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MODULATION OF NEURONAL ACTIVITY IN THE HIPPOCAMPUS BY 5-HYDROXYTRYPTAMINE AND 5-HYDROXYTRYPTAMINE$_{1A}$ SELECTIVE DRUGS

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Summary—The interactions between 5-hydroxytryptamine (5-HT), 8-hydroxy-2-(*N*,*N*-dipropylamino)-tetralin (8-OH-DPAT), buspirone, 2-(4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl)-1,2-benzisothiazol-3-(2H)one-1,1-dioxide-hydrochloride (TVX Q 7821) and ketanserin, and putative 5-HT receptors were analyzed using both radioligand techniques and an *in vitro* hippocampal slice preparation. The potencies of the drugs were determined at 5-HT$_{1A}$ binding sites labelled by [^{3}H]8-OH-DPAT in hippocampal membranes from the rat. The binding site had similar affinity for 5-HT, 8-OH-DPAT, buspirone and TVX Q 7821, whereas ketanserin was essentially inactive. Physiological effects of these drugs were also examined using an *in vitro* hippocampal slice preparation. With the exception of ketanserin, application of each drug to the bath modulated the amplitude of the field potential recorded in the pyramidal layer of CA1 evoked by stimulation of Schaffer collaterals. Application of micromolar concentrations of 5-HT produced an initial increase in the population spike followed by a return to near baseline levels within 5 min. By contrast, the amplitude of the population spike was reduced in a dose-dependent manner by micromolar concentrations of 8-OH-DPAT, buspirone and TVX Q 7821, beginning 5 min after application of drug. Ketanserin did not affect the amplitude of the population spike and it did not antagonize the effects of 5-HT, buspirone or TVX Q 7821. Neither buspirone nor 8-OH-DPAT altered the initial increase in population spike induced by 5-HT. Therefore, the physiological effects of the novel anxiolytics 8-OH-DPAT, buspirone and TVX Q 7821 in the hippocampus appear to be independent of their interactions with 5-HT$_{1A}$ receptors.

Key words: 5-HT, 5-HT$_{1A}$, 8-OH-DPAT, buspirone, TVX Q 7821.

Radioligand binding studies have been used to differentiate two major classes of 5-HT receptors in the central nervous system (Leysen, Niemegeers, Tollenaere and Laduron, 1978; Peroutka and Snyder, 1979). Designated 5-HT$_1$ and 5-HT$_2$ sites, these receptors have differential affinities for serotonergic agonists and antagonists. The 5-HT$_2$ site appears to mediate multiple effects of 5-HT such as the head-twitches induced by 5-hydroxytryptophan seizures induced by tryptamine and contractions of vascular smooth muscle induced by 5-HT (Leysen, Niemegeers, Van Nueten and Laduron, 1981; Leysen, 1983). However, a physiological role for total 5-HT$_1$ sites labelled by [^{3}H]5-HT has been more difficult to establish (Fozard, 1983; Peroutka, 1984). Most likely, this difficulty is secondary to the fact that the binding of [^{3}H]5-HT has been shown to be heterogeneous (Pedigo, Yamamura and Nelson, 1981; Schnellmann, Waters and Nelson, 1984; Peroutka, 1986).

In recent radioligand studies, three distinct subpopulations of 5-HT$_1$ sites have been identified. Thus, the 5-HT$_{1A}$ site has high affinity for 8-OH-DPAT, buspirone and TVX Q 7821 and can be directly radiolabelled by [^{3}H]8-OH-DPAT or [^{3}H]TVX Q 7821 (Gozlan, El Mestikawy, Pichat, Glowinski and Hamon, 1983; Traber, Davies, Dompert, Glaser, Schuurman and Seidel, 1984; Dompert, Glaser and Traber, 1985; Hall, El Mestikawy, Emerit, Pichat, Hamon and Gozlan, 1985; Peroutka, 1985b). The 5-HT$_{1B}$ site has been more difficult to characterize but may have high affinity for 5-methoxy-3-(1,2,3,6-tetrahydro-4-pyridinyl)1H indole (Ru 24969), 1-(*m*-trifluro-methylphenyl)piperazine (TFMPP) and quipazine (Sills, Wolfe and Frazer, 1984; Asarch, Ransom and Shih, 1985; Pazos, Engel and Palacios, 1985). Finally, the 5-HT$_{1C}$ site is most prevalent in membranes from the choroid plexus and displays a relatively high affinity for methysergide and mianserin (Pazos, Hoyer and Palacios, 1984; Yagaloff and Hartig, 1985).

