Dopamine Induces a Slow Afterdepolarization in Lateral Amygdala Neurons

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Yamamoto R, Ueta Y, Kato N. Dopamine induces a slow afterdepolarization in lateral amygdala neurons. J Neurophysiol 98: 984–992, 2007. First published June 6, 2007; doi:10.1152/jn.00204.2007. The amygdala and dopaminergic innervation thereunto are considered to cooperatively regulate emotional states and behaviors. The present experiments examined effects of dopamine on lateral amygdala (LA) neuron excitability by whole cell recordings. Bath application of dopamine induced slow afterdepolarization (sADP). This sADP lasted for 3–5 s, and its magnitude varied in a concentration-dependent manner. Co-application of the D1 receptor antagonist SKF83566 reduced its amplitude. The D1 receptor agonist SKF38393, applied alone, induced sADP of a smaller amplitude. Induction of the full sADP required 5-HT1A and noradrenalin α1 receptor activation as well. D2 receptor activation or blockade did not affect sADP induction. The calcium channel blocker cadmium or intracellular calcium chelator bis-(o-aminophenoxy)-N,N,N′,N′-tetraacetic acid (BAPTA) blocked induction of the sADP, which was suggested to be triggered by calcium influx. Under voltage clamp, membrane conductance decreased at the peak of sADP current (I_{sADP}). I_{sADP} was suppressed by cesium included in pipettes. The I–V curve of the net I_{sADP} was shifted as the external concentration of potassium was raised, and the reversal potential was identical to that of potassium, suggesting that dopamine decreases potassium conductance to induce the sADP. The present sADP may serve as a positive-feedback regulator of excitability in LA neurons.

INTRODUCTION

The amygdala plays significant roles in affective learning (Fenselov and Gale 2003; LeDoux 2000; Maren and Quirk 2004). A moderate dopaminergic innervation onto the amygdala has been well known (Asan 1997, 1998). The cooperative activity of amygdala neurons and dopaminergic input thereunto is important to acquire fear memory and to express affective responses appropriately. This is revealed by studies done with systemic administration of dopamine (DA) receptor antagonists (Rosenkrantz and Grace 2002) and their direct injection into the lateral amygdala (Greba and Kokkinidis 2000; Greba et al. 2001; Lamont and Kokkinidis 1998; Nader and Ledoux 1999). It was also reported that, in affective learning and memory retrieval, the concentration of dopamine in the lateral amygdala (LA) is raised (Harmer and Phillips 1999; Inglis and Moghaddam 1999; Yokoyama et al. 2005). These results suggest pivotal roles played by dopamine in regulating the neuronal activity in the amygdala. In fact, it has been reported that dopamine enhances excitatory transmission (Pickel et al. 2006), suppresses inhibitory transmission (Bissiere et al. 2003; Rosenkrantz and Grace 1999, 2001), and alters the activity of interneurons (Kroner et al. 2005; Marowsky et al. 2005).

With all these reports, direct effects of dopamine on the LA principal neurons have not been elucidated extensively. Although a recent report has shown that dopamine enhances membrane excitability of LA neurons by inhibiting D-type potassium current (Kroner et al. 2005), it would be unlikely that this provides the sole mechanism by which dopamine regulates excitability of LA principal neurons given that effects of dopamine on various other ion channels have been reported in the cortex (Gorelova and Yang 2000; Seamans and Yang 2004; Yang and Seamans 1996; Young and Yang 2004).

Spike afterpotentials, consisting of afterhyperpolarization and -depolarization (AHP and ADP), result from spike-induced changes in ion channel conductance (Constanti and Bagetta 1991; Faber and Sah 2002; Madison and Nicoll 1984; Schwindt et al. 1988). Typically, AHP represents a spike-induced opening of specific classes of potassium channels (Sah 1996). Making use of AHP as the index with which to assess neocortex pyramidal cell excitability, we have recently investigated cholinergically operated feedback regulation of spike firing (Yamamoto et al. 2000, 2002a,b), and then have pinned down the channel involved (Yamada et al. 2004). Spike afterpotentials thus seem to be useful for initial survey of neuro-modulator-based regulation of neuron excitability. We attempted to apply this strategy for studying dopamine-operated regulation of amygdala neuron excitability in the present study, and started assessing dopamine effects on spike afterpotentials in these neurons. Although we have not yet specified the channel involved, several characteristics of dopamine-operated ADP in amygdala principal neurons were clarified in the present report.

