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Sites and mechanisms of action of catechol (1,2-dihydroxybenzene) in the rat olfactory cortex slice

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1 Synaptic transmission in the isolated olfactory cortex slice from the rat was monitored by recording the surface field potentials evoked on lateral olfactory tract (LOT) stimulation. Catechol (approximately 0.05 to 2 mM) caused a concentration-dependent, partially reversible increase in the amplitudes of all field potentials.

2 In a series of conditioning experiments, catechol (1 mM) potentiated postsynaptic inhibition by a mechanism which was at least partially picrotoxin-insensitive.

3 When the relationship between the stimulus input and evoked output was investigated in picrotoxin-treated slices, for a given tract action potential amplitude, catechol (0.25 and 0.5 mM) increased the amplitude of the field potential known as the N-wave; in contrast, for a given N-wave amplitude, the latency of the population spike was increased.

4 Catechol (1 mM) increased the K^+-evoked release of endogenous aspartate by a tetrodotoxin-insensitive mechanism whereas the release of glutamate and γ-aminobutyric acid (GABA) was unaffected.

5 Catechol (1 mM) had no effect on submaximal depolarizations evoked by L-aspartate, L-glutamate or GABA.

6 It is concluded that catechol potentiates excitatory transmission at the LOT-superficial pyramidal cell synapse, possibly by increasing evoked transmitter release. Other synaptic actions of catechol may be consequent upon this increased excitatory input but the results do not exclude the possibility of separate and distinct actions on polysynaptic transmission.

Introduction

Catechol (1,2-dihydroxybenzene) is the most potent of the polyhydroxylicphenol convulsants (Angel & Rogers, 1968) and is active in a wide variety of animal species. In rodents, the convulsions evoked by parenterally administered catechol, which are of central origin, occur either spontaneously or in response to sensory stimuli and are characterized by a severe body tremor and brief clonic jerking of the body musculature (Angel & Lemon, 1973a, b; Dewhurst, 1984). Such convulsions are antagonized by cholinoceptor blockers and potentiated by anticholinesterases suggesting that catechol may affect central cholinergic transmission (Angel *et al.*, 1977; Angel & Dewhurst, 1978): this conclusion is indirectly supported by the finding that catechol increases acetylcholine release at the mammalian neuromuscular junction (Gallagher & Blaber, 1973). The present study examines the possible interaction of catechol with other central transmitter systems by investigating its effects on field potentials evoked in slices of rat olfactory cortex, a brain region where aspartate, glutamate and γ-aminobutyrate (GABA) are neurotransmitter candidates (Brown & Scholfield, 1979; Collins, 1979; Collins *et al.*, 1981; Pickles & Simmonds, 1976, 1978). Preliminary accounts of part of this work have been published (Dewhurst & Collins, 1985a,b).

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Methods

Slices of olfactory cortex were prepared from male rats (Wistar origin, Sheffield University strain) using a bow cutter and perspex guide recessed either to 400 or 500 μm and preincubated for 2 h at room temperature in a salt solution (composition, mM: NaCl 118.1, $CaCl_2$ 2.5, KCl 2.1, $MgSO_4$ 1.1, KH_2PO_4 0.93,

