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Blockade of a Resting Potassium Channel and Modulation of Synaptic Transmission by Ecstasy in the Hippocampus

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ABSTRACT

3,4-Methylenedioxymethamphetamine (ecstasy, MDMA) and related amphetamines are CNS stimulants that have euphoric, memory-enhancing and neurotoxic properties. When applied in pharmacological doses to cultured rat hippocampal neurons, ecstasy reduced the conductance of a 50-pS barium-sensitive resting K^+ channel and increased neuronal excitability. Ecstasy enhanced synaptic strength by irreversibly increasing the amplitude of excitatory autaptic currents and the frequency of spontaneous excitatory postsynaptic currents. Ecstasy did not alter the amplitude of inhibitory autaptic currents or the frequency of spontaneous inhibitory postsynaptic currents but reversibly prolonged the decay phase of inhibitory autaptic currents and spontaneous inhibitory postsynaptic currents. These results suggest that K^+ channel blockade and the effects on synaptic transmission may contribute to the pharmacological effects of ecstasy and other amphetamines.

Amphetamines are an important class of CNS stimulants widely used therapeutically (Weiner, 1985) and as drugs of abuse (Peroutka, 1987). The pharmacological properties of amphetamines include locomotor stimulation in lobster, euphoria (Weiner, 1985; Seiden *et al.*, 1993), enhancement of memory (Delanoy *et al.*, 1983; Gold *et al.*, 1984; Holdefer and Jensen, 1987; Strupp *et al.*, 1991; Janak and Martinez, 1992; Soetens *et al.*, 1993) and neurotoxicity (Ricaurte *et al.*, 1985; Sonsalla *et al.*, 1989; Farfel *et al.*, 1992) in higher animals. These properties are thought to result from the inhibition of monoamine reuptake at nerve terminals (Weiner, 1985; Seiden *et al.*, 1993). For instance, ecstasy, a ring-substituted amphetamine, potently blocks 5-HT reuptake (Rudnick and Wall, 1992) and produces marked euphoria (Peroutka, 1987). However, it is unclear whether the properties of these drugs arise solely from the inhibition of monoamine reuptake. Recently a number of reports have demonstrated that both the locomotor stimulation (Karler *et al.*, 1994) and the neurotoxicity (Sonsalla *et al.*, 1989; Farfel *et al.*, 1992) associated with amphetamines can be blocked by glutamate receptor antagonists. In addition, tricyclic antidepressants are known also to inhibit 5-HT reuptake but have different psychoactive properties from ecstasy (Baldessarini, 1985). Finally, some ecstasy analogs are non-neurotoxic despite being potent reuptake inhibitors (Rudnick and Wall, 1993). These observations indicate that amphetamines may express some of their effects independently of 5-HT reuptake, possibly by modulating EAA transmission. Indeed, amphetamine has been reported to increase the release of glutamate in rat central neurons *in vivo* (Moroni *et al.*, 1981; Mora and Porras, 1993) and in the lobster neuromuscular junction (Turkanis *et al.*, 1988). A potentiation of EAA transmission by amphetamines may account for their neurotoxic and locomotor stimulatory effects and is consistent with the observation that they can enhance memory formation. However, no currently known mechanism can explain an amphetamine-induced increase in glutamate release. The present experiments were therefore conducted to investigate the electrophysiological effects of ecstasy in cultured hippocampal neurons.

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Materials and Methods

Hippocampal neurons in culture for 1 to 2 weeks (Premkumar *et al.*, 1990) were studied using patch-clamp techniques (Hamill *et al.*, 1981). The bath solution contained (in mM) NaCl, 124; KCl, 2.5 or 10; $CaCl_2$, 2; $NaHCO_3$, 26; NaH_2PO_4, 2.5 and was equilibrated with a gas mixture of 95% CO_2 and 5% O_2 (pH 7.2–7.3). Patch electrodes were made from thick-walled borosilicate glass tubes (Clark Electromedical) and filled with a solution that contained, unless otherwise indicated (in mM), K-gluconate, 140; $MgCl_2$, 1; HEPES, 10; pH adjusted to 7.3 with KOH. Electrodes had a resistance of 5 to 15 MΩ. Currents were recorded with a current-to-voltage converter (Axopatch 200), filtered at 2 kHz, digitized at 44 kHz (Sony-PCM) and stored on video tape. All experiments were performed at room temperature (22°C–28°C). Agar-bridge electrodes were used to avoid changes in the junction potential. The capacitative current was always canceled, and the series resistance compensation was set at