METHODS

All experiments were performed in accordance with the guiding principle of the Physiological Society of Japan and with the approval of the Animal Care Committee of Kanazawa Medical University.

Slice preparation

Brain slices containing the lateral nucleus of the amygdala were prepared from Wistar rats (16–20 days old). Rats were decapitated under ether anaesthesia. The brain was removed and sectioned with a microslicer at 300 μm (Pro7; Dosaka, Kyoto, Japan) in ice-cold artificial cerebrospinal fluid (ACSF) composed (in mM) of 234 NaCl, 1.25 NaH2PO4, 10 MgSO4, 2.5 CaCl2, 26 NaHCO3, and 20 glucose. Slices were kept at 30°C for 15 min and then at room temperature for ≥45 min before experiments. Recordings were done in normal ACSF composed (in mM) of 124 NaCl, 3.0 KCl, 2.5 CaCl2, 2.0 MgSO4, 1.3 NaH2PO4, 26 NaHCO3, and 20 glucose. Also,

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ascorbate (0.02 mM) was used to prevent dopaminergic agents from oxidation in all experiments. The slices were placed in a recording chamber on the stage of an upright microscope (BX51WI, Olympus) with a ×60 water-immersion objective (LUMPlanFIIR). Recordings were made from slices submerged in normal ACSF at 30°C. In experiments in which cadmium was added to the perfusate to block voltage-gated calcium channels, MgSO₄ was replaced with MgCl₂ and NaH₂PO₄ was omitted. All solutions were aerated with 95% O₂-5% CO₂.

**Electrophysiology**

Whole cell recordings were made from the soma of visually identified pyramidal-like neurons located in the nucleus of the LA. Recordings were continued only in cells that had resting membrane potential below −55 mV. In current- and voltage-clamp recordings, glass pipette electrodes were filled with a solution containing (in mM) 140 K-glucuronate, 10 KCl, 2 MgCl₂, 2 Na₂-ATP, 0.4 Na₂-GTP, 0.2 EGTA, and 10 HEPES, with pH adjusted to 7.2–7.3 with KOH. In some current-clamp recordings, 10 mM BAPTA was added in the pipette solution to chelate intracellular free calcium. In some voltage-clamp recordings, glass pipettes were filled with a solution containing (in mM) 120 Cs-methanesulfonate, 10 CsCl, 2 MgCl₂, 2 Na-ATP, 0.4 Na₂-GTP, 0.2 EGTA, 10 HEPES, 10 TEA-Cl, and 5 QX314-Cl, with pH adjusted to 7.2–7.3 by adding CsOH. Liquid junction potentials of the K-glucuronate-based internal solution and Cs-methanesulfonate-based internal solution were about 10 and 5 mV, respectively. These potentials were not corrected. To induce slow ADP (sADP) in current-clamp mode, we used current injection (200 pA, 500 ms) through the patch electrode. To induce sADP current (IₛADP) in voltage-clamp mode, we used various voltage steps (for 500 ms, to 0 mV from the holding potentials of −40, −50, −60, −70, and −80 mV). To quantify the amplitude of sADP or IₛADP, we calculated integration of sADP from 300 ms for a 5-s period after the action potential of A, B, and P. Dopamine induced sADP

Principal neurons in the LA responded to a depolarizing current injection (200 pA, 500 ms), exhibiting a burst of spikes followed by an AHP (Fig. 1A, control). With bath application of dopamine (50 μM), this AHP was eliminated and instead a sADP was induced (Fig. 1A, dopamine). The sADP lasted for >5 s. To quantify the amplitude of sADP, we calculated integration of sADP from 300 ms for a 5-s period after the termination of current injection. We refer to this integration as the area sADP. The area sADP was decreased from −4.00 ± 1.58 to 15.70 ± 4.49 mV·S (n = 7, P < 0.005) within 3–5 min by bath application of dopamine and was decreased to 5.70 ± 3.09 mV·S by washing out dopamine (Fig. 1A, washout, and B). This sADP was induced in a concentration-dependent manner (Fig. 1C). The area sADPs induced by dopamine (1, 5, 10, and 50 μM) were 0.10 ± 0.76 mV·S (n = 7), 2.64 ± 1.15 mV·S (n = 12), 8.57 ± 2.20 mV·S (n = 10), and 17.08 ± 2.50 mV·S (n = 13), respectively. With bath application of dopamine, principal neurons showed a small membrane depolarization in agreement with previous reports (Kroner et al. 2005; Shi et al. 1997). Hereafter we use dopamine at the concentration of 50 μM.