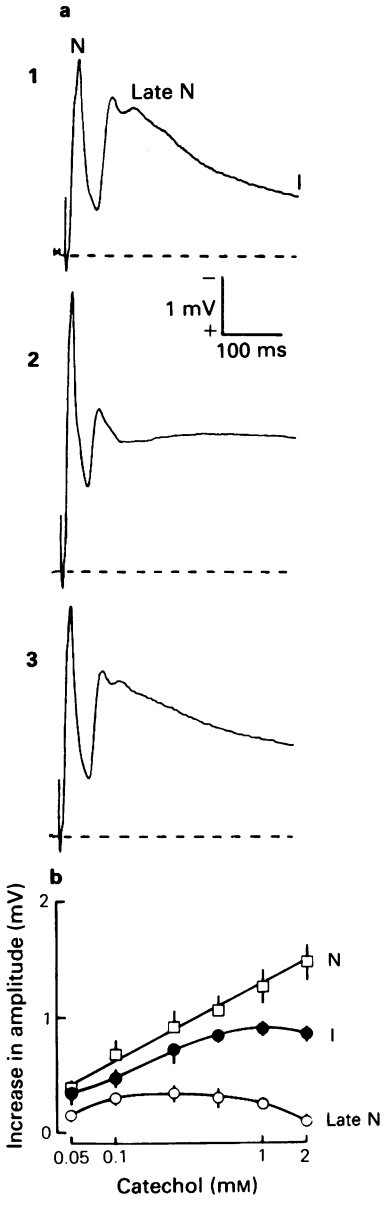

Figure 1 Effects of catechol on evoked field potentials. (a1) Control surface field potentials evoked on lateral olfactory tract stimulation. (a2) Field potentials in presence of catechol (1 mM) applied to the pial surface of the slice for 5 min. (a3) Recovery on superfusion with drug-free solution for 30 min. In (a1–3) the recording baseline is indicated by the broken line. (b) Cumulative dose-response curves for catechol. Each drug concentration was applied to the slices for 10 min before recording the evoked activity. Each point is the mean of 5 values and the s.e.mean, when greater than the symbols, is indicated by the vertical lines.

$NaHCO_3$ 25, glucose 11), pH 7.3–7.4, continuously bubbled with 5% CO_2 and 95% O_2. In most experiments, slices were then transferred to a superfusion system where they were mounted cut side down such that the undersurface was superfused with solution at a rate of approximately 2 ml min^{-1} (Pickles & Simmonds, 1976). The upper pial surface of slices was exposed to water-saturated 5% CO_2 and 95% O_2 to prevent drying out. Slices were stimulated (supramaximal voltage, 50 μs pulse width, frequency of 0.011 or 0.0033 Hz) by way of a bipolar electrode placed across the lateral olfactory tract (LOT); the evoked field potentials were recorded using a surface Ag/AgCl wire electrode usually positioned in the area of the pyriform cortex, amplified using a d.c. preamplifier and either captured in a Datalab DL 1080 transient recorder connected to a Bryans 28000 plotter or immediately recorded using a Medelec UV system. The indifferent electrode was in the superfusion solution subadjacent to the slice.

A single stimulus applied to the LOT evokes a complex surface field potential consisting of (with increasing latency) a stimulus artefact, a positive-negative-positive triphasic tract action potential (Figure 1), a negative-going massed excitatory postsynaptic potential, the N-wave, and two longer latency negative potentials, the late N- and I-waves (Figure 1). Depending on the position of the recording electrode, one or more positive-going population spikes may be superimposed on the N-wave. The N-wave is generated by the LOT transmitter synchronously depolarizing the apical dendrites of a population of superficial pyramidal cells (Richards & Sercombe, 1968; 1970; Stevens, 1969; Haberly, 1973a,b; Halliwell, 1976) and the synchronous firing of these cells is reflected as the population spikes (Richards & Sercombe, 1968; 1978; Halliwell, 1976; Pickles & Simmonds, 1978). The late N- and I-waves are the surface manifestations of GABA-mediated pre- and postsynaptic inhibition respectively (Pickles & Simmonds, 1976; 1978). In slices in which GABA-mediated transmission is blocked the pattern of evoked field potentials differs in that a shoulder (the N'b'-wave) appears on the N-(N'a'-) wave and the late N- and I-waves are replaced by a long latency positive field potential (the P-wave; see Figure 2). The N'b' field potential reflects depolarization of a population of deep pyramidal cells by the transmitter released from superficial pyramidal cell collaterals (Gilbey & Wooster, 1979), whereas the P-wave is the surface correlate of depolarization of deeper-lying structures including the cell bodies of the GABA-utilising inhibitory interneurones (Collins *et al.*, 1982).