ABBREVIATIONS: MDMA, 3,4-methylenedioxymethamphetamine; IK_{rest}, a resting potassium conductance; K^+, potassium ion; Ba^{++}, barium ion; EPSCs, excitatory postsynaptic currents; IPSCs, inhibitory postsynaptic currents; EACs, excitatory autaptic currents; IACs, inhibitory autaptic currents; 5-HT, 5-hydroxytryptamine; EAA, excitatory amino acid; NMDA, N-methyl-D-aspartate; AMPA, α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid; GABA, γ-amino butyric acid.

80%–90%. The whole-cell data were digitized at 100 Hz, and every 10th point has been plotted. The single-channel and synaptic current data were filtered at 2 kHz and digitized at 5 kHz using an IBM-compatible-PC and were analyzed using the CHANNEL2 computer program written by Michael Smith. Experimental values are presented as mean ± S.E.M. Student's t test was used to estimate significance. Cells under voltage/current-clamp were perfused continuously with the control solution from a 300-μm barrel positioned about 100 to 200 μm from the cells, and the drugs were applied from another barrel moved into position with a hydraulic manipulator for the required period of time.

Hippocampal neurons, when grown individually on microislands without contact with neighboring cells, make synapses onto the same neuron, resulting in an autaptic cell (Segal, 1991; Bekkers and Stevens, 1991). These neurons are either excitatory or inhibitory. A 2-ms depolarizing pulse from the holding potential of −80 to 0 mV evoked either EACs or IACs. currents were isolated electrophysiologically, the composition of the solutions reversed the EACs close to 0 mV, whereas the IACs were reversed around −70 mV. The data were filtered at 2 kHz and digitized at 5 or 10 kHz, and every fifth point has been plotted. Spontaneous EPSCs were recorded at a holding potential of −80 mV (more negative than E_K) with 140 mM potassium gluconate in the pipette and sodium chloride in the bath. All spontaneous EPSCs were abolished when the cell was exposed to CNQX (20 μM) and APV (100 μM) or MK-801 (10 μM). The inhibitory currents were isolated and recorded at a holding potential of 0 mV with the same solutions as above and were blocked with 100 μM bicuculline. The spontaneous synaptic currents were partly analyzed using criteria described by Manabe *et al.*, (1992).

Drugs. Drugs used in this study were obtained from the following companies: ecstasy (Makor Chemical Co., Israel), APV, bicuculline methiodide D-amphetamine (Sigma Chemical Co., St. Louis, MO), Ephedrine sulfate (David Bull Laboratories, Australia), noradrenaline (Winthrop Laboratories, Australia), and CNQX, MK-801 (Research Biochemicals Inc., Natick, MA). Drugs were dissolved in external solution, and the required concentration was made from a stock before the experiment.

Results

Ecstasy blocks a resting K^+ conductance. Application of ecstasy (100 nM–200 μM) produced an inward current when the neurons were voltage clamped at −60 mV. The amplitude of the current became smaller at hyperpolarized membrane potentials, and the current reversed around −90 mV (see fig. 1, A and C). The current recorded at 0 mV with 200 μM ecstasy had a mean amplitude of 98.8 ± 7.7 pA (mean ± S.E.M, n = 44, range 28–256 pA). The inward current was associated with a decrease in membrane conductance (fig. 1B), which indicates that the inward current was due to a current relaxation. The inward current could be recorded only with potassium ions in the pipette solution and was not affected by whether it contained potassium gluconate or potassium chloride. Furthermore, changing the extracellular K^+ concentration from 2.5 mM to 10 mM shifted the reversal potential from −92.1 ± 0.4 mV to −51.1 ± 0.4 mV (n = 3) (fig. 1C); the shift is consistent for a potassium-selective channel with a P_{Na}/P_K ratio of 0.02/0.04. These observations indicate that the effect is due to a current relaxation produced by the closure of K^+ channels. The whole-cell currents recorded in response to increasing concentrations of ecstasy are shown in figure 2A. Normalized dose-response data obtained from four different experiments in which the ecstasy concentration was varied were fitted by a single site binding scheme with half-maximal response at