Autoradiographic studies have demonstrated that the CA1 region of the hippocampus contains an extremely large concentration of 5-HT$_{1A}$ binding sites (Deshmukh, Yamamura, Woods and Nelson, 1983; Marcinkiewicz, Verge, Gozlan, Pichat and Hamon, 1984; Glaser and Traber, 1985; Pazos and Palacios, 1985). This region is also particularly amenable to neurophysiological analysis. Stimulation of Schaffer collaterals in the *stratum radiatum* evokes a well-characterized field potential in the pyramidal cell layer of CA1. Previous neurophysiological studies have shown that the amplitude of this field potential is affected by 5-HT, although both an increase (Rowan and Anwyl, 1985) and decrease in amplitude

(Segal and Gutnick, 1980; Olpe, Schellenberg and Jones, 1984; Rowan and Anwyl, 1985; Beck and Goldfarb, 1985) have been noted under various experimental conditions.

The present study utilized 5-HT, three selective 5-HT_{1A} drugs (8-OH-DPAT), busipirone and TVX Q 7821) and a 5-HT_2 selective antagonist (ketanserin). Besides a high affinity for 5-HT_{1A} receptors, 8-OH-DPAT, buspirone and TVX Q 7821 are similar in that they all possess anxiolytic activity in animal models (Engel, Hjorth, Svensson, Carlsson and Liljequist, 1984; Riblet, Eison, Eison, Taylor, Temple and VanderMaelan, 1984; Traber *et al.*, 1984). Effects of drugs were analyzed both a 5-HT_{1A} binding sites labelled by [^{3}H]8-OH-DPAT in hippocampal membranes from the rat and on the field potential recorded in CA1 using an *in vitro* hippocampal slice preparation.

METHODS

Radioligand binding studies

Receptor binding assays were performed according to the methods of Peroutka and Snyder (1979). Briefly, adult rat brains were obtained either immediately after decapitation or purchased from Pel-Freeze Biologicals, Inc. (Rogers, AK) and stored at $-20°C$ until needed. On the day of the study, the brains were defrosted and the hippocampi were dissected as needed. Tissues were homogenized in 20 volume of 50 mM Tris-HCl buffer (pH 7.7 at 25°C) using a Brinkmann Polytron and then centrifuged in an IEC B20A centrifuge at 49,000 × ***g*** for 10 min. The supernatant was discarded and the pellet was resuspended in the same volume of Tris-HCl buffer and incubated at 37°C for 10 min prior to a second centrifugation at 49,000 × ***g*** for 10 min. The final pellet was resuspended in 80 volume of Tris-HCl buffer containing 10 μM pargyline, 4 mM calcium chloride and 0.1% ascorbic acid. The suspensions were immediately used in the binding assay.

Binding assays for drug displacement studies consisted of 0.1 ml [^{3}H]8-OH-DPAT (final concentration of 0.15–0.20 nM), 0.1 ml buffer or displacing drug and 0.8 ml tissue suspension. After incubation at 25°C for 30 min, the assays were rapidly filtered under vacuum through No. 32 glass fiber filters with two 5 ml washes using 50 mM Tris-HCl buffer. Radioactivity was measured by liquid scintillation spectroscopy in 5 ml of Aquasol (New England Nuclear, Boston, MA) at 54% efficiency. Specific binding was defined using 10 μM 5-HT in all experiments. Generally, 75–80% of total binding was specific for [^{3}H]8-OH-DPAT.