In the present experiments, action potential amplitudes were measured from peak positivity to peak negativity, whilst unless otherwise indicated the amplitudes of other field potentials were measured

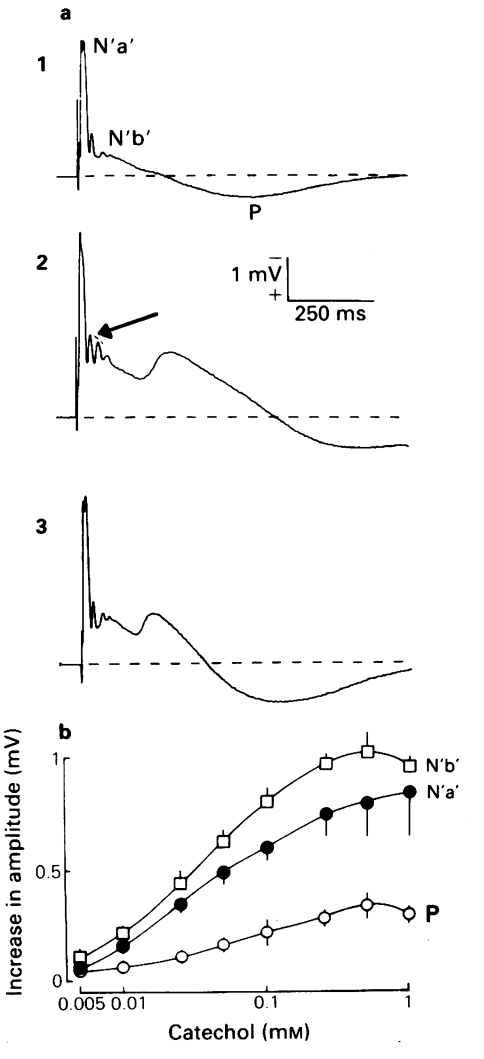

Figure 2 Effects of catechol on evoked field potentials in slices perfused with picrotoxin (25 μM). The form of the Figure is the same as Figure 1. Note that catechol (1 mM) increased the number and amplitudes of the population spikes in the experiment illustrated in (a) (arrow in a2).

from the recording baseline to the peak irrespective of latency. In experiments in which the population spike was of no interest, the recording electrode was positioned so that the N-wave was uncontaminated by evoked spikes (Figure 1).

Postsynaptic inhibition was monitored in a series of conditioning experiments. Slices were presented with pairs of stimuli such that the delay between the conditioning and test stimuli ranged from 0.01 to 10 s. An increase in the latency of the test population spike has been assumed to reflect an increase in postsynaptic inhibition (Pickles & Simmonds, 1978).

The preparation and method of application of drugs has been described in an earlier publication (Collins *et al.*, 1984). With the exception of picrotoxin, which was present in the superfusion fluid, approximately 0.3 ml of the drugs was applied dropwise to the pial surface of slices every 90 s for a sufficient time period to produce a sustained plateau response (5 min for catechol), followed by drug-free solution to allow full recovery. Cumulative dose-response curves to catechol were constructed by applying each concentration for 10 min to slices, although in these studies recovery was not attempted.

Input-output studies

In order to indentify whether the site of action of catechol was pre- or postsynaptic, a series of experiments was performed in which the relationship between stimulus input to evoked potential output was monitored using a procedure based on that originally described by Voskuyl & ter Keurs (1978, 1981). Briefly, following preincubation for 2 h and stimulation at 0.011 Hz for a further 2 h (Collins *et al.*, 1984) to allow the majority of the time-dependent increase in field potential amplitudes to occur (Pickles & Simmonds, 1976; 1978), 400 μm thick slices were stimulated using a range of voltages from threshold to supramaximal. In these experiments, the amplitude of the N-wave was measured at a fixed latency on the rising phase of the field potential (between 3 and 8 ms) as the presence of superimposed population spikes obscured the true peak amplitude of the N-wave. Graphs were then plotted of the stimulus voltage versus amplitude of the tract action potential, action potential versus N-wave and N-wave versus the latency of the population spike. The procedure was repeated during the application of catechol and finally after superfusion with drug-free solution. This procedure does not allow drug effects to be expressed quantitatively (see Collins *et al.*, 1985) although qualitatively consistent effects are readily observed. In this series of experiments, picrotoxin (25 μM) was present throughout to block GABA-mediated transmission.

Measurement of agonist-evoked depolarizations

In some experiments, agonist-evoked changes in the d.c. potential across slices were monitored using the technique described by Brown & Galvan (1979) as modified by Surtees & Collins (1985). In principle, extracellular electrodes measure the potential difference across 500 μm thick slices; when an excitant drug is applied to one surface of the slice it will

depolarize neurones adjacent to that surface which will therefore become negative with respect to the other surface. The experimental procedure and method of drug application are described in detail elsewhere (Surtees & Collins, 1985; Collins & Surtees, 1986).