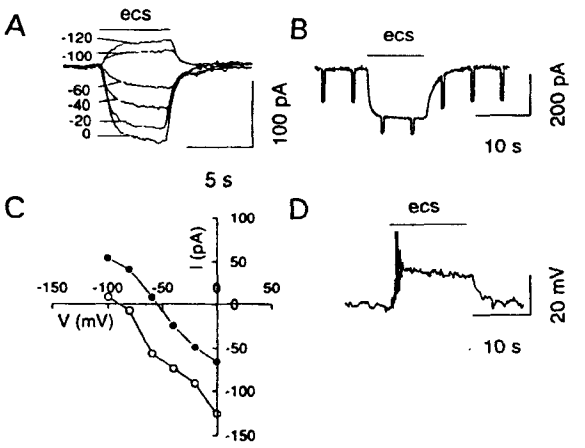

Fig. 1. Ecstasy blocks background potassium channels in cultured hippocampal neurons. A) Family of responses recorded by the application of 200 μM ecstasy. Numbers indicate holding potentials in millivolts. B) Response produced by ecstasy is due to the blockade of ion channels indicated by the decrease in the current recorded in response to a voltage step (20 mV, 200 ms, 0.2^{-1}). C) Current-voltage relationship of the response produced by ecstasy when the concentration of potassium ions in the extracellular solution was 2.5 mM (open circles) and 10 mM (closed circles). D) Ecstasy (200 μM) depolarized the membrane under current-clamp.

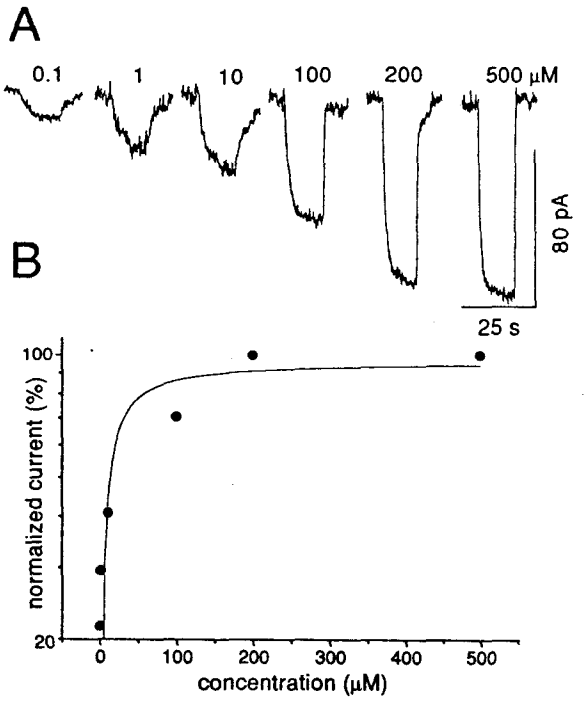

Fig. 2. Concentration-dependent response to ecstasy. A) Whole-cell currents elicited in response to application of increasing concentrations of ecstasy. The currents were recorded at a holding potential of 0 mV. B) Normalized data from four different experiments are plotted. The symbols represent the average responses, and the continuous line is the best fit to the equation $i_s = i_{max's}/1 + k_s/[S]$. The concentration for half-maximal response (k_s) is 11.9 μM.