Hippocampal slice studies

Hippocampal slices were prepared and maintained *in vitro* using standard procedures. Female Wistar rats (180–240 g) were anesthetized with sodium pentobarbital (65 mg/kg, i.p.), rapidly exsanguinated by carotid section and the dorsal surface of the brain exposed by removing the overlying bone. A 6 mm block of one hemisphere was removed by making cuts with a scalpel blade at the midline and at a 30° angle from the coronal plane. The tissue block was immediately placed in cold (4°C), modified Krebs solution (124 mM NaCl, 3.0 mM KCl, 2.0 $MgSO_4$, 2.0 mM $CaCl_2$, 26.0 mM $NaHCO_3$, 1.3 mM NaH_2PO_4 and 10.0 mM dextrose saturated with 95% O_2 and 5% CO_2) and then glued to the stage of a vibratome. Sections 400 μm thick were cut from the entire block. The hippocampal sections were then dissected and placed in a submersion-type chamber for slices of brain. The chamber was continuously perfused with modified Krebs solution (6 ml/min) and maintained between 33–34°C. The sections were allowed to stabilize for at least 1 hr prior to all experiments.

Field potentials were recorded from the pyramidal cell layer of CA1 with glass microelectrodes filled with 3 M NaCl (d.c. resistance ranged from 5–15 MΩ). Schaffer collaterals were stimulated by delivering 40 μsec cathodal, constant current pulses through a tungsten microelectrode positioned in the stratum radiatum. In most experiments, the intensity of the stimulus was adjusted to obtain a 60% of maximal pupulation spike. Stimuli were presented once every 6 sec. Signals were amplified and digitized with a Nicolet 1174 signal averager and stored on magnetic tape.

Stimulation of the stratum radiation in CA1 evokes a well-defined field potential in the pyramidal cell layer (see Fig. 2; Anderson and Lomo, 1965). An initial small amplitude negativity corresponds to the action potential activity in the afferent fibers. This early negativity is followed by a large amplitude positive potential which corresponds to the source current of the population excitatory post-synaptic potential (EPSP) occurring in the dendrites. A sharp negative potential arises from the population EPSP. This negativity corresponds to sink current associated with synchronous action potential activity in the pyramidal cells (population spike). Actions of drugs were examined by assessing their effects on the amplitude of the population spike as measured from the crest of the EPSP to the most negative portion of the spike. Application of drugs began after the amplitude of the field potential had been stable for at least 10 min.

Drugs

All drugs were dissolved and diluted in assay buffer for radioligand studies. For neurophysiological studies, drugs were mixed fresh for each experiment in modified Krebs solution and were applied in the bathing medium. Drugs were obtained from the following sources: [^{3}H]8-OH-DPAT (80 Ci/mmol; Research Products International Corp., Mount Prospect, IL); 5-HT (Sigma Chemical Co., St. Louis, MO); 8-OH-DPAT (Research Biochemicals, Inc., Waltham, MA); buspirone (Bristol-Myers, Evans-

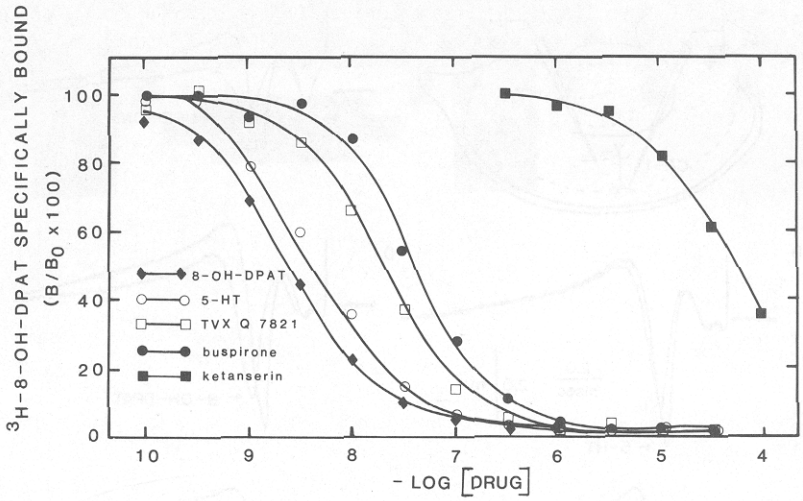

Fig. 1. Interactions between drugs and 5-hydroxytryptamine$_{1A}$ binding sites labelled by [^{3}H]8-OH-DPAT in hippocampal membranes from the rat. Receptor binding assays were performed as described in Methods. The data shown are the results of a single experiment, performed in triplicate. Each experiment was repeated 3–5 times with results which varied less than 20%.

ville, IN); TVX Q 7821 (Troponwerke, Cologne); ketanserin (Janssen Pharmaceuticals, Beerse).