Release studies

The effect of catechol on the K^+-evoked release of endogenous aspartate, glutamate and GABA from small cubes of olfactory cortex tissue was also measured. The experimental procedures employed in preparing and perfusing the tissue fragments are described elsewhere (Collins *et al.*, 1981). Amino acids were estimated using a double label microdansylation assay system (Clark & Collins, 1976).

Results

Preliminary experiment

When catechol (0.5 to 2 mM) was applied to the pial surface of 5 olfactory cortex slices there was a concentration-dependent and partially reversible increase in the amplitudes of the N-, late N- and I-waves (Figure 1), suggesting that the drug potentiated both excitatory transmission at the LOT-pyramidal cell synapse and GABA-mediated pre- and postsynaptic inhibition (see Methods section). The following experiments were designed to identify the sites and

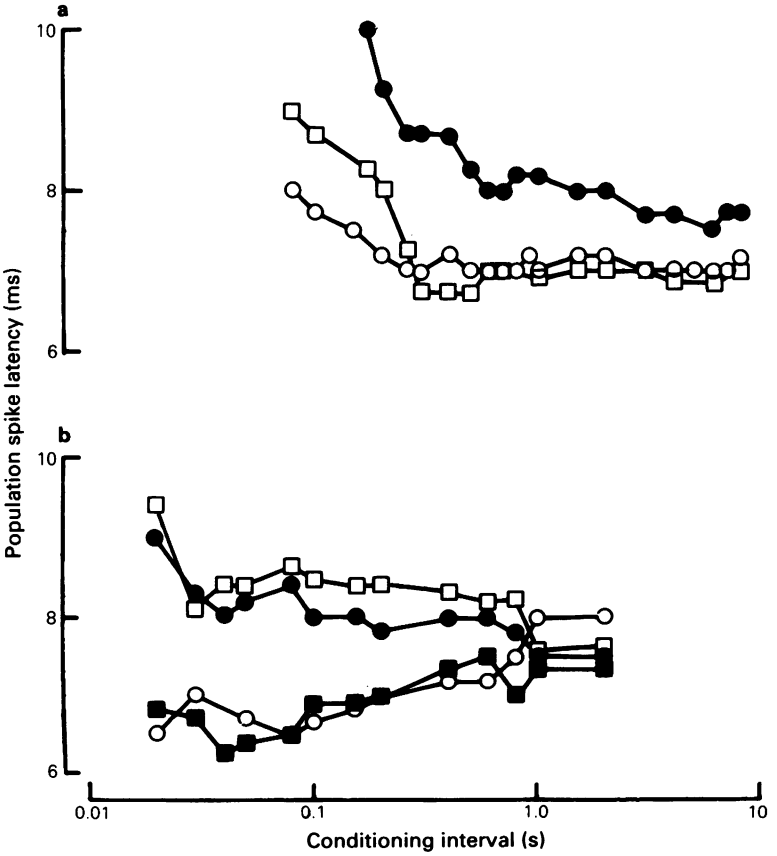

Figure 3 Effect of catechol on postsynaptic inhibition in slices preincubated and perfused with drug-free solution (a) or 25 μM picrotoxin (b). The latency of the population spike evoked by the test stimulus plotted against the conditioning interval are shown. (a) Control curve (○); plus catechol (1 mM) (●); recovery after perfusion with drug-free solution for 45 min (□). Note that catechol shifted the curve upward and to the right, indicating an increase in inhibition. (b) Control curve (○); plus catechol (1 mM) (●); plus catechol (1 mM) in the presence of an increased picrotoxin concentration of 75 μM (□): recovery after perfusion with 25 μM picrotoxin for 45 min (■). Note that catechol increased postsynaptic inhibition even in the presence of high concentrations of picrotoxin.

mechanism(s) by which catechol produced these effects.

