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REVIEW

Arachidonic acid and ion channels: an update

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Arachidonic acid (AA), a polyunsaturated fatty acid with four double bonds, has multiple actions on living cells. Many of these effects are mediated by an action of AA or its metabolites on ion channels. During the last 10 years, new types of ion channels, transient receptor potential (TRP) channels, store-operated calcium entry (SOCE) channels and non-SOCE channels have been studied. This review summarizes our current knowledge about the effects of AA on TRP and non-SOCE channels as well as classical ion channels. It aims to distinguish between effects of AA itself and effects of AA metabolites. Lipid mediators are of clinical interest because some of them (for example, leukotrienes) play a role in various diseases, others (such as prostaglandins) are targets for pharmacological therapeutic intervention.
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Keywords: arachidonic acid; ion channels; leukotrienes; prostaglandins; TRP channels; SOCE channels

Abbreviations: AA, arachidonic acid; ETYA, 5,8,11,14-eicosatetraynoic acid; TRP, transient receptor potential; SOCE, store-operated calcium entry

Introduction

Arachidonic acid (AA), a 20-carbon omega-6 polyunsaturated fatty acid liberated from membrane phospholipids by phospholipases of the class A_2, continues to attract interest. The effects of AA on different ion channels have been reviewed by Meves (1994). Since then, many new findings have been published. Interest has shifted from the classical ion channels (for example, Na^+ and Ca^{2+} channels) to new types of channels (for example, transient receptor potential (TRP) and none-store-operated calcium entry (non-SOCE)). The present review summarizes the work done in the last 10 years.

A review by Brash (2001) discusses the physical properties of this 'slippery molecule' and the mechanisms responsible for its uptake into cells (protein-mediated transport vs flip-flop of the protonated fatty acid). The concentration at which AA occurs in tissues and cells is low: 2 μM nonesterified arachidonate in the arterial blood of dogs (see Table 2 of Van der Vusse *et al*., 1982), 9–16 μM in the plasma of rats (see Table 1 of Rapoport, 2003) and 5.3–13.1 μM in human plasma (see Burtis *et al*., 2006). Much higher concentrations are found in secretagogue-stimulated pancreatic islets; increments in cellular levels of 38–75 μM are reported by Wolf *et al*. (1991). A total of 99.9% of the non-esterified arachidonate is bound to albumin. Therefore, the effects of fairly low (2–10 μM) AA concentrations are of particular interest.

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Mechanisms of action

Arachidonic acid exerts its effects by different mechanisms: either by a direct action of the AA molecule itself or by an effect of the AA metabolites. The latter are products of three different pathways: the cyclooxygenase pathway (for example, prostaglandins), the epoxygenase or CYP-450 pathway (for example, 20-HETE) and the three lipoxygenase pathways (for example, leukotrienes). A direct effect of AA seems likely, if the AA effect is mimicked by 5,8,11,14-eicosatetraynoic acid (ETYA), the non-metabolizable analogue of AA with triple instead of double bonds. ETYA is an inhibitor of AA metabolism (for details about ETYA and further literature, see Sergeeva *et al*. (2003)). The direct effect of AA may result from AA binding to membrane molecules at the outer or inner side of the membrane. Alternatively, AA may insert itself between the membrane molecules, thereby altering bilayer mechanical properties, which in turn modulate channel function. Some AA effects are mediated by the activation of PKC, for example, the effect of AA on the excitability of *Hermissenda* photoreceptors (Muzzio *et al*., 2001) or on the currents through neuronal ACh receptors (Yagushi *et al*., 2005). Recently, AA effects caused by changes in the affinity of the channels for the membrane phospholipid phosphatidyl inositol 4,5-bisphosphate (PIP_2) were described (see page 3).

The direct effect of AA on potassium channels

The effect of AA on the various types of K^+ channels has two characteristic properties: (a) it is mimicked by ETYA, suggesting a direct effect of AA—the exceptions where AA acts through its metabolites are some Ca^{2+}-activated K^+ channels $I_{K(Ca)}$); (b) in most cases, AA inhibits K^+ currents—only a few types of K^+ currents (for example, some inward rectifiers and EAG (*ether-à-go-go)* currents) are enhanced by AA.