11.8 μM (fig. 2B). Pharmacological concentrations for ecstasy in human plasma range from 0.5 to 30 μM (Dowling, 1990).

Ecstasy blocks a barium-sensitive IK_{rest}. Application of $BaCl_2$(1 mM), which is known to block IK_{rest} (Storm, 1990), also produced a current relaxation (128.1 ± 17.8 pA, n = 12, range 40–243 pA). To test whether ecstasy and barium chlo-

ride blocked the same potassium channels, we applied ecstasy (200 μM) in the presence of $BaCl_2$ (1 mM). The current relaxation produced by ecstasy and barium chloride was not additive, which suggests that the same types of resting potassium channels were blocked by ecstasy and barium chloride (n = 5, fig. 3A). The currents were recorded at a holding potential of 0 mV. The current relaxation produced by ecstasy is due neither to the blockade of ATP nor to Ca^{++}-sensitive K^+ channels, because inclusion of ATP (2 mM, n = 4) or of the calcium chelator 1,2-bis(2 aminophenoxy)ethane-N,N,N′,N′-tetraacetic acid (BAPTA, 20 mM, n = 4) in the pipette did not affect the response to ecstasy. Application of noradrenaline (500 μM, n = 6), which is known to close cyclic AMP-dependent K^+ channels in hippocampal slices (Nicoll, 1988), did not produce any response in these dialyzed cells (n = 6).

Single-channel currents were recorded using inside-out or outside-out membrane patches to identify the type of channel blocked by ecstasy and to clarify the mechanism of block. At a holding potential of 0 mV, several background channels were recorded. Application of ecstasy (50–200 μM, n = 9, 6 outside-out and 3 inside-out patches) selectively blocked a 50-pS potassium channel (46.7 ± 1.8 pS) by holding it in a partly open state that had a conductance of about 15 pS (15.9 ± 1.2 pS fig. 3B). $BaCl_2$ (1 mM) completely blocked the 50-pS channel (Fig. 3C). This current could not be recorded unless the pipette solutions contained potassium ions, and the single-channel currents reversed around −90 mV. Related amphetamines also blocked IK_{rest}, and we found that other sympathomimetic amines, D-amphetamine (n = 6) and ephedrine (n = 7), produced a blockade of IK_{rest} in whole-cell and single-channel recording. The relative potency was 1: 0.6: 0.3 for ecstasy, D-amphetamine and ephedrine, respectively. However, noradrenaline did not block IK_{rest} (n = 6; data not shown). Because ecstasy is an inhibitor of 5-HT reuptake, it is possible that the blockade of IK_{rest} is mediated by 5-HT, which has been shown to block K^+ conductance (Andrade and Nicoll, 1987; Belardetti and Siegelbaum, 1988). However, we (Premkumar and Gage, 1994) found, as have others (Uneyama *et al.*, 1993), that direct application of 5-HT to cultured hippocampal neurons in fact activated K^+ conductance.