**Dopamine induced sADP current**

Recordings were then performed in the voltage-clamp mode. An AHP current (I_AHP) was induced in principal neurons in the LA by a voltage step (+50 mV for 500 ms from the holding potential of −50 mV; Fig. 1A, control). This is consistent with a feature of the principal neurons in the LA previously reported (Faber and Sah 2002). With bath application of dopamine (50 μM), this I_AHP was replaced by a sADP current (IₛADP; Fig. 1D, dopamine). We calculated the area IₛADP by integrating IₛADP for a 5-s period starting from 300 ms after the termination of a voltage step. The area IₛADP was initially positive and became negative within 2–3 min after bath application of dopamine (50 μM; Fig. 1E; from 35.21 ± 19.24 to −52.09 ± 6.08 pA·S; n = 8, P < 0.001). The present findings obtained under the voltage- and current-clamp modes agree with each other.

**D1 but not D2 receptors are involved in sADP**

To determine which group of dopamine receptors was involved in generating this sADP, we examined effects of dopaminergic agents on this sADP. When a D1-like receptor agonist (SKF83939, 30 μM) was bath-applied, the area sADP was increased within 4–6 min (Fig. 2, A and C; from −1.13 ± 1.04 to 7.02 ± 1.99 mV·S; n = 6, P < 0.001). However, the amplitude of area sADP induced by SKF83939 was smaller than that induced by dopamine. We tested another selective D1-like receptor agonist SKF81297. SKF81297 (20 μM) failed to induce sADP and only reduced the AHP (from −3.78 ±
noradrenalin and that sADPs were induced by activating 2006; Cornil et al. 2002; Malenka and Nicoll 1986; Wood-

More than one classes of monoamine receptors is involved in this sADP

We observed that selective D1 receptor agonists induced only a small sADP. It has been reported that dopamine activates other monoamine receptors (Bhattacharyya et al. 2006; Cornil et al. 2002; Malenka and Nicoll 1986; Woodward et al. 1992) and that sADPs were induced by activating noradrenalin α1 receptors or 5-HT2 receptors in other structures (Araneda and Andrade 1991; Spain 1994; Zhang andArsenault 2005). To test the possibility that the present DA-induced sADP may result from activating these mono-

Calcium influx triggered sADP

Similar sADPs induced by stimulation of muscarinic acetylcholine receptors or metabotropic glutamate receptors were reported in layer V neocortex neurons (Greene et al. 1994; Haj-Dahmene and Andrade 1998), layer II–III olfactory cortex neurons (Constanti et al.1993) and hippocampal CA1 pyramidal neurons (Fraser and MacVicar 1996). All these studies unanimously revealed that sADP is triggered by calcium influx. We therefore assumed that the present sADP induced by dopamine in LA neurons was also triggered by calcium influx. First, to check whether action potentials are necessary for the sADP or not, we used TTX (0.5 μM) to block sodium channels. Even in the presence of TTX, DA-induced sADP was observed (Fig. 3, A and D; from –2.70 ± 1.22 to 20.47 ± 5.64 mV·S, n = 6, P < 0.005). Next we tested effects of calcium channel blockade on the sADP. After bath application of dopamine, the sADP

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polarization (sADP). A, left: response of a lateral amygdala neuron to current injection (200 pA, 500 ms) under control condition (control). A, middle: after bath application of dopamine (50 μM), sADP was induced (dopamine). A, right: after dopamine washout, the amplitude of sADP was decreased (washout). B: time course of the dopamine effects on the area sADP. In this and follow-

1.17 to 0.35 ± 1.23 mV·S, n = 4). Bath application of a D2-like receptor agonist (quinpirole, 10 μM) failed to induce sADP (Fig. 2, B and C; from –3.35 ± 1.37 to –1.12 ± 1.40 mV·S, n = 6). Next we tested effects of antagonists of D1- and D2-like receptors. Bath application of a D1-like receptor antagonist (SKF83566, 10 μM) reduced the amplitude of sADP induced by dopamine (50 μM; Fig. 2, D and F; from –1.22 ± 1.08 to 4.89 ± 2.03 mV·S, n = 4). The area sADP induced in the presence of SKF83566 was significantly smaller than that induced without SKF83566 (Fig. 2F; 4.89 ± 2.03 vs. 17.08 ± 2.50 mV·S, P < 0.002). On the other hand, even in the presence of a D2-like receptor antagonist (sulpiride, 10 μM), bath application of dopamine (50 μM) induced the full sADP (Fig. 2, E and F; from –3.80 ± 1.58 to 17.50 ± 4.07 mV·S, n = 6, P < 0.005). These results indicate that induction of the present dopamine (DA)-induced sADP requires activation of D1-like, but not D2-like, receptors and that even activation of D1-like receptors still fails to induce the full DA-induced sADP, suggesting that dopamine may activate receptors other than those for dopamine.