K^+ channels are very AA-sensitive and this is true for the fast inactivating A-type channels, which give rise to a transient K^+ current, the delayed rectifier channels and some inwardly rectifying K^+ channels. An inhibitory effect on A-type K^+ current was first demonstrated on bullfrog sympathetic neurons by Villarroel (1993). He found 50% inhibition with 1.75 μM AA. Figure 1 shows the effects of AA on voltage-gated Kv4.2 currents expressed in Xenopus oocytes (a and b) and on hippocampal A-current (c–f). In all these examples, concentrations below 2 μM are effective. Inhibition of the transient K^+ current of pituitary melanotrophs by medium with 20 μM AA was reported by Kehl (2001). With intracellular application through patch pipette, even a concentration as small as 1 pM markedly inhibits I_A (but not the delayed rectifier) in hippocampal slices (Bittner and Müller, 1999; Angelova and Müller, 2006).

Arachidonic acid and other polyunsaturated fatty acids have a typical effect on the delayed rectifier channels: a marked acceleration of current decay and a pronounced reduction of I_K amplitude (Figure 2). This type of dual effect of polyunsaturated fatty acids has been observed in the 1990s in cloned and expressed K^+ channels of the Kvl.5, Kvl.l and Kvl.2 classes (for literature, see Smirnow and Aaronson, 1996, who found the same effect in rat pulmonary myocytes) and in NG108-15 neuroblastoma × glioma cells (Rouzaire-Dubois *et al*., 1991). The latter cells have delayed rectifier channels encoded by NGK2, now designated as mKv3.1a (see Yokoyama *et al*., 1993). Oliver *et al*. (2004) studied this AA effect (acceleration of inactivation and decrease of the peak current) on Kv3.1, Kv3.2, Kv1.1 and Kv4.3 delayed rectifier channels expressed in *Xenopus* oocytes. The half-maximal effect on Kv3.1 channels occurred at 80 nM. They found no effect on the non-inactivating KCNQ2/3 and the large-conductance voltage- and calcium-activated (BK-type) K^+ channels. Recently, Gavrilova-Ruch *et al*. (2007) demonstrated the AA effect on Kv1.5 channels