RESULTS

Interactions between drugs and 5-HT$_{1A}$ binding sites, labelled by [^{3}H]8-OH-DPAT in between hippocampal membranes from the rat

The interactions between 5-HT, 8-OH-DPAT, buspirone, TVX Q 7821 and ketanserin (a selective 5-HT$_2$ receptor antagonist) were analyzed at 5-HT$_{1A}$ binding sites labelled by [^{3}H]8-OH-DPAT in hippocampal membranes from the rat (Fig. 1). The displacement of specific [^{3}H]8-OH-DPAT binding was sigmoidal for 5-HT, 8-OH-DPAT, buspirone and TVX Q 7821, with Hill slope values of approximately unity for each drug. With the exception of ketanserin, each of the four agents had a nanomolar affinity for 5-HT$_{1A}$ sites labelled by [^{3}H]8-OH-DPAT. Displacement by ketanserin of specific binding of [^{3}H]8-OH-DPAT began at concentrations greater than 1000 nM. Therefore, ketanserin was approximately 1000-fold less potent at this 5-HT binding site in hippocampal membranes from the rat than the other four agents.

The apparent K_i value of each drug for the 5-HT$_{1A}$ site was determined; 8-OH-DPAT was the most potent agent (1.4 ± 0.4 nM). However, the affinity of 5-HT (3.0 ± 1 nM), TVX Q 7821 (7.4 ± 1 nM) and buspirone (12 ± 1 nM) were similar. Thus, less than an order of magnitude difference in affinity existed between 8-OH-DPAT and buspirone for the 5-HT$_{1A}$ site. By contrast, the apparent K_i value for inhibition by ketanserin of the binding of [^{3}H]8-OH-DPAT to 5-HT$_{1A}$ receptors was $12{,}000 \pm 2000$ nM.

Effects of 5-HT and 5-HT$_{1A}$ selective drugs on the activity of hippocampal pyramidal cells

The amplitude of the population spike in CA1 was measured after stimulation of Schaffer collaterals in the stratum radiatum (Fig. 2A). Two distinct patterns of effects on the amplitude of hippocampal population spikes were observed upon application of 5-HT to the bath. In most experiments (85%), the amplitude of the population spike was increased at 2 min after application of 50 μM 5-HT (Fig. 2B1) and then gradually returned to near baseline levels. In the remaining experiments (15%), 50 μM 5-HT produced a decrease in the amplitude of population spikes which peaked at 5 min after application of drug (Fig. 2B2) and then remained stable for the next 25–30 min. By contrast, application of 50 μM buspirone, 8-OH-DPAT or TVX Q 7821 invariably led to a gradual reduction in amplitude of the population spike (Figs 2C–E).

As mentioned above, the effects of 5-HT were most pronounced in the first 5 min after application to the bath. As shown in Fig. 3, the amplitude of the population spike was measured at various times after application of drug. Large increases in the amplitude of the population spike (30–40%) were observed 0.5–2 min after application of 50 μM 5-HT. This increase slowly subsided such that the amplitude of the population spike was only 10% greater than baseline 5 min after application. This small increase was maintained over the remaining 30 min of application to the bath. The same concentration of buspirone, TVX Q 7821 or 8-OH-DPAT led to a reduction in the amplitude of the population spike that began slowly over the first few minutes and progressed to a maximum reduction within 25–30 min (Fig. 3). For each drug, the effects on the