Field potential experiments

In olfactory cortex slices preincubated and perfused with picrotoxin (25 μM) to abolish GABA-mediated transmission (Collins *et al.*, 1982), catechol (0.005 to 1 mM) produced a concentration-dependent and partially reversible increase in the amplitudes of the N'a'-, N'b'- and P-waves (Figure 2). In 2 out of 5 slices, this action was accompanied by an increase in the number and amplitudes of the population spikes (see Figure 2a). However, in the other preparations there was a decrease in population spike amplitude and an increase in latency, effects characteristic of an inhibitory drug action.

The possible inhibitory effects of catechol were investigated in a series of conditioning experiments (see Methods). In slices superfused in the absence of picrotoxin, at short conditioning intervals there was complete suppression of the population spike evoked by the test stimulus. As the interval increased, a population spike of reduced amplitude (not shown) and increased latency was evoked by the test stimulus (Figure 3a). Eventually, at longer conditioning intervals the amplitude and latency of the test-evoked population spike were the same as those evoked by the conditioning stimulus. Catechol (1 mM) increased the conditioning interval over which the test stimulus failed to evoke any population spike (in Figure 3a from approximately 80 to 1000 ms) and even at conditioning intervals of 10 s, there was an increase in latency of the test-evoked population spike.

In 6 slices perfused with a solution containing 25 μM picrotoxin, the test stimulus evoked a population spike at very short conditioning intervals (see Figure 3b for an example). Under these circumstances, catechol (1 mM) caused a marked increase in population spike latency evoked by the test stimulus up to conditioning intervals of approximately 1.0 s. Increasing the concentration of picrotoxin to 75 μM did not antagonize this effect of catechol. The concentration-dependency of the phenomenon is illustrated in Figure 4. In these

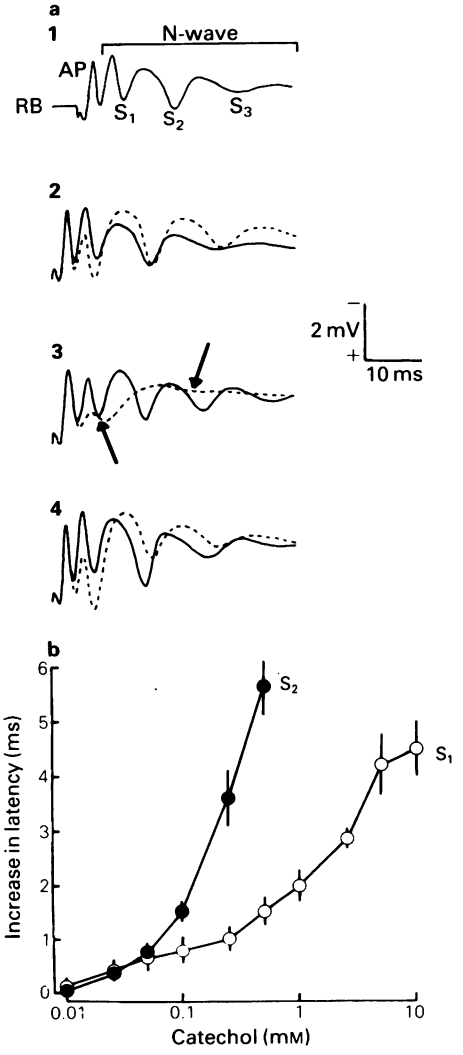

Figure 4 Effect of catechol on population spike latency in slices preincubated and perfused with picrotoxin (25 μM). (a1–4) are records from a single slice and have been retouched. (a1) Surface field potentials evoked on supramaximal lateral olfactory tract stimulation showing the recording baseline (RB), tract action potential (AP) and 3 population spikes S_1, S_2, S_3) superimposed on the N-wave. (a2) Superimposed field potentials evoked on stimulating twice, the second test stimulus (broken line) being presented 100 ms after the first conditioning pulse. Note that when compared with the field potential evoked by the conditioning stimulus, S_1 of the test stimulus was slightly decreased and S_2 increased in latency. (a3) Twin stimulation as in (a2) but following application of 1 mM catechol for 5 min. There was a marked increase in S_1 and S_2 latencies (see arrows) compared with those evoked by the conditioning stimulus (S_2 barely visible, S_3 disappeared). (a4) Recovery after perfusion with catechol-free solution for 30 min. (b) Cumulative dose-response curve for catechol. The increase in latency of the first (S_1) and second (S_2) population spikes evoked by the test stimulus with a conditioning interval of 100 ms is shown. Each drug concentration was applied for 10 min before recording evoked activity. Each point is the mean of 4 values and the s.e.mean is indicated by the vertical lines. At concentrations of catechol greater than 0.5 mM, S_2 disappeared.