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was induced within 3-5 min. Bath application of the voltage-dependent calcium channel (VDCC) blocker cadmium (250 \( \mu \)M) abolished sADP induced by dopamine (Fig. 3, B and D; control, \(-2.31 \pm 1.27 \text{ mV} \cdot \text{S} \); dopamine, \(19.10 \pm 3.69 \text{ mV} \cdot \text{S} \); cadmium, \(2.54 \pm 3.53 \text{ mV} \cdot \text{S} \); \( n = 4 \), \( P < 0.05 \)). To further confirm the necessity of calcium influx for sADP, we chelated intracellular calcium by adding BAPTA (10 mM) to the internal solution. With BAPTA (10 mM), bath application of dopamine failed to induce sADP (Fig. 3, C and D; from \(-7.81 \pm 1.56 \) to \(1.09 \pm 1.03 \text{ mV} \cdot \text{S} \); \( n = 7 \)). To test involvement of calcium release from internal stores in the present sADP, we used the calcium store depletor CPA (30 \( \mu \)M). Bath application of CPA still allowed induction of the DA-induced sADP (Fig. 3D; from \(-1.96 \pm 2.16 \) to \(16.47 \pm 7.22 \text{ mV} \cdot \text{S} \); \( n = 3 \)), ruling out an essential involvement of calcium stores. These results showed that the present DA-induced sADP is triggered by calcium influx, and is generated by membrane depolarization irrespective of whether action potentials are fired or not.

Voltage dependency of DA-induced \( I_{\text{sADP}} \)

We have thus shown that calcium influx triggered induction of the DA-induced sADP. A next question would be what kind of currents mediate expression of the sADP. It was previously shown that both calcium-activated currents and decrease of potassium currents could be responsible for sADP as follows. Constanti et al. (1993) reported that, in the olfactory cortex, sADP was induced by decrease of potassium current. According to Greene et al. (1994), sADP was induced by both calcium-activated current and decrease of potassium current in the prefrontal cortex. In the neocortex and hippocampal CA1 neuron, it was reported that sADP was induced by calcium-activated current alone (Fraser and MacVicar 1996; Haj-Dahmane and Andrade 1998). To elucidate what class of currents are responsible for the present sADP, we first examined voltage dependency of the DA-induced \( I_{\text{sADP}} \). Voltage steps (500 ms, to 0 mV from holding potentials \(-80 \), \(-70 \), \(-60 \), \(-50 \), and \(-40 \text{ mV} \)) were applied to neurons in the presence of TTX.
(0.5 μM). The currents induced were compared before and 5 min after bath application of dopamine (50 μM). Before the application, each voltage step induced outward currents (Fig. 4A, control). After the application, by contrast, the voltage steps induced inward currents ($I_{sADP}$) at the holding potentials of either −80, −70, −60, −50, or −40 mV, 500 ms) were superimposed (control). A, middle: after bath application of dopamine (50 μM). A, right: by subtracting the currents induced under control condition from the currents induced after bath application of dopamine, the net current (subtracted $I_{sADP}$) induced by dopamine was obtained. Each trace represents the average of 2 trials (subtract). B: amplitudes of the subtracted $I_{sADP}$ recorded at 1.5 s after the termination of the voltage steps were plotted.

Membrane conductance was decreased at the peak of $I_{sADP}$

To clarify whether the event underlying $I_{sADP}$ is current activation or decrease of current, we measured change in membrane conductance during the $I_{sADP}$. We applied a voltage step (+10 or −10 mV) and compared the amplitude of currents induced at rest and during the $I_{sADP}$. The outward currents induced by the +10-mV voltage step commands were decreased in synchrony with $I_{sADP}$ (Fig. 5A) and the inward currents induced by the −10-mV voltage step were also decreased (Fig. 5B). This is consistent with the previous descriptions although based on recordings from different classes of neurons (Constanti et al. 1993; Haj-Dahmane and Andrade 1998). These previous reports and the present experiments alike indicate that, during the $I_{sADP}$, the membrane conductance was decreased, suggesting that the $I_{sADP}$ resulted from decrease of currents.
Involvement of a potassium current in the DA-induced $I_{sADP}$