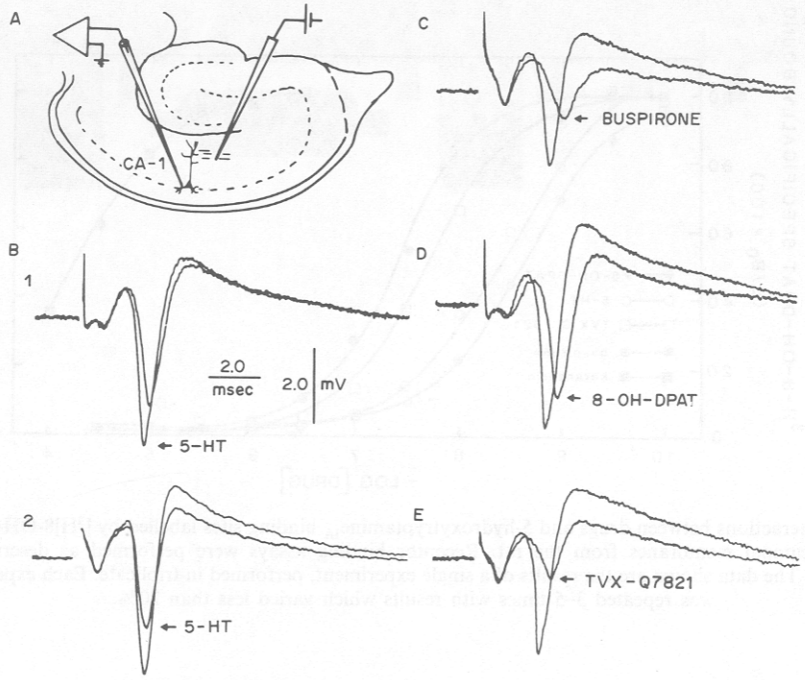

Fig. 2. Effects of application of drugs on CA1 population spikes. A. Schematic representation of the hippocampal slice preparation. B. Two effects of 5-HT application: (1) increase in population spike at 2 min after application of 5-HT, (2) decrease in population spike at 5 min after application. C. Buspirone. D. 8-OH-DPAT. E. TVX Q 7821.

population spike were reversed by washing with modified Krebs solution.

Dose–response characteristics of 5-HT$_{1A}$-selective drugs

Buspirone and TVX Q 7821 displayed similar dose–response characteristics in terms of their ability to reduce the amplitude of the population spike. The data in Fig. 4 were obtained at 30 min after application of the drugs to the bath. Concentrations as small as 3 μM of either drug resulted in reduction in amplitude of the population spike of approximately 20%. The amplitude of the population spike was reduced by 50% after application of either 25 μM buspirone or TVX Q 7821. The population spike was essentially abolished by the application of 100 μM buspirone or TVX Q 7821 to the bath. Larger concentrations of 8-OH-DPAT were required to alter the amplitude of the population spike. The amplitude of the population spike was unaffected by concentrations of 8-OH-DPAT of less than 25 μM. At

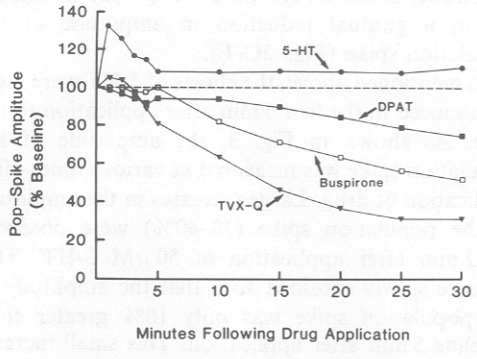

Fig. 3. Amplitude of the population spike as a function of time after continuous application to the bath of 5-HT, 8-OH-DPAT, buspirone or TVX Q 7821. Data shown are the results of a single experiment in which 50 μM drug was applied to the hippocampal slice preparation. Amplitude is expressed as the percentage of pre-drug baseline. Drugs studied are: 5-HT (●); 8-OH-DPAT (■); buspirone (□); TVX Q 7821 (▼).