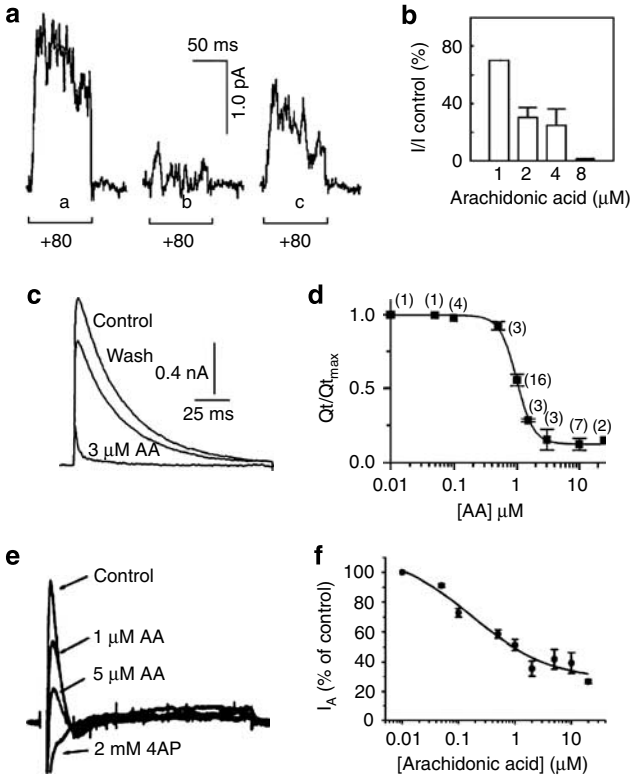

Figure 1 Effects of low (<10 μM) concentrations of arachidonic acid on A-type transient K^+ currents. (**a**) The transient A-type current expressed by Kv4.2 in Xenopus oocytes is inhibited by 4 μM AA; the figure shows averaged records from an inside-out macropatch subjected to five depolarizations from −80 to +80 mV in the control (curve a), in 4 μM AA (curve b) and after wash (curve c). (**b**) Current amplitude in percent of control at four concentrations of AA (**a** and **b** from Villarroel and Schwarz, 1996). (**c**) Inhibition of the A-type transient K^+ current of hippocampal pyramidal neurons by 3 μM AA; test pulse to +40 mV following prepulse to −110 mV; τ of inactivation is 35 ms in control and 2.6 ms in 3 μM AA. (**d**) Dose-response curve for the effect of AA on the charge transfer associated with the transient current; the numbers of measurements are given in brackets. (**c** and **d** from Keros and McBain, 1997). (**e**) AA (1 and 5 μM) reduces the amplitude of the A-type current of a hippocampal pyramidal cell; the current is fully blocked by 2 mM 4AP; test pulse to +30 mV following prepulse to −120 mV. (**f**) Average dose-response curve (n = 4–6) showing that the EC_{50} for AA is 0.27 μM (**e** and **f** from Ramakers and Storm, 2002). AA, arachidonic acid.

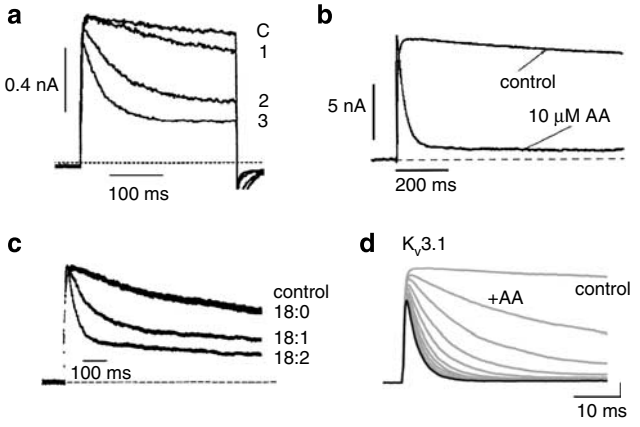

Figure 2 Polyunsaturated fatty acids accelerate the inactivation of the delayed rectifier current. (**a**) Records from a rat pulmonary arterial myocyte in control and 1, 2 and 3 min after application of 10 μM arachidonic acid. (**b**) Records from hKv1.5 channels expressed in CHO cells in control and after application of 10 μM AA. (**c**) Records from a NG108-15 neuroblastoma × glioma cell in control and in the presence of 5 μM stearic acid (18:0), oleic acid (18:1) and linoleic acid (18:2); peak current in control and stearic acid 3.2 nA; currents in oleic and linoleic acid multiplied by 1.8 and 1.2, respectively. (**d**) Effect of 4 μM AA on delayed rectifier channels expressed in *Xenopus* oocytes; AA applied to the cytoplasmic side of the membrane; currents recorded at 2 s intervals; scale bar 1 nA. Pulse potential +60 mV in panel a, +20 mV in panel b, +50 mV in panel c. Holding potential −60 mV in panel a, −100 mV in panel b, −80 mV in panels c and d. Experiments were carried out at room temperature. Panel a from Smirnow and Aaronson, 1996; panel b from Gavrilova-Ruch *et al*., 2007; panel c from Rouzaire-Dubois *et al*., 1991 and panel d from Oliver *et al*. (2004). AA, arachidonic acid.

expressed in CHO cells. Figure 2 shows records from rat pulmonary myocytes, CHO cells expressing Kv1.5 channels, NG108-15 cells and *Xenopus* oocytes expressing Kv3.1 channels. Figure 2c illustrates that the effect increases with the number of double bonds. Arachidonic acid (5 μM) reduces the delayed rectifier currents of pancreatic β-cells (Kv2.1) by 33.4% and accelerates their inactivation (Jacobson *et al*., 2007).

