The swallowing reflex induced by 5-hydroxytryptophan in rats anaesthetized with urethane was substantially reduced by tryptamine injected into the internal carotid artery. This effect was seen in rats pretreated with saline or tranylcypromine, in the latter case the effects being more profound and longer lasting. In addition, swallowing evoked by the 5-HT uptake blocker, fluoxetine, and the 5-HT releaser, *p*-chloroamphetamine, was also reduced by tryptamine.

4 5-HT or noradrenaline injected intravenously into 5 day-old chicks caused a dose-dependent behavioural depression resembling sleep. Tryptamine at high doses caused behavioural alerting effects. Tryptamine at low doses had no overt effects but enhanced depression induced by 5-HT. At behaviourally excitatory doses tryptamine reduced the duration of the 5-HT depression. Noradrenaline-induced depression was not affected by high or low doses of tryptamine.

5 The results show that tryptamine can have complex actions on 5-HT systems depending on the parameter studied and support the notion that tryptamine may be a controlling factor in 5-HT-mediated transmission.

Introduction

The indoleamine tryptamine has been identified as a normal constituent of brain tissue (Martin, Sloan, Christian & Clements, 1972; Saavedra & Axelrod, 1972; Philips, Durden & Boulton, 1974) although there is quite a large variation in the levels found by different groups. Although much more attention has been paid to its hydroxylated derivative (Aghajanian & Wang, 1978; Fuller, 1980), 5-hydroxytryptamine (5-HT), there is evidence to support a role for tryptamine in neurotransmission in the CNS. It appears to be located subcellularly in nerve terminals (Boulton & Baker, 1975). Dewhurst (1968) suggested that tryptamine may be an excitatory transmitter in the CNS on the basis of behavioural evidence (Dewhurst & Marley, 1965). Martin and his colleagues have suggested that tryptamine may be a transmitter of certain descending spinal pathways (Martin, Sloan, Bell, Vaupel & Nozaki, 1976). Quock & Weick (1978) have also suggested the existence of specific tryptaminergic transmission in the CNS on the basis of differential antagonism of tryptamine and 5-hydroxytryptophan (5-HTP)-induced hyperthermia in the rabbit. Also of considerable interest are the studies of Marsden & Curzon (1978; 1979) and Atterwill & Green (1980). In essence these experiments have suggested that changes in brain tryptamine are responsible in part for the behavioural syndrome seen in rats following administration of the indoleamine precursor, tryptophan. However, this action of tryptamine is probably not direct but may be related to a facilitatory effect on 5-HT transmission (Marsden & Curzon, 1978; 1979). A recent iontophoresis study (Jones & Boulton, 1980) investigated the interactions of tryptamine with 5-HT on single spontaneously active cortical neurones in the rat. When applied with very weak ejecting currents, such that it had no effect on baseline firing rate, tryptamine profoundly enhanced depressant neuronal responses to 5-HT. On the other hand, when the cell under study was excited by 5-HT, low concentrations of tryptamine resulted in abolition of the excitatory response and the appearance of a depressant response (Jones & Boulton, 1980).

The purpose of the present experiments was to determine whether the interactions between tryptamine and 5-HT demonstrable at the cellular level are reflected by an interaction at the behavioural level. Three different methods have been used to assess the

0007-1188/81/060485-009 $01.00

action of 5-HT on central 5-HT receptors: (1) 5-HTP-induced head twitches in mice. The head twitches seen following administration of 5-HTP to mice are supposed to result from an action of 5-HT on 5-HT receptors (Corne, Pickering & Warner, 1963). (2) Spontaneous and 5-HTP-induced deglutiatory reflex in rats. The automatic swallowing movements seen in rats anaesthetized with urethane seem to be mediated in part by a tonically active central 5-HT system (Hockman, Bieger & Weerasuriga, 1979) and the increased activity seen following 5-HTP is presumed to result from increased 5-HT release (Hockman *et al.*, 1979). (3) 5-HT-induced behavioural depression in young chicks. Since young chicks lack a mature blood-brain barrier (Lajtha, 1957), the behavioural effects seen following systemic administration of 5-HT are probably due to an action of the amine on central receptors (Dewhurst & Marley, 1965). The effects of tryptamine on these manifestations of the central actions of 5-HT have been studied.