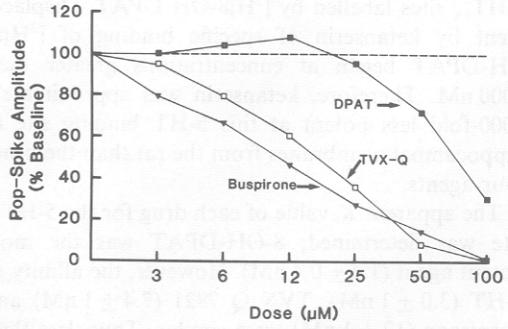

Fig. 4. Dose–response effects of 8-OH-DPAT, buspirone and TVX Q 7821 on the amplitude of the population spike. Increasing concentrations of 8-OH-DPAT (■), buspirone (▼) and TVX Q 7821 (□) were applied to the hippocampal slice preparation. The amplitude of the population spike is expressed as the percentage of pre-drug baseline.

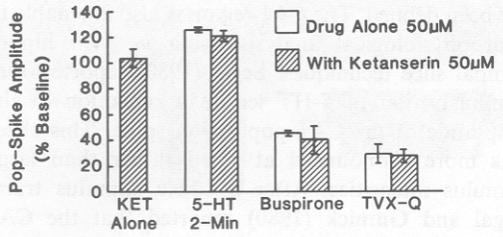

Fig. 5. Effects of ketanserin in the absence or presence of 5-HT, buspirone and TVX Q 7821 on the amplitude of the population spike. The data shown for 5-HT experiments were obtained 2 min after application of drugs to the bath. Amplitudes of population spikes for experiments using ketanserin in the absence or presence of buspirone or TVX Q 7821 were measured 30 min after application of drugs to the bath.

50–100 μM, 8-OH-DPAT reduced the amplitude of the population spike by approximately 30–70%.

Effects of ketanserin on 5-HT-, buspirone- and TVX Q 7821-mediated effects on the population spike

The potent and selective 5-HT_2 antagonist agent, ketanserin, had no effect on the population spike when applied to the slice preparation at a concentration of 50 μM (Fig. 5). Furthermore, application of 50 μM ketanserin in combination with 50 μM 5-HT, buspirone or TVX Q 7821 did not alter the independent effects of these agents on the population spike (Fig. 5). These results suggest that the electrophysiological effects of 5-HT, buspirone or TVX Q 7821 in the CA1 region of the hippocampus are not mediated by 5-HT_2 receptors.

Effects of combined application of 5-HT and buspirone

It has been suggested that the novel anxiolytic agent buspirone may antagonize the effects of 5-HT on membrane potentials (Andrade and Nicoll, 1985). In order to study the possible antagonist properties of buspirone on effects mediated by 5-HT on synaptic activity in the hippocampus, experiments were performed in which 5-HT and buspirone were applied in combination. As shown in Fig. 3, the amplitude of the population spike was initially increased by 5-HT while it was decreased by buspirone. Simultaneous application of these two agents (50 μM each) resulted in an early enhancement of the population spike (occurring over the first 4 min) followed by a distinct reduction in the amplitude of the population spike (Fig. 6). Similarly, administration of 50 μM 5-HT and 50 μM 8-OH-DPAT together resulted in an initial augmentation of the amplitude of the population spike. These data suggest that the physiological effects of 5-HT compared to buspirone and 8-OH-DPAT were additive and therefore, at least, partially independent.

DISCUSSION

The major finding of the present study was that 5-HT_{1A}-selective agents modulated CA1 activity in the hippocampus induced by stimulation of Schaffer collaterals. 5-Hydroxytryptamine, 8-OH-DPAT, buspirone and TVX Q 7821 were similar in that they displayed a high affinity for 5-HT_{1A} binding sites labelled by [^{3}H]8-OH-DPAT in membranes from the hippocampus. However, the drugs differed in that 5-HT also had a high affinity for 5-HT_{1B} and 5-HT_{1C} sites, whereas 8-OH-DPAT, buspirone and TVX Q 7821 were significantly less potent at these subtypes of 5-HT_1 binding sites (Middlemiss and Fozard, 1983; Pazos *et al.*, 1985; Peroutka, 1985b). 5-Hydroxytryptamine also differed from the 5-HT_{1A}-selective agents in its effect on neuronal activity at the level of the evoked field potential in the CA1 region. 5-Hydroxytryptamine caused an increase in the amplitude of the population spike recorded in the CA1 region in 85% of slice preparations. On the other hand, 8-OH-DPAT, buspirone and TVX Q 7821 caused a dose-dependent decrease in the amplitude of the population spike at micromolar concentrations. Ketanserin, a potent and selective 5-HT_2 receptor antagonist, had no effect on the evoked population spike in the CA1 region nor did it alter the physiological effects of equimolar concentrations of 5-HT, buspirone or TVX Q 7821. Simultaneous application of buspirone or 8-OH-DPAT with 5-HT had no effect on the initial increase in the population spike observed after administration of 5-HT alone. The results of the present study demonstrate a similar physiological effect of the novel anxiolytics 8-OH-DPAT, buspirone and TVX Q 7821.