experiments, which were carried out using 4 slices, a fixed conditioning interval of 0.1 s was used. Catechol (0.1 to 10 mM) caused a concentration-dependent increase in the population spike latency evoked by the test stimulus: longer latency population spikes were more sensitive to catechol than those evoked at short latencies (Figure 4).

Input-output study

In a series of 5 experiments, catechol (0.25 and 0.5 mM) had no effect on the relationship between stimulus voltage and tract action potential amplitudes (not shown). However, for a given action potential amplitude, catechol increased the amplitude of the N-wave (Figure 5a) and for a given N-wave amplitude, catechol increased the corresponding latency of the population spike (Figure 5b).

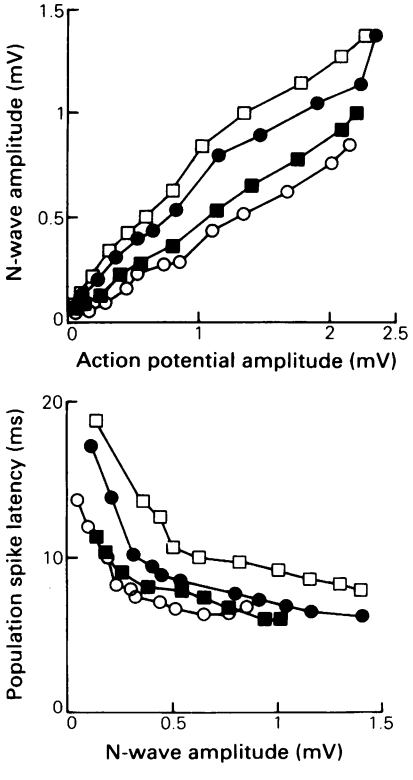

Figure 5 Input-output study for catechol in a single slice preincubated and superfused with picrotoxin (25 μM). The preparation was stimulated with a range of voltages (see Methods section) and graphs plotted of the stimulus voltage versus the amplitude of the tract action potential (not shown), action potential versus N-wave (a) and N-wave versus population spike latency (b). Control (○). The study was repeated in the presence of 0.25 mM (●) and 0.5 mM (□) catechol and finally after perfusion with drug-free solution for 30 min (■). In this experiment, the amplitude of the N-wave was measured at a latency of 4 ms.

Effect of catechol (1 mM) on agonist-evoked depolarizations

When submaximal doses of L-aspartate, L-glutamate and GABA are applied to the pial surface of olfactory cortex slices they depolarize surface neurones (Surtees & Collins, 1985). Application of catechol alone did not depolarize either control slices or slices perfused with picrotoxin (25 μM), neither did it affect responses to submaximal concentrations of L-aspartate, L-glutamate or GABA (6 slices, not shown).

Release experiments

Superfusion of small slices of rat olfactory cortex with 50 mM K^+ evokes a Ca^{2+}-dependent release of endogenous glutamate, aspartate and GABA (Collins *et al.*, 1981). In the presence of catechol (1 mM), there was a significant increase in the K^+-evoked release of aspartate whilst that of glutamate and GABA was unchanged (Table 1). Catechol alone did not increase amino acid release and the increase in K^+-evoked aspartate release was not prevented by tetrodotoxin present at a concentration (0.5 μM) sufficient to abolish synaptic transmission (Surtees & Collins, 1985).

Discussion

When catechol was applied to slices of rat olfactory cortex there was a concentration-dependent increase in the amplitudes of all evoked field potentials (Figures 1 and 2), indicative of a potentiation of both excitatory and inhibitory synaptic transmission. The mechanisms by which catechol produced such actions might include: (1) a non-selective increase in neuronal excitability; (2) potentiation of transmission at the LOT-superficial pyramidal cell synapse, thereby augmenting the excitatory drive of the preparation; (3) separate and direct actions on excitatory and inhibitory transmission.