Methods

5-Hydroxytryptophan-induced head twitch experiments

Female albino Swiss mice (20–30 g) were used. These were divided into two main groups, one of which was given tranylcypromine (12 μmol/kg i.p.) 4 h before the experiment and the other given 0.9% w/v NaCl solution (saline) injections. The experimental design was similar for the drug and saline-treated mice. Subgroups of 10 mice were given 5-HTP (i.p. see below for doses) and 16 min later given tryptamine (12, 24, 48 μmol/kg s.c.). Twenty minutes after 5-HTP injection the mice were observed for 2 min and the number of mice in each group showing at least one head twitch noted. Preliminary experiments determined that in animals pretreated with saline 7–9 mice out of 10 showed at least one twitch following 680 μmol/kg of 5-HTP. Similar effects were obtained in tranylcypromine treated mice with 112 μmol/kg. These doses were used in all tryptamine interaction studies. The doses of tryptamine administered to the mice were not revealed to the investigator until the experiments were completed. A four-fold table test was used for statistical comparison of groups (Documenta Geigy, Scientific Tables).

Swallowing experiments

Male albino Wistar rats (180–150 g) were used. Again rats were either given saline or tranylcypromine (12 or 60 μmol/kg i.p.) 4 h before the experiment. Animals were anaesthetized with urethane (1.2 g/kg), the trachea was cannulated and the laryngeal nerves were cut close to the larynx. Cannulae were also inserted in one internal carotid artery and one femoral vein for injection purposes. A small balloon, blown in the end of a length of PE 190 tubing, was filled with distilled water and inserted into the pharynx. The other end of the tubing was attached to a blood pressure transducer and this enabled the recording of changes in pressure caused by swallowing activity (Hockman *et al.*, 1979). The oral and pharyngeal mucosa were topically anaesthetized with 2% xylocaine jelly. Body temperature was maintained at 37 ± 0.5°C. Tryptamine was injected into the internal carotid artery and all other drugs were administered via the femoral vein cannula.

5-Hydroxytryptamine-induced behavioural depression experiments

White leghorn cockerels (5–7 days old, 45–55 g) were used. All experiments were carried out in a sound-proofed room with constant conditions of lighting and room temperature (23 ± 1°C). Drugs were injected directly into the wing vein and the animal immediately placed in a sound-proofed observation box.

Injection of 5-HT (3–36 μmol/kg) resulted in a characteristic biphasic behavioural syndrome (see Results). This consisted of a brief period of behavioural excitation followed by a much longer lasting behavioural depression. The duration of the depression was timed for each individual animal and used as an index of the action of 5-HT. The timer was started as soon as the chest and beak touched the ground and the eyes closed. When the chick showed signs of arousal in the absence of external stimuli the timer was stopped.

Noradrenaline (NA) (12–36 μmol/kg) also induced behavioural depression although this differed from that seen following 5-HT (see Results). However, the criteria described above were used to determine the duration of NA-induced depression.

In all experiments, at all dose levels, 5 chicks per group were used, each animal being used once only. When interactions with tryptamine were studied, tryptamine was given simultaneously with either 5-HT or NA. The interaction studies were performed 'semi-blind' in that while the dose of 5-HT or NA was known to the investigator the doses of tryptamine were not. Statistical comparisons were made by use of Student's *t* test.

Drugs

The following drugs were used: 5-HT creatinine sulphate (mol. wt. 387.4, Sigma); noradrenaline HCl (mol. wt. 205.7, Sigma); L-5-HTP (mol. wt. 220.2, Sigma; L-DOPA (mol. wt. 297, Calbiochem); tryptamine HCl (mol. wt. 196.7, Sigma); fluoxetine HCl (mol. wt. 337, Eli Lilly); *p*-chloroamphetamine (mol.

wt. 206.1, Sigma); tranylcypromine HCl (mol. wt. 169.7, Sigma).