Arachidonic acid potently and reversibly increases currents flowing through a cloned human inwardly rectifying K^+ channel hKir2.3 ($EC_{50} = 447$ nM at −97 mV), but has no effect on the currents flowing through Kir2.1, Kir2.2 or Kir2.4 channels (Liu *et al*., 2001b, 2002). According to Wang *et al*. (2008), this effect is caused by the enhanced interaction of the Kir2.3 channels with PIP_2. Arachidonic acid shifts the concentration-response curve for water-soluble diC_8PIP_2 to the left: 3 μM AA reduces EC_{50} for diC_8PIP_2 activation from 36.3 to 11.8 μM. Sohn *et al*. (2007) reported the inhibition of GABA-activated I_{GIRK} in hippocampal neurons by AA. The effect is reversed completely by the exogenous application of PIP_2, that is, probably caused by a decrease in PIP_2 affinity of the channel. In the heart and brain, the binding of neurotransmitters (for example, ACh) to their specific G protein-coupled receptors activates an inwardly rectifying K^+ channel $I_{K(Ach)}$ (also called GIRK and Kir3) through the βγ subunit of G proteins. Arachidonic acid inhibits $I_{K(Ach)}$ (Figure 3), probably by antagonizing the interaction of PIP_2

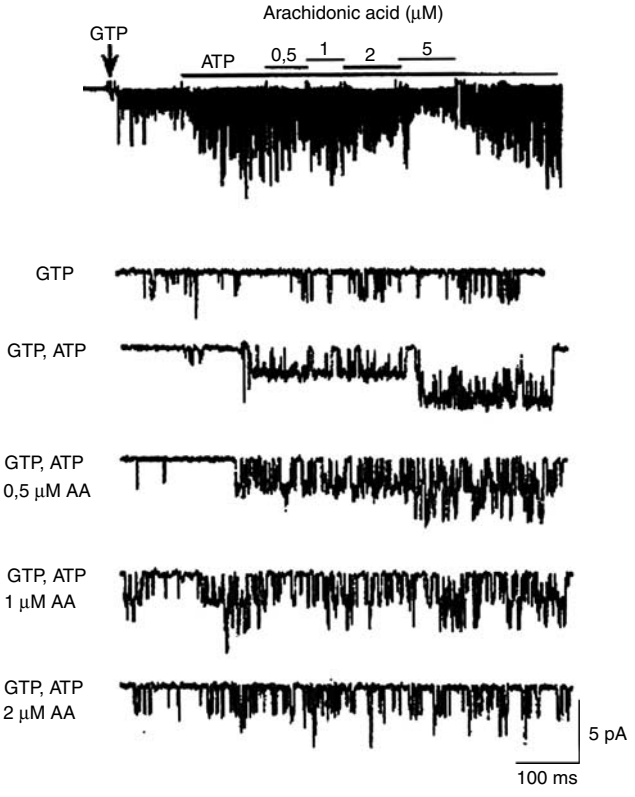

Figure 3 Inhibitory effect of small AA concentrations on the K_{Ach} channel. Native K_{Ach} channels in rat atrial cells are activated by 100 μM GTP and 4 mM ATP in an inside-out patch. AA, applied in stepwise increased concentration, inhibits channel activity (Kim and Pleumsamran, 2000). AA, arachidonic acid.

with the channel (Kim *et al*., 1989; Kim and Pleumsamran, 2000; Rogalski and Chavkin, 2001). The AA concentration at which channel activity decreases by half is 1.7 μM. Here too, AA itself is the inhibitor, not a metabolite. Arachidonic acid produced the same inhibitory effect in the presence of indomethacin and nordihydroguaiaretic acid, blockers of cyclo- and lipoxygenase. Fatty acids that are not substrates for these enzymes are also potent inhibitors of ATP-dependent gating, for example, oleic and linoleic acid (half inhibition at 1.5 and 1.2 μM, respectively).

K^+ channels of the EAG and ERG (*EAG-related gene*) families are also sensitive to polyunsaturated acids, including AA. The amplitude of the hEAG1 currents increases with increasing AA concentration ($EC_{50} = 4.6 \pm 1.4$ μM), inducing a strong left-shift of about 25 mV in the voltage dependence of hEAG1 channel activation (Gavrilova-Ruch *et al*., 2007). EAG activation is in part responsible for the proliferative effect of AA. By contrast, AA blocks ERG1 channels expressed in Chinese hamster ovary cells (Guizy *et al*., 2005) and ERG1 currents in anterior pituitary cells (Schledermann *et al*., 2001); in the latter, an extreme acceleration of ERG1 current deactivation occurs.