The $I-V$ relationship of subtracted $I_{sADP}$ (Fig. 4) and the reduction of membrane conductance during the $I_{sADP}$ (Fig. 5) imply that this $I_{sADP}$ resulted from decrease of potassium current. To test this possibility, we examined $I-V$ relationship of subtracted $I_{sADP}$ at different concentration of potassium (5 and 10 mM) in the external solution. The $I-V$ curve was shifted upward significantly as the external concentration of potassium ($[K^+]_o$) was raised to 10 mM (Fig. 6, A, 10 mM KCl, and B; 3.69 ± 1.43 pA at -70 mV, 1.49 ± 1.51 pA at -60 mV, -13.61 ± 2.07 pA at -50 mV; n = 7; P < 0.001 ANOVA). The $I-V$ curve was shifted upward when $[K^+]_o$ was raised to 5 mM (Fig. 6, A, 5 mM KCl, and B; -2.24 ± 2.31 pA at -70 mV, -4.29 ± 2.28 pA at -60 mV, -15.42 ± 3.28 pA at -50 mV; n = 7).

In the light of the reversal potential ($E_{rev}$), as well, the involvement of potassium currents was confirmed. DA-induced net $I_{sADP}$, which was inward at -50 mV, was almost undetectable at -60 mV, and was outward at -70 mV. These findings obviously point to a potassium reversal potential of about -60 mV, which is consistent with the prediction on the basis of the Goldman-Hodgkin-Katz equation (-61.4 mV with $[K^+]_o$ 10 mM, including the liquid junction potential).

To confirm the involvement of potassium conductance further, we examined effects of potassium channel blockade on this $I_{sADP}$. To block potassium channels, we made patch-clamp recording with cesium-based internal solution containing TEA (10 mM). With cesium, bath application of dopamine failed to induce $I_{sADP}$ (Fig. 6, C and D; area $I_{sADP}$).
from $-17.75 \pm 3.22$ to $-14.75 \pm 7.07$ pA•S, $n = 8$, not significant). These results clearly indicate involvement of potassium conductance in this $I_{\text{ADP}}$.

**DISCUSSION**

Although simple DA-induced depolarization and changes in membrane resistance have been reported in LA neurons (Kroner et al. 2005), the present study is the first to demonstrate a DA-induced sADP, which is regarded as a positive feedback regulation of membrane excitability in LA neurons. We have shown that 1) this sADP was mediated by D1-like receptors, 2) was triggered by calcium influx, and 3) was underlain by decrease in potassium conductance. However, involvement of receptors for other monoamines has also been suggested. The present sADP with decreasing potassium conductance would enhance the excitability of LA neurons activity-dependently.

**Role of D1-like receptors in the present sADP**

In the present experiments, activation of D1-like receptors by SKF38393 only partially mimicked the effect of dopamine itself, and blockade of D1-like receptors failed to abolish the DA-induced sADP completely. The present experiments indeed showed that the full expression of DA-induced sADP requires activation of noradrenalin $\alpha_1$ receptors and 5-HT$_2$ receptors. There are two possibilities as to how dopamine activates these two classes of receptors. One possibility is that dopamine directly activates not only D1-like receptors but also these two classes of monoamine receptors as if effects of these three receptors are additive and in parallel. Another possibility is that dopamine activates presynaptic D1-like receptors at noradrenergic and serotonergic terminals, which might elicit release of these monoamines. However, this possibility is unlikely because specific activation of D1-like receptors failed to reproduce the dopamine effect. At the very least, the present study excluded involvement of D2-like receptors. The present findings therefore points to collaboration participated by D1-like, noradrenalin $\alpha_1$ and 5-HT$_2$ receptors in inducing the present DA-induced sADP. What different roles are played by these receptors in this collaboration has yet to be clarified.

The present experiments also showed that DA increases the number of action potentials induced by injecting depolarizing current and depolarizes the resting membrane potential slightly. These are in agreement with the previous report (Kroner et al. 2005).