Results

5-Hydroxytryptophan-induced head twitch

5-Hydroxytryptophan alone Administration of 5-HTP (680 μmol/kg) to previously untreated mice resulted in the characteristic head twitch response in approximately 80% of animals tested (Table 1). Few other overt behavioural changes were observed although a small proportion of animals (1 or 2 out of 10) did display slight body tremor, side to side head weaving, abduction of hind limbs and 'padding' or 'treading' of the forepaws. In mice pretreated 4 h previously with tranylcypromine, similar effects were observed with a much lower dose of 5-HTP (112 μmol/kg).

Tryptamine alone Given subcutaneously in the absence of other drugs, tryptamine had no detectable effect on behaviour in doses up to 48 μmol/kg and did not induce head twitches in any mice (Table 1). Likewise, tryptamine administered to mice pretreated with tranylcypromine did not induce head twitches or cause any other gross behavioural changes.

5-Hydroxytryptophan and tryptamine When administered to mice which did not receive tranylcypromine, 17 min following 5-HTP, tryptamine at 12, 24, and 48 μmol/kg failed to alter significantly the number of mice displaying at least one twitch in the observation period 3 min later (Table 1). In these groups as in the control groups an occasional animal displayed the behavioural symptoms described above (limb abduction, etc.).

In contrast, in mice pretreated with tranylcypromine, tryptamine at 24 and 48 μmol/kg caused a significant reduction in the number of mice showing 5-HTP-induced head twitches. Tryptamine at 12 μmol/kg did not affect head twitches in tranylcypromine-treated mice.

Although no attempt was made to quantify the other occasional behavioural changes seen following 5-HTP (abduction of hind limbs, tremor, etc.), a subjective assessment suggested that in tranylcypromine- but not saline-treated mice there was an increase in the frequency of occurrence of these behavioural effects when tryptamine was also given. Thus in the control groups (i.e. mice receiving saline + 5-HTP or tranylcypromine + 5-HTP), 1 or 2 mice displayed such symptoms whereas with the highest dose of tryptamine 5 or 6 mice were affected.

5-Hydroxytryptophan-induced swallowing

Effects of 5-hydroxytryptophan and tranylcypromine Previously untreated rats anaesthetized with urethane exhibited a periodic spontaneous twitch of the branchiometric muscles of the floor of the mouth which is identical to the buccopharyngeal stage of swallowing (Bieger, Giles & Hockman, 1977). The automatic swallowing rate in untreated animals measured over at least a 4 min period before any drug was given was 3.15 ± 0.51 swallows/min (mean ± s.e. mean, n = 10). Administration of tranylcypromine (12 μmol/kg) 4 h before anaesthetization increased the swallowing rate to 6.33 ± 0.89 swallows/min (n = 6). Swallowing rate was further increased to 10.7 ± 0.72/min (n = 6) in rats given 60 μmol/kg of tranylcypromine. 5-HTP (225–450 μmol/kg i.v.) resulted in an increase in swallowing rate in previously untreated rats (n = 7) and the effect was related to the dose of 5-HTP. The

Table 1 Effect of tryptamine on 5-hydroxytryptophan (5-HTP)-induced head twitch in mice

Saline pretreated			*Tranylcypromine pretreated*		
5-HTP (μmol/kg)	*Tryptamine (μmol/kg)*	*Head twitch No. reacting / No. treated*	*5-HTP (μmol/kg)*	*Tryptamine (μmol/kg)*	*Head twitch No. reacting / No. treated*
680	—	8/10	112	—	9/10
—	12	0/10	—	12	0/10
—	24	0/10	—	24	0/10
—	48	0/10	—	48	0/10
680	12	8/10	112	12	8/10
680	24	8/10	112	24	3/10*
680	48	6/10	112	48	2/10**

Significant difference compared to group receiving 5-HTP alone, * $P < 0.025$ (4 fold table test), ** $P < 0.01$.
The groups of mice in the left half of the table were given saline injections 4 h prior to 5-HTP. Tryptamine was administered 16 min following 5-HTP and the 2 min observation period started 20 min following 5-HTP (i.e., 4 min after tryptamine). The groups on the right side of the table were given tranylcypromine 4 h before 5-HTP.