Conceivably, the 5-HT_{1A} receptor may mediate part or all of the effects of the novel anxiolytics in the hippocampus. The interactions between 8-OH-DPAT, buspirone and TVX Q 7821 and 5-HT receptors were first noted in radioligand binding studies. The drugs are potent inhibitors of the binding of [^{3}H]5-HT in certain regions of the rat brain such as the hippocampus (Glaser and Traber, 1983; Hamon, Bourgoin, Gozlan, Hall, Goetz, Artaud and Horn, 1984; Traber *et al.*, 1984; Glaser and Traber, 1985). The drugs are even more potent at the 5-HT_{1A}

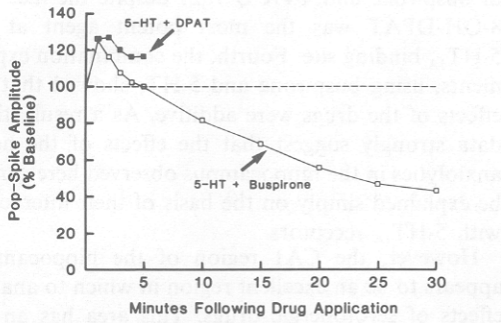

Fig. 6. Amplitude of the population spike as a function of time following application of 5-HT in combination with buspirone or 8-OH-DPAT to the bath.

binding site, a subtype of total 5-HT_1 sites, which can be directly labelled with either [^{3}H]8-OH-DPAT or [^{3}H]TVX Q 7821 (Gozlan *et al.*, 1983; Traber *et al.*, 1984; Peroutka, 1985b; Dompert *et al.*, 1985). By contrast, these agents are approximately three orders of magnitude less potent at 5-HT_{1B} and 5-HT_2 sites as measured by radioligand techniques (Middlemiss and Fozard, 1983; Peroutka, 1985a,b). Moreover, buspirone and TVX Q 7821 are significantly less potent at alpha-adrenergic, dopamine D_2, histamine H_1 and muscarinic cholinergic receptors and are inactive at benzodiazepine receptors labelled by [^{3}H]flunitrazepam at concentrations of less than 100,000 nM (Peroutka, 1985a). Thus, the 5-HT_{1A} site is the only known radioligand binding site where 5-HT, 8-OH-DPAT, buspirone and TVX Q 7821 have similar potencies.

A variety of other evidence also supports an interaction between 8-OH-DPAT, buspirone and TVX Q 7821 with serotonergic transmission. The drug 8-OH-DPAT decreases levels of 5-hydroxyindoleacetic acid rates of synthesis and utilization of 5-HT (Hjorth, Carlsson, Lindberg, Sanchez, Wikstrom, Arvidsson, Hacksell and Nilsson, 1982). Behaviorally, 8-OH-DPAT produces the behavioral syndrome induced by 5-HT while TVX Q 7821 induces portions of the entire syndrome (Hjorth *et al.*, 1982; Spencer, Glaser, Schuuman and Traber, 1984). Physiologically, both 8-OH-DPAT and buspirone have been shown to depress the spontaneous firing of raphe neurons (Hjorth *et al.*, 1982; VanderMaelan and Wilderman, 1984).