The present results provide no evidence that catechol increases neuronal excitability. Not only did catechol fail to affect the relationship between the stimulus voltage and the amplitude of the tract action potential, but also both in control and picrotoxin-treated slices, the drug failed to increase responses evoked by submaximal concentrations of the neurotransmitter candidates L-aspartate and L-glutamate. Similarly, it did not affect responses evoked by GABA. It is possible that catechol might increase terminal excitability but the results of the

release experiments suggest that any such action is confined to the terminals of the LOT (see below).

In contrast, the ability of catechol to increase the N-wave amplitude (Figure 1) suggests a potentiation of excitatory transmission at the LOT-superficial pyramidal cell synapse. The input-output study (Figure 5) demonstrates that for a given LOT action potential, catechol induced an increase in the amplitude of the N-wave. Others (Voskuyl & ter Keurs, 1978; 1981) have interpreted similar effects to reflect increased neurotransmitter release from the tract terminals. Much evidence is consistent with aspartate being one of the transmitters of the LOT (see, for example, Collins, 1979; 1984; Collins & Probett, 1981; Collins *et al.*, 1981). In the present study, although catechol alone did not increase aspartate release, it selectively and significantly increased the K^+-evoked release of aspartate, an effect which was insensitive to tetrodotoxin (Table 1). Thus in spite of aspartate being a transmitter candidate at additional sites in the olfactory cortex (Collins *et al.*, 1981), these findings are consistent with catechol potentiating excitatory transmission at the LOT-pyramidal cell synapse by a direct action on the tract terminals somehow causing an increase in evoked release of the neurotransmitter.

By increasing the excitatory drive, catechol should also potentiate polysynaptically-evoked excitation and inhibition in the olfactory cortex. The present results confirm this prediction. For example, in picrotoxin-treated preparations, catechol enhanced the amplitudes of the N'b'- and P-waves (Figure 2) and in some slices, the numbers and amplitudes of the population spikes were also increased. In conditioning experiments, catechol invariably increased recurrent postsynaptic inhibition (Figure 3). The duration of this effect was limited to approximately 1 s (Figure 3b) suggesting a synaptic origin rather than a direct depressant action of catechol on pyramidal cell membranes. Of some interest was the observation that at least a portion of this increase in inhibition was picrotoxin insensitive (Figures 3b and 5), implying that either the effect was not GABA-mediated or that receptors of the $GABA_B$ category (Collins *et al.*, 1981) were involved.

In conclusion, the results show that catechol potentiates transmission at the LOT-superficial pyramidal cell synapse, possibly by increasing evoked transmitter (aspartate) release. The consequent increased excitatory drive to the preparation would explain the concomitant potentiation of transmission at other sites, but the results do not exclude the possibility of separate and direct actions of catechol on polysynaptically-evoked excitation and inhibition. The relationship between the actions of catechol described in this paper and its well known convulsant properties is unknown. However, it is clear that the interaction of catechol with central cholinergic transmission (Angel *et al.*, 1977; Angel & Dewhurst, 1978) is only one of a number of its sites of action.

Table 1 K^+-evoked release of endogenous amino acids from slices of olfactory cortex

Drugs	*Amino acid* *Aspartate*	*Glutamate*	*GABA*
50 mM K^+ (control)	28.6 ± 4.4 (5)	128 ± 23 (6)	81.3 ± 9.9 (6)
50 mM K^+ plus 1 mM catechol	140 ± 7.8[a] (5)	182 ± 47 (6)	110 ± 20 (6)
50 mM K^+ plus 1 mM catechol plus 0.5 μM tetrodotoxin	121 ± 25[b] (4)	119 ± 15 (6)	77.8 ± 9.4 (6)
1 mM Catechol	2.7 ± 4.7[b] (5)	8.9 ± 12[a] (6)	1.1 ± 10[a] (6)

Each value is a mean release of amino acid (pmol mg^{-1} wet $weight^{-1}$) ± s.e.mean, the number of observations being shown in parentheses.
Significant difference (unpaired Student's *t* test) when compared with control [a]$P < 0.001$; [b]$P < 0.01$.

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