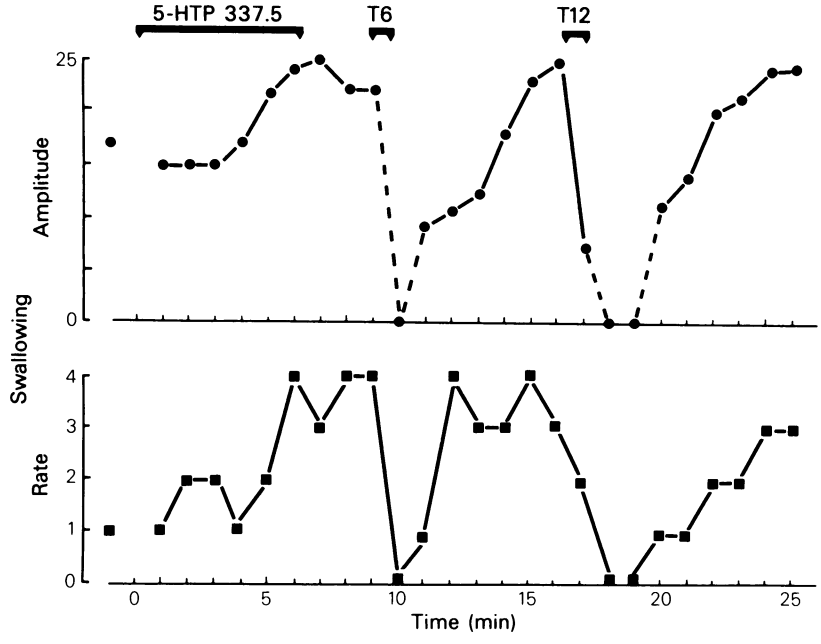

Figure 1 Effect of tryptamine on 5-hydroxytryptophan (5-HTP)-induced swallowing. The rate of swallowing/min is shown on the lower graph. The upper graph shows the mean amplitude/min of the swallow using arbitrary units (mm). Each point on the lower graph is the number of swallows observed during the preceding minute. Similarly, each point of the upper graph shows the mean amplitude of the swallows during the preceding minute. The initial point on each graph represents the mean rate and amplitude of swallowing over the previous 10 min. The start of the intravenous infusion of 5-HTP (337.5 μmol/kg) is taken as time 0. There is a progressive increase in both rate and amplitude of swallowing. When a plateau level was reached, tryptamine (6 μmol/kg (T6)) was injected into the internal carotid artery in a volume of 0.1 ml of saline and this decreased both the amplitude and the rate of swallowing; 12 μmol/kg of tryptamine (T12) caused a longer lasting reduction of both parameters.

swallowing rate in rats pretreated with tranylcypromine (12 μmol/kg) was also increased by 5-HTP (n = 8) although much smaller doses were needed (2.25–9 μmol/kg i.v.).

Effects of tryptamine alone The effect of tryptamine on spontaneous swallowing in untreated rats was tested in 6 animals. Swallowing was never increased by tryptamine. However in 3 rats there was a decrease in both the rate and amplitude of swallowing following administration of tryptamine. This effect was weak and transient.

Effect of tryptamine on 5-hydroxytryptophan responses Tryptamine was administered following 5-HTP when the swallowing rate had increased and reached a plateau level. In all 8 rats tested, tryptamine caused a clear cut decrease in both amplitude and rate of swallowing. This effect was related to the dose of tryptamine given. One study is illustrated in Figure 1. Following a cumulative dose of 337.5 μmol/kg of 5-HTP the swallowing rate was increased from 1 per min to 3–4 per min. Six μmol/kg of tryptamine caused complete cessation of swallowing for 2 min. Swallowing then resumed at a similar frequency but reduced amplitude and eventually after a further 3 min there was recovery of the amplitude. Twelve μmol/kg of tryptamine also caused cessation of swallowing but in this case when swallowing resumed both amplitude and frequency were reduced and in fact recovered almost simultaneously. The dissociation of effects of tryptamine on amplitude and frequency of swallowing was a commonly observed phenomenon. Generally the amplitude of reflex was more sensitive to reduction by tryptamine while the frequency reduction required higher doses.