**Similarity to other sADPs induced in various neurons**

There is no other report on sADP in LA neurons although similar sADPs have been reported in other types of neurons. In the olfactory cortex, sADP is induced by activation of muscarinic acetylcholine receptors or metabotropic glutamate receptors (Constanti and Bagetta 1991; Constanti and Libri 1992; Constanti et al. 1993). In the neocortex, sADP is also induced by activation of muscarinic acetylcholine receptors (Haj-Dahmane and Andrade 1998; Schwindt et al. 1988), group I metabotropic glutamate receptors (Greene et al. 1992, 1994), $\alpha_1$-noradrenalin receptors (Araneda and Andrade 1991) and 5-HT$_2$ receptors (Araneda and Andrade 1991; Spain 1994; Zhang and Arsenault 2005). In the hippocampal CA1, sADP was induced by activating muscarinic acetylcholine receptors (Fraser and MacVicar 1996; McQuiston and Madison 1999).

The present sADP and those sADPs reported previously are all triggered by calcium influx and have similar voltage dependency. These similarities of sADPs suggest that appearance of sADP by activating G-protein-coupled receptors is a common mechanism with which to modulate neuronal excitability.

**Involvement of potassium current**

Even though sADPs induced in various neurons resemble one another in many features, the currents underlying sADPs are diverse. Three types of sADPs were reported; sADP induced by decreasing potassium current (Constanti and Bagetta 1991; Constanti et al. 1993), that induced by activation of cation current and decreasing potassium current (Greene et al. 1994), and that induced by activation of calcium activated nonselective cation current (Haj-Dahmane and Andrade 1998).

In the present experiments, we revealed involvement of potassium current in the DA-induced sADP based on the following grounds; membrane conductance was reduced during $I_{\text{ADP}}$; the $I-V$ relation curve of the net DA-induced $I_{\text{ADP}}$ was shifted upward as $[K^+]_o$ was raised; the reversal potential of the net $I_{\text{ADP}}$ was identical to that of potassium; and with cesium and TEA, dopamine failed to induce this $I_{\text{ADP}}$. These results clearly indicate that decrease in potassium conductance underlies the present DA-induced $I_{\text{ADP}}$.

**Physiological role of the DA-induced sADP in LA**

We showed that dopamine not only reduces AHP but also induces sADP in LA neurons. This sADP may be a part of a positive-feedback regulation of neuronal excitability in the following sense. Once a neuron is excited by an excitatory synaptic input, sADP is induced, during which the same neuron would be excited more easily than before. Such a positive-feedback enhancement of excitability will occur not only by consecutively incoming homosynaptic inputs but also by any combination of homo- and heterosynaptic inputs. It is thus suggested that sADP offers a platform on which various synaptic inputs are associatively integrated.

Also, because sADP lasts for seconds, two incoming volleys with time delay shorter than seconds could as well be associatively integrated. Such heterosynaptic integration with time delay, especially that with delay of subsecond order, may be important in delayed fear learning, given that the time sequence of conditioned and unconditioned stimuli is especially critical in the associative conditioning. The later phase of the sADP, which spans a few second after spikes, may be too late to be relevant to delayed fear conditioning obtained by specific pairs of conditioned and unconditioned stimuli. However, in a more generalized sense, once neuron circuits in the amygdala are activated, the late phase of sADP would render the amygdala circuit more sensitive to the next input in a positive feedback manner. Such a highly sensitized amygdala might be subject to context-independent activation, which could possibly underlie “fear of unrealistic danger.”

The DA-induced sADP may also modulate long-term synaptic plasticity. Reduction of AHP is reported to facilitate LTP (Cohen et al. 1999; Disterhoft and Oh 2006; Kramar et al. 2004; Sah and Bekkers 1996), and both membrane depolariza-
tion and decrease in potassium conductance are advantageous to occurrence of LTP (Johnston et al. 2000; Lisman and Spruston 2005). LTP occurs in the amygdala during fear learning, and this LTP has been shown to be necessary for fear learning (Blair et al. 2001; Maren and Quirk 2004; Rodrigues et al. 2004). Concentration of dopamine in the amygdala is reported to increase during fear conditioning (Harmer and Phillips 1999; Inglis and Moghaddam 1999; Yokoyama et al. 2005), suggesting a critical role of dopamine in fear learning. In fact, the blockade of dopamine receptors impairs acquisition of fear memory (Greba and Kokkinidis 2001; Greba et al. 2000; Lamont and Kokkinidis 1998; Nader and LeDoux 1999). All these combined together, the present DA-induced sADP of fear memory (Greba and Kokkinidis 2001; Greba et al. 2005), suggesting a critical role of dopamine in fear learning. 

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