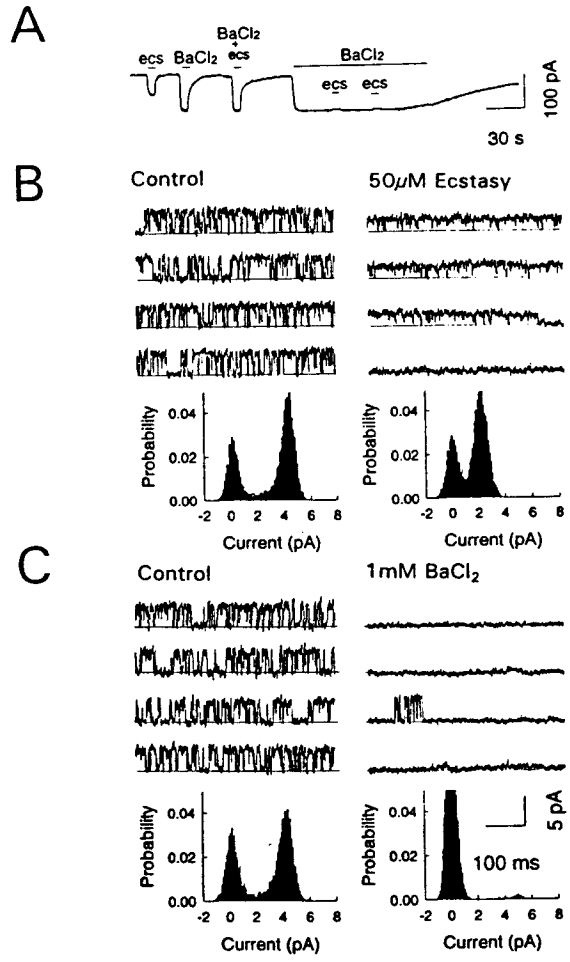

Fig. 3. Ecstasy blocks barium-sensitive potassium channels. A) Whole-cell current recorded at 0 mV shows that the current relaxation produced by ecstasy (200 μM) and that produced by $BaCl_2$ (1 mM) are not additive. B) Single-channel potassium currents recorded in an outside-out patch were held in a partly open state by ecstasy (50 μM). All point histograms that were constructed from 15-s data obtained before and after application of ecstasy show predominant peaks at 4.3 and 2.2 pA, respectively, C) $BaCl_2$ (1 mM) completely blocked the same potassium channel.

Ecstasy increases neuronal excitability. Blockade of IK_{rest} by ecstasy should enhance neuronal excitability, and to clarify this, we conducted experiments under current-clamp conditions. Ecstasy 50-μM and 200 μM depolarized the membrane by 5.3 ± 0.6 mV (n = 5) and 10.7 ± 3.4 mV (n = 3, fig. 1D), respectively. Ecstasy also increased action potential frequency without affecting the duration, but amplitude of the action potentials was reduced and appeared to be concentration-dependent. Voltage-dependent Na^+ and K^+ currents were marginally attenuated at lower concentrations (50 μM) but were significantly blocked at higher concentrations (200 μM). The sodium and potassium currents were activated by a voltage pulse from −120 mV to +20 mV. Ecstasy (50 μM) blocked the sodium and potassium currents 18.2% ± 3% and 11.2% ± 1.9%, respectively (n = 8), compared to 59% ± 9% and 48% ± 5.7%, respectively (n = 3), with 200 μM ecstasy.

Effect of ecstacy on synaptic transmission. During the course of these experiments, we observed a consistent increase in the frequency of the spontaneous synaptic currents. To determine whether ecstasy modulated synaptic transmission, we studied its effects on EACs and IACs recorded from cultured hippocampal neurons grown on microislands (Segal, 1991; Bekkers and Stevens, 1991). In five of eight excitatory cells, application of ecstasy (20–50 μM) produced a clear and irreversible increase in the amplitude of evoked EACs (29% ± 13%, range 5%–64%), and the increase was maintained after 5 to 15 min washout (53% ± 18%, range 12% to 89%, fig. 4A). No further increase was noted in cells from the same culture plates that had already been exposed to ecstasy. In contrast, in 12 of 12 inhibitory cells, ecstasy did not affect current amplitude but prolonged that decay of the current by 87% ± 8% (range 29% to 120%), an effect that was readily reversible (fig. 4B). Application of ecstasy (50–200 μM) induced up to a 4-fold increase in the frequency of spontaneous EPSCs (2.78 ± 0.34-fold, n = 7, fig. 3C) without affecting the frequency of spontaneous IPSCs (0.94 ± 0.25-fold, n = 7, $P <$ .005, Student's t-test). However, as with autaptic currents, ecstasy prolonged the decay phase of spontaneous IPSCs. The effects were not due to changes in cable properties, because the rise time (10%–90%) and the amplitude of the spontaneous synaptic currents were unaffected (fig. 4, D and E). To determine whether the effects were mediated by a block of IK_{rest}, we investigated the effects of Ba^{++} on evoked