Arachidonic acid induces the activation of large-conductance voltage-independent K^+ channels and membrane hyperpolarization in mouse B lymphocytes while inhibiting voltage-gated and Ca^{2+}-activated K^+ channels (Zheng *et al*., 2005). Calcium-activated K^+ channels of intermediate conductance (hIK1) are likewise inhibited by small AA concentrations ($IC_{50} = 1.4$ μM), an effect caused by AA interacting with the pore-lining amino acids Thr^{250} and Val^{275} (Hamilton *et al*., 2003).

ATP-dependent K^+ channels from mouse pancreatic β-cells are activated by AA applied from outside the cell (Eddlestone, 1995) but inhibited by treatment with secretory phospholipase A_2 (Juhl *et al*., 2003).

In some cells, the effect of AA on Ca^{2+}-activated K^+ channels is mediated through its metabolites (see below).

The importance of subunits

Holmquist *et al*. (2001) drew attention to an interesting detail: In neurons, bath-applied AA reduces both the amplitude of I_A and its time constant of inactivation (Figure 1c), but in Xenopus oocytes the latter effect is missing. The reason is that native (but not heterologous) cells contain auxiliary subunits (called KCHIPs, K-channel interacting proteins) that mediate the change in kinetics. A similar discrepancy between native and heterologously expressed channels was observed with regard to Kv1.4. Arachidonic acid slightly increases the current through Kv1.4 channels expressed in Xenopus oocytes (Villarroel and Schwarz, 1996), but markedly decreases the current flowing through native Kv1.4 channels in adrenal zona fasciculata cells (Danthi *et al*., 2003).

Another example for the importance of subunits has recently been reported by Sun *et al*. (2007). They expressed large conductance calcium-activated K^+ channels (Hslo BK channels) in Xenopus oocytes. Arachidonic acid enhanced the hslo-α current and slowed its inactivation only when

β2/3 subunits were coexpressed but not in the absence of these subunits. These results suggest that AA removes inactivation by interacting with β2/3 to prevent the inactivation ball from reaching its receptor. In accordance with these observations, AA has been shown to activate BK channels in various types of native cells (where β2/3 is present); Denson *et al*., 2000; Clarke *et al*., 2002) but not in Xenopus oocytes (Oliver *et al*., 2004, see above).

2P-K channels are targets for AA and other polyunsaturated fatty acids

In the last 10 years, two other types of ion channels, 2P-domain and TRP, were also found to be AA-sensitive. The two-pore domain K channel family (2P-K) consists of channels with two pore-forming regions and four transmembrane domains (see inset in Figure 4d; for reviews, see Lesage, 2003; Besana *et al*., 2005; Goldstein *et al*., 2005; Kim, 2005). 2P-K channels are leak or background K^+ channels that are resistant to block by the classical K channel-blocking drugs, TEA and 4-AP. They play an important role in setting the resting membrane potential. There are currently 16 members in the 2P-K family, encoded by 15 mammalian genes. They can be divided into six subfamilies. In the nervous system, the main representatives are the subfamilies TASK and TREK, the latter consisting of TREK-1, TREK2 and TRAAK. The abbreviations stand for tandem-pore acid-sensing K^+ channel, TWIK-related K^+ channel and TWIK-related AA-stimulated K^+ channel. TASK-1 and TASK-3 are inhibited by AA (see Table 2 of Patel and Honoré, 2001, and Table 2 of Han *et al*., 2002). By contrast, TRAAK expressed in cultured mammalian cells is rapidly activated by many unsaturated fatty acids, including AA (Fink *et al*., 1998; see Figure 4). Potentiation of TRAAK current by AA cannot be prevented by blockers of AA metabolism. Two other 2P-K channels activated by polyunsaturated fatty acids, including AA, TREK-1 and TREK-2, were discovered shortly after TRAAK (Patel *et al*., 1998; Bang *et al*., 2000). They share with TRAAK the relatively high single-channel conductance (see Table 2 of Kim, 2005) and the high sensitivity to membrane stretch and changes in intracellular pH. There are, however, important differences: TREK-1 and TREK-2 are stimulated by intracellular acidosis, whereas TRAAK opens upon intracellular alkalosis. The C-terminus of TRAAK shares little identity with those of TREK-1 and TREK-2. The C-terminus of TREK-1 and TREK-2 is critical for providing sensitivity to pressure, fatty acid and pH_i (Patel *et al*., 1998; Kim *et al*., 2001b), but replacing the C-terminus of TRAAK with that of TASK does not affect the response to pressure, AA or pH_i (Kim *et al*., 2001a). Two 2P-K channels weakly activated by AA are TWIK-2 (tandem-pore weak inward rectifying K^+ channel; Patel *et al*., 2000) and THIK-1 (tandem-pore halothane-inhibited K^+ channel) (Girard *et al*., 2001; Rajan *et al*., 2001). TWIK-2 is the first reported 2P-K channel that inactivates. THIK-1 is reversibly blocked by the inhalation anaesthetic halothane (which activates TREK).

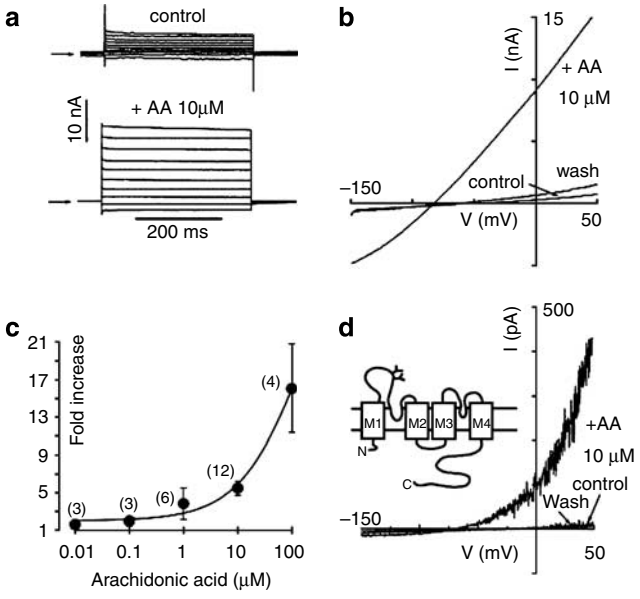

Figure 4 Activation of TRAAK in COS cells. (**a**) Whole-cell currents elicited by voltage pulses ranging from −130 to +50 mV in 20 mV steps from a holding potential of −80 mV before and after 2 min perfusion with 10 μM AA. (**b**) Current-voltage curves obtained with voltage ramps (from −150 to +50 mV in 0.5 s) in control, after 3 min perfusion with 10 μM AA and after wash. (**c**) Dose-response curve for the current at +50 mV (relative to control) with number of tested cells in brackets. (**d**) Current-voltage curves obtained from inside-out patch with voltage ramps (from −150 to +50 mV in 0.5 s) in control, after 3 min perfusion with 10 μM AA and after wash (**a**–**d** from Fink *et al*., 1998). Inset in panel d shows membrane topology of TRAAK (Kim *et al*., 2001a). AA, arachidonic acid; TRAAK, TWIK-related AA-stimulated K^+ channel. COS is a fibroblast cell line from the kidney of the African green monkey.

Native channels similar to TREK-1 and TREK-2 have been described several years before their molecular identification. They were referred to as K_{AA} and K_{FA} channels, as they were activated by AA and other free fatty acids. Three types of K_{FA} channels were found in neurons cultured from the mesenphalic and hypothalamic areas of rat brain (Kim *et al*., 1995). The defining characteristics of these channels were the same as those of the TREK channels, namely activation by unsaturated fatty acids, pressure and pH_i. Based on single-channel conductances, gating kinetics and modulation by pharmacological agents and pH, functional correlates of TREK-2 (but not of TREK-1 and TRAAK) were found in cerebellar granule neurons (Han *et al*., 2002). Eight different K^+ channels were identified in the magnocellular neurosecretory cells of the supraoptic nucleus in the rat hypothalamus: one indistinguishable from TRAAK, three with properties similar to TREK-type 2P-K channels and two functional correlates of TASK-1 and TASK-3 (Han *et al*., 2003). In cultured rat cortical astrocytes, AA activates a K^+ conductance that exhibits many similarities to TREK-2 channels (Ferroni *et al*., 2003). Under pathological conditions, when the concentration of free fatty acids and H^+ ions rises, the activation of K_{FA} channels will oppose depolarization, thereby protecting the cell from further damage. TREK-$1^{-/-}$ mice display an increased sensitivity to ischaemia and epilepsy (Heurteaux *et al*., 2004).

K^+ channels, which are activated by AA, are also found outside the brain. Examples are the 0_2-sensing glossopharyngeal neurons (Campanucci *et al*., 2003), the bovine adrenal zona fasciculata cells (Danthi *et al*., 2003), the chick

dorsal root ganglion cells (Fioretti *et al*., 2004) and the vascular smooth muscle cells of the rat (Bryan *et al*., 2006). The channels exhibit similarities to members of the 2P-K family. In the experiments of Danthi *et al*. (2003) on adrenal zona fasciculata cells, AA strongly activated native TREK-1 leak channels and simultaneously inhibited the transient Kv1.4 outward current. ETYA neither mimicked nor blocked AA activation of the leak channels but was effective in inhibiting Kvl.4.

TRP channels

Transient receptor potential channels constitute a large and functionally versatile superfamily of cation channels that are expressed in many cell types (for reviews, see Inoue *et al*., 2006; Owsianik *et al*., 2006; Venkatachalam and Montell, 2007). Several channels of the TRPV (**v**anilloid subtype) family are targets of fatty acids and AA metabolites. Arachidonic (or linolenic) acid activates the TRP channels shown in Figure 5, the native light-sensitive (TRP) channels in *Drosophila* photoreceptors, the capsaicin-activated TRPV1 channels and the TRPV4 and TRPV4-like non-selective cation channels. The underlying mechanisms are, however, quite different. Polyunsaturated fatty acids act directly (rather than through a metabolite) on the native TRP

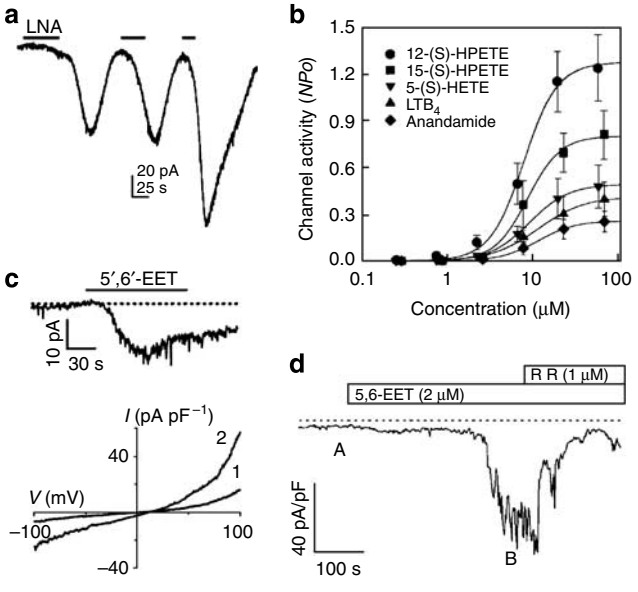

Figure 5 TRP channels are targets of fatty acids and AA metabolites. (**a**) A unit of 20 μM linoleic acid repeatedly activates light-sensitive TRP channels of *Drosophila*; whole-cell record at −70 mV in the dark (Chyb *et al*., 1999). (**b**) Lipoxygenase products and anandamide activate the capsaicin-activated channel TRPV1 in isolated membrane patches of rat dorsal root neurons; channel activity (NP_o) was calculated as the product of functional channels (N) in the patch and channel open probability (P_o) (Hwang *et al*., 2000). (**c**) Activation of TRPV4 channels in HEK-293 cells by 5 μM 5′,6′-epoxyeicosatrienoic acid (EET); top: whole-cell record at 0 mV; bottom: current-voltage curves in control (1) and EET (2) (Watanabe *et al*., 2003). (**d**) Activation of TRPV4-like non-selective cation channels in B lymphocytes by 2 μM 5′,6′-EET and blockage by 1