Effect of tryptamine on responses to 5-hydroxytryptophan plus tranylcypromine Tryptamine was tested for effects on spontaneous and 5-HTP-induced swallowing in rats pretreated with the monoamine oxidase inhibitor, tranylcypromine. In the case of spontaneous swallowing (7 rats) there was a clear-cut inhibition of swallowing and this effect was long lasting

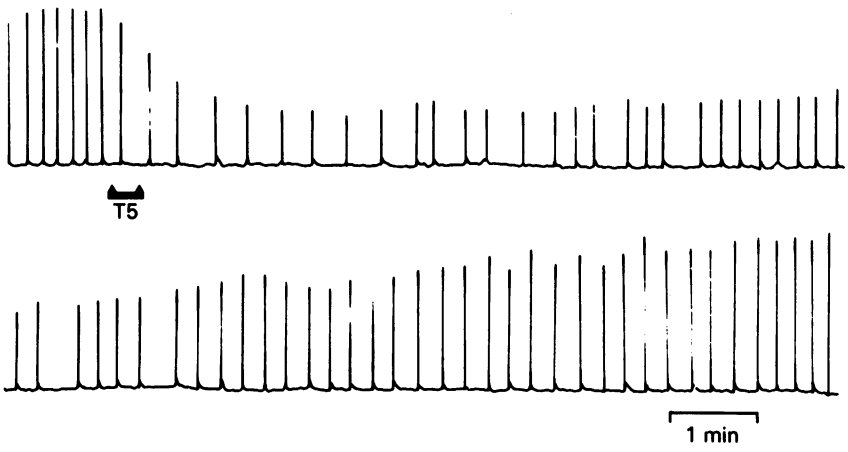

Figure 2 Effect of tryptamine on automatic swallowing in a tranylcypromine-treated rat. Part of the polygraph trace is shown. The buccopharyngeal pressure changes associated with swallowing are recorded as an upward deflection of the pen. The size of the twitches varied greatly from rat to rat and indeed with the initial pressure inside the oesophageal balloon, but remained remarkably constant for any particular rat. Since the actual pressure changes associated with each twitch are largely irrelevant, a calibration bar is not shown. Tryptamine (5 μmol/kg intra-arterially (T5)) reduced both amplitude and duration, an effect which was long lasting.

(up to 40 min). Part of the polygraph record of one study is shown in Figure 2. Both frequency and amplitude of swallowing were reduced at doses of tryptamine as low as 0.05 μmol/kg. Although much lower doses of 5-HTP were needed to evoke increase in swallowing in tranylcypromine-treated rats, tryptamine again caused long lasting reduction in both amplitude and frequency.

Effect of tryptamine on responses to p-*choloro-amphetamine and fluoxetine* Finally in four previously untreated rats there was no spontaneous automatic swallowing and swallowing was not evoked by 5-HTP (up to 400 μmol/kg). However, in two of these animals swallowing was then evoked by *p*-chloro-amphetamine, a drug causing release of 5-HT (Sanders-Bush, Gallager & Sulser, 1974) and in the other two rats swallowing was evoked by the 5-HT uptake blocker, fluoxetine. In all four cases tryptamine reduced or abolished the evoked swallowing. Results from one study are shown in Figure 3. *p*-Chloroamphetamine (2.5 μmol/kg) induced swallowing, the rate and amplitude of which was reduced by tryptamine.

Effect of tryptamine on L-*DOPA-induced swallowing* L-DOPA greatly increased swallowing in rats. The effects of tryptamine on L-DOPA (2.5–8 μmol/kg)-induced swallowing were tested in 6 rats pretreated with tranylcypromine (12 μmol/kg). Tryptamine had little effect on L-DOPA-induced swallowing although slight decreases in amplitude (10–20%) were noted at higher doses (25–50 μmol/kg).

5-Hydroxytryptamine-induced behavioural depression in chicks

Effects of 5-hydroxytryptamine and noradrenaline alone Injection of 5-HT resulted in a characteristic biphasic behavioural syndrome. There was an initial period during which the animals displayed apparent signs of excitation (increased vocalization, marked extension of neck and wings, pronounced head twitching). This period was short lasting (30–60 s approximately) and was rapidly followed by profound behavioural depression characterized by signs of sleep. During this depression the chest and beak rested on the ground, marked drooping of the wings occurred and the eyes were completed closed. At this time the chick could be partially aroused by auditory or tactile stimuli, but reverted to signs of sleep when the stimulus was stopped. Recovery from the depression was usually quite rapid.