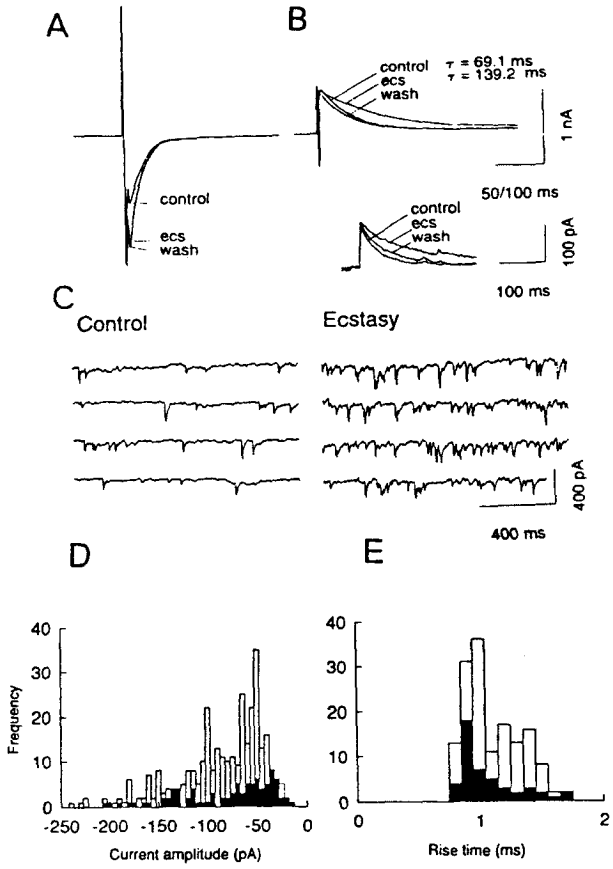

Fig. 4. Effect of ecstasy on synaptic transmission. A) Ecstasy (50 μM) irreversibly increased the amplitude of the EAC recorded at −80 mV. B) The amplitude of the IAC was not affected by ecstasy (50 μM), but the decay phase of the current was reversibly prolonged. The current was recorded at −40 mV. The autaptic currents were averages of five sweeps. Inset shows prolongation of the decay phase of spontaneous LPSCs. Traces were averages of 2 to 6 well-defined spontaneous currents recorded at 0 mV in the presence of TTX (500 nM). C) Spontaneous EPSCs recorded at a holding potential of −80 mV in the presence of TTX. B) After the application of 200 μM ecstasy, the frequency of spontaneous EPSCs increased from 8.3^{s-1} to 27^{s-1}. D) Histogram showing the amplitude distribution of spontaneous EPSCs before (filled bars) and after (open bars) the application of ecstasy. E) Histogram of rise time (10%–90% of the peak current) distribution of the spontaneous EPSCs before (filled bars) and after (open bars) application of ecstasy.

and spontaneous currents. Ba^{++} produced a response similar to that produced by ecstasy in that it prolonged the decay phase of IACs (n = 4) and increased the amplitude of EACs (n = 5), which suggests that these effects do result from blockade of IK_{rest}. However, unlike the response to ecstasy, the increase in EAC amplitude induced by Ba^{++} was reversible, and Ba^{++} failed to increase spontaneous EPSC frequency. Whole-cell currents recorded (with CsCl in the pipette) in response to NMDA (n = 9) and AMPA (n = 11) were unaffected by ecstasy (50–100 μM), which suggests that the potentiation of EAC was not postsynaptic. Whole-cell responses to GABA (n = 6) were unaffected by ecstasy, so a direct effect on the GABA receptor channel is unlikely.