However, the results of the present study strongly suggest that the physiological effects of the novel anxiolytics are in addition to, or independent of, their effects at the 5-HT_{1A} receptor. First, the effect of the novel anxiolytics on the CA1 population spike was qualitively different to the effect observed with 5-HT under identical conditions. Second, the effect of 5-HT was observed within the first 5 min after application to the bath, whereas the effects of the novel anxiolytic did not begin until 5 min after application to the bath and did not maximize until 25–30 min after application of the drug. Third, the equimolar effects of 8-OH-DPAT were less pronounced than the effects of buspirone and TVX Q 7821 despite the fact that 8-OH-DPAT was the most potent agent at the 5-HT_{1A} binding site. Fourth, the combination experiments, using buspirone and 5-HT, showed that the effects of the drugs were additive. As a result, these data strongly suggest that the effects of the novel anxiolytics in the hippocampus observed here cannot be explained simply on the basis of their interaction with 5-HT_{1A} receptors.

However, the CA1 region of the hippocampus appears to be an excellent region in which to analyze effects of serotonergic drugs. This area has an extremely high density of 5-HT_{1A} sites and a paucity of 5-HT_{1B} and 5-HT_2 sites (Pazos and Palacios, 1985). The density of 5-HT_{1C} sites in the CA1 region has not yet been defined. The CA1 region is also amenable to neurophysiological analysis using *in vitro* hippocampal slice techniques. Segal (1980) reported that administration of 5-HT led to a reduction in the amplitude of the CA1 population spike. This effect was more pronounced at small rather than large stimulus intensities. After a 10 Hz stimulus train, Segal and Gutnick (1980) reported that the CA1 population spike could be reduced by a droplet of 0.5 mM 5-HT in the CA1 region. A reversible reduction in amplitude of the CA1 population spike was also observed by Olpe *et al.* (1984) and Beck and Goldfarb (1985) after superperfusion with micromolar concentrations of 5-HT. By contrast, Rowan and Anwyl (1985) found that superperfusion of 5-HT onto the hippocampal slice caused a transient (1–2 min) increase in the amplitude of the CA1 population spike followed by a decrease in amplitude.

The predominant effect of 5-HT on the population spike in the present study was an increase in amplitude that was greatest within the first few minutes of application of 5-HT to the bath. However, in 15% of slices, the population spike was reduced in amplitude. What might account for the different effects of 5-HT on the amplitude of the hippocampal population spike? It is well established that the primary effect of 5-HT on CA1 pyramidal neurons in the hippocampus is membrane hyperpolarization (Segal, 1980; Andrade and Nicoll, 1985). The hyperpolarization would move the membrane potential away from the EPSP equilibrium potential and thereby lead to an increase in amplitude of the EPSP. If spike failure does not occur there will also be an increase in the amplitude of spikes. Therefore, at relatively large stimulation intensities, where synaptic transmission may be more secure, an increase in the amplitude of the population spike after the application of 5-HT would be predicted. However, if the stimulation intensity is small enough, such that the stimulus-evoked spike was at or minimally above threshold, then the 5-HT-induced hyperpolarization could cause spike failure and a reduction in the extracellularly recorded population spike.

The effects of 8-OH-DPAT, buspirone and TVX Q 7821 on synaptically-mediated activity in the hippocampus were in contrast to the effects of 5-HT, a dose-dependent reduction in both the population EPSP and population spike. Andrade and Nicoll (1985) have demonstrated that buspirone, in contrast to 5-HT, caused only a modest hyperpolarization of CA1 pyramidal neurons. It is unlikely that the reduction in the population EPSP described in this report was the result of this small hyperpolarization. Indeed, slight hyperpolarization would be expected to lead to an increase in the amplitude of the population spike (as appears to be the case with 5-HT). Therefore, the results of the present study suggest that 5-HT and 5-HT_{1A}-selective agents are not operating through identical populations of receptors in the CA1 region of the neurons in the hippocampus. Since

8-OH-DPAT, buspirone and TVX Q 7821 appear to represent a novel class of anxiolytic agents, a greater understanding of their neurophysiological effects may elucidate the pathophysiology of anxiety.

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