NA also induced behavioural depression although this differed from that seen following 5-HT. There was no initial period of excitatory behaviour. The behavioural depression was slow in onset (approximate latency, 2–3 min) and during the depression the animals were more refractory to arousal by external stimuli than during the 5-HT-induced depression.

Observations of chicks for prolonged periods following both 5-HT and NA administration showed that the animals displayed symptoms of 'drowsiness' for up to 2 h (immobility, lack of vocalization, occasional drooping of head and wings), although they did not display the profound depression seen in the short term following the amines.

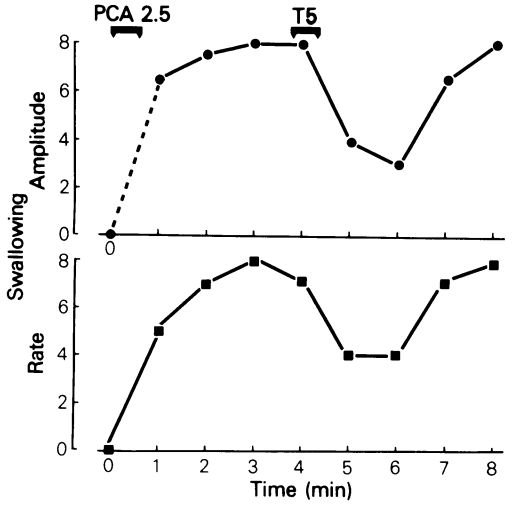

Figure 3 Effect of tryptamine on *p*-chloroamphetamine-induced swallowing. Details as for Figure 1. In this rat there was no automatic swallowing. 5-Hydroxytryptophan (200 μmol/kg) 15 min before the injection of *p*-chloroamphetamine (PCA, 2.5 μmol/kg) did not evoke swallowing. However, intravenous injection of *p*-chloramphetamine evoked immediate rapid swallowing. Both the amplitude and duration were reduced by tryptamine, 5 μmol/kg (T5).

The relationship between dose of these amines and the duration of the behavioural depression is shown in Figure 4. Increasing doses of both amines produced an increased duration of depression. However, for 5-HT this effect was apparently maximal at 36 μmol/kg whereas the effect of NA at this dose was still increasing. 5-HT at 36 μmol/kg occasionally caused convulsions and death.

Effects of tryptamine alone Tryptamine at doses up to 12 μmol/kg had no observable effects on behaviour. Doses higher than this resulted in signs of behavioural excitation (vocalization, abduction of wings away from body, signs of aggressiveness, ataxic gait, etc.). No signs of behavioural depression were seen up to 2 h following injection of tryptamine at any dose level tested.

Effects of tryptamine on 5-hydroxytryptamine- and noradrenaline-induced depression The effects of various doses of tryptamine given simultaneously with 12 μmol/kg of 5-HT are shown in Figure 5. With 3, 6 and 12 μmol/kg of tryptamine there was a progressive enhancement of the duration of the 5-HT-induced depression reaching a maximum of 10% of control with 12 μmol/kg. However, when a dose of 24 μmol/kg of tryptamine was given the effect of 5-HT was significantly reduced. In contrast, the duration of sleep induced by 12 μmol/kg of NA was not significantly affected by 6, 12 or 24 μmol/kg of tryptamine.

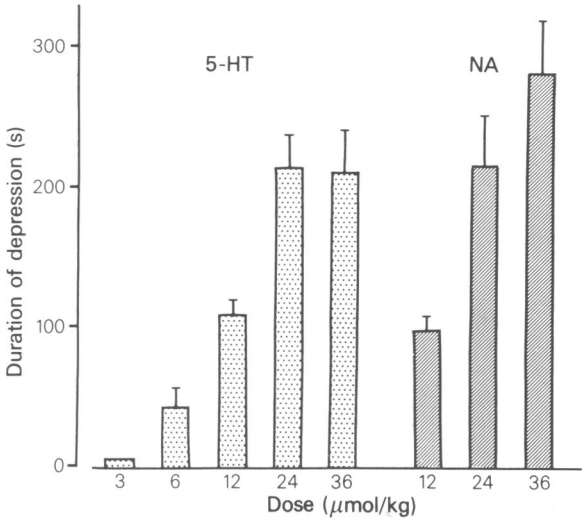

Figure 4 Duration of behavioural depression induced by 5-hydroxytryptamine (5-HT, stippled columns) and noradrenaline (NA, hatched columns) in five day-old chicks. Both amines caused increasing depression with increasing doses. The effect of 5-HT seemed to reach a maximum whereas that of NA was still increasing with the highest doses used.

Discussion

In mice not treated with a monoamine oxidase inhibitor, moderate doses of tryptamine had no effect on head twitches induced by 5-HTP. However, when the animals were pretreated 4 h beforehand with the monoamine oxidase inhibitor, tranylcypromine, tryptamine was effective in preventing the 5-HTP-induced head twitches. The lack of effect of tryptamine in untreated mice is probably due to its very high affinity as a substrate for monoamine oxidase and consequent extremely short half life (Durden & Philips, 1980). Tranylcypromine has been shown to be extremely effective in preventing the breakdown of tryptamine by monoamine oxidase (Philips & Boulton, 1979). The antagonism of the head twitches in animals pretreated with tranylcypromine is a previously undescribed effect. In a recent study, Jones & Boulton (1980) have shown that the excitatory effects of iontophoretically applied 5-HT on cortical neurones are abolished when small amounts of tryptamine are applied concurrently. Thus the antagonism of the 5-HTP-induced head twitches could result from antagonism by tryptamine on an excitatory effect of 5-HT. McCall & Aghajanian (1980) have suggested

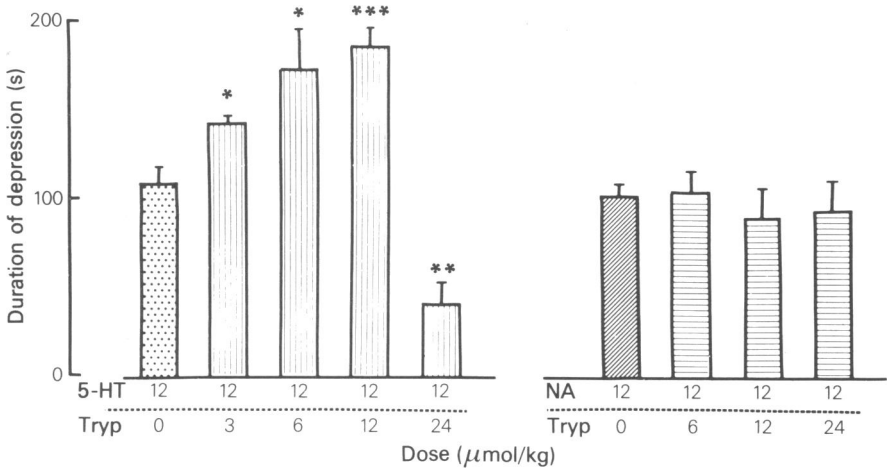

Figure 5 Effect of administration of tryptamine on 5-hydroxytryptamine (5-HT)- and noradrenaline (NA)-induced depression in 5 day-old chicks. The duration of the depression induced by 5-HT (2 μmol/kg) was progressively enhanced by tryptamine up to 12 μmol/kg. At 24 μmol/kg of tryptamine however the duration was decreased. There was no detectable change in NA-induced depression with any of the doses of tryptamine tested. Significant difference compared to control values: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

that the behavioural effects of 5-HTP in rats may be mediated via facilitation by 5-HT of excitatory inputs to brain stem and spinal motor neurones. It is possible that the head twitch response in mice is the result of 5-HT facilitation in motor nuclei and tryptamine may antagonize this facilitation. However, in the present experiments tryptamine, while antagonizing head twitching, apparently enhanced the other behavioural effects of 5-HTP (head weaving, forepaw treading, etc.), a result in agreement with the studies of Marsden & Curzon (1978; 1979) in rats. Iontophoretically, tryptamine enhances the depressant actions of 5-HT on cortical neurones (Jones & Boulton, 1980) and this could suggest that many of the components of the 5-HTP-induced behavioural syndrome may result from central depressant actions of 5-HT.

In a second series of experiments, tryptamine was found to antagonize the automatic swallowing seen in rats anaesthetized with urethane. Extensive studies have shown this reflex to depend partly on dopaminergic mechanisms and partly on 5-HT mechanisms (for review see Hockman *et al.*, 1979). Thus the swallowing can be increased by administration of the amino acid precursors of dopamine and 5-HT, L-DOPA and L-5-HTP respectively (Hockman *et al.*, 1979) and the present studies confirmed this observation. Intra-arterial injection of tryptamine reduced both the amplitude and the rate of spontaneous and 5-HTP-induced swallowing, effects which were greatly enhanced by prior treatment with tranylcypromine. In addition swallowing induced by fluoxetine and *p*-chloroamphetamine was also reduced by tryptamine.

The most parsimonious interpretation of these results is that tryptamine is acting as a 5-HT antagonist. Results from binding studies could support this notion since tryptamine is potent in displacing 5-HT binding in brain tissue (Middlemiss, Carrol, Fisher & Mounsey, 1980). As mentioned previously, iontophoresis studies (Jones & Boulton, 1980) have suggested that tryptamine antagonizes the neuronal excitatory effects of 5-HT and it is probable that automatic swallowing is the result of an excitatory action of 5-HT in neurones in the ponto-medullary region (Bieger, 1977; Hockman *et al.*, 1979). Of course, it is possible to speculate that in an analogous situation to the head twitch experiments tryptamine antagonizes actions of 5-HT on the motoneurones subserving the swallowing responses.

The final set of experiments described here investigated the effects of tryptamine on the 5-HT- and NA-induced behavioural depression in young chicks. 5-HT had a biphasic effect on behaviour, causing initial behavioural excitation followed by profound depression. In contrast, NA exhibited no apparent excitatory actions but did cause behavioural depression. These observations agree with those of Dewhurst & Marley (1965) who found analogous effects on behaviour and electrocorticogram in young chicks. Also in agreement with these authors, tryptamine injected by itself induced behavioural excitation but not depression.

When tryptamine was administered (at doses that had no overt effects on behaviour) in conjunction with 5-HT it had no detectable effect on the initial excitatory phase elicited by 5-HT although this was not quantified. However, the subsequent depression

was greatly prolonged. At higher doses, which by themselves caused behavioural alerting, tryptamine reduced the duration of the 5-HT-induced depression. At neither low nor high doses did tryptamine detectably change the duration of the NA-induced depression.

These results are difficult to interpret but there are some possible explanations. The potentiation of the 5-HT depressant effects could result from competitive inhibition of monoamine oxidase since tryptamine possesses a very high affinity for the enzyme (Durden & Philips, 1980). However, under these circumstances it might be expected that a similar potentiation of NA effects would occur. Inhibition of presynaptic uptake of 5-HT by tryptamine (Horn, 1973) could also account for the potentiation.

The antagonism of 5-HT-induced depression with a high dose of tryptamine possibly results from direct competition between excitatory and depressant influences on behaviour. Although the same dose of tryptamine had no effect on NA-induced depression, this is probably the result of the different time course of action of the various amines. The onset of the depressant effects of 5-HT occurred 4 to 60 s after it was administered, a time when the excitatory effects of tryptamine were reaching a peak. In contrast the depressant effects of NA occurred after a 2–3 min delay, when the action of tryptamine was rapidly waning.

The present results show that tryptamine can influence behavioural manifestations of central 5-HT-mediated transmission in a complex fashion depending upon the parameter studied. The dangers inherent in extrapolating results obtained on single cells to the whole animal are acknowledged. Nevertheless, it is obvious from the foregoing discussion that certain parallels can be drawn. While the physiological role of tryptamine is presently unknown, these and previous results (Marsden & Curzon, 1978; 1979; Jones & Boulton, 1980) together with the known location of tryptamine in nerve terminals (Boulton & Baker, 1975) suggest that tryptamine may be involved in regulating 5-HT-mediated neurotransmission in the CNS.

The author thanks Dr D. Bieger for helpful advice concerning the swallowing experiments and Drs A.A. Boulton and A.V. Juorio for constructive criticism of the manuscript. Financial support from Saskatchewan Health, Province of Saskatchewan and the Medical Research Council is acknowledged.

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(Received October 3, 1980.
Revised December 11, 1980.)