Discussion

Ecstasy in pharmacological doses blocked a barium-sensitive resting potassium channel, depolarized the membrane and increased action potential frequency. In addition, a blockade of IK_{rest} by itself should increase neuronal excitability by increasing the input resistance and making the cells more electrotonically compact. Single-channel recordings indicated that ecstasy specifically blocked a 50-pS barium-sensitive resting potassium channel by reducing the channel conductance without affecting the open probability. The blockade by Ba^{++}, in contrast, appeared to be due to total block of the channel. The blockade by ecstacy was effective in channels recorded in both inside-out and outside-out patches, which suggests that ecstasy directly interacts with the channel pore. At higher concentration, ecstasy also blocked voltage-activated sodium and potassium currents. Inhibition of the Na^+ current may appear paradoxical but is consistent with the mild anesthetic action produced by amphetamines (Weiner, 1985) at pharmacological doses. Cocaine, which is a central stimulant and a drug of abuse, also blocks the voltage-dependent sodium channels (Crumb and Clarkson, 1990).

The effects of ecstasy on synaptic transmission are profound and complex. These effects are different in excitatory and inhibitory synapses. The amplitude of EACs increased irreversibly, and the frequency of spontaneous EPSCs recorded in the presence of TTX also increased. In contrast, both the amplitude of IACs and the frequency of spontaneous IPSCs were unchanged, and the decay phase of these currents was reversibly prolonged. The effects on inhibitory transmission are likely to result from the blockade of IK_{rest} because ecstasy and Ba^{++} produced similar responses. However, Ba^{++} failed to produce a response identical to that produced by ecstasy in the excitatory synapse. One interpretation of this result is that Ba^{++} may have an additional effect of antagonizing Ca^{++}-dependent changes in transmitter release (for example, phosphorylation/dephosphorylation), and this may mask the effects of depolarization. Another possibility is that ecstasy has a separate and as yet unknown action on stimulating transmitter release. Whatever the case, it is an interesting observation that ecstasy has different effects at excitatory and inhibitory synapses. A postsynaptic locus of action is ruled out by the observation that whole-cell currents in response to the application of NMDA, AMPA or GABA were unaffected. Thus in the excitatory synapse, ecstasy appears to act presynaptically by blocking resting potassium channels and thus causing depolarization of the presynaptic terminal, which in turn may facilitate transmitter release. In contrast, the prolongation of evoked and spontaneous inhibitory currents indicates a postsynaptic locus. But the whole-cell current in response to GABA was unaffected, so a direct effect on the GABA receptor channel is unlikely. One possibility is that ecstasy may slow reuptake of GABA from the cleft, either directly or through an IK_{rest}-dependent mechanism. It is also possible that ecstacy facilitates rebinding of GABA, as shown with benzodiazipines (Study and Barker, 1981). Alternatively, although less likely, the open time of GABA receptor channels may be prolonged by depolarization in the dendrites, which is ineffectively voltage-clamped.

Significance of K^+ channel blockade. Up and down-regulation of K^+ channels have been previously shown to influence neuronal excitability and synaptic transmission. In *Aplysia,* closure of K^+ channels by 5-HT (Belardetti and Siegelbaum, 1988) causes excitation and presynaptic facili-

tation, whereas in the hippocampus, K^+ channel blockers produce a form of long-term potentiation (LTP_K) attributed to enhanced presynaptic glutamate release (Aniksztejn and Ben-Ari, 1991). Stimulation of metabotropic glutamate receptors also blocks K^+ channels (Charpak *et al.*, 1990) and produces LTP (Bortolotto and Collingridge, 1993; O'Connor *et al.*, 1994). Blockade of IK_{rest} and enhancement of synaptic strength by ecstasy may contribute to the locomotor stimulatory and the memory-enhancing properties of amphetamines. In addition, excessive release of glutamate, which is neurotoxic (Ricaurte *et al.*, 1985), may underlie amphetamine neurotoxicity; this is consistent with the neuroprotection afforded by glutamate receptor antagonists. Conversely, up-regulation (opening) of K^+ channels is neuroprotective (Heurteaux *et al.*, 1993) and has been shown to underlie actions of certain general anesthetics (Franks and Lieb, 1988) and antihistamines (Reiner and Kamondi, 1994). In conclusion, our results demonstrate a novel action of ecstacy that may account for some of the pharmacological properties of amphetamines and may prove useful in developing treatments for their abuse and in employing them as tools for understanding synaptic release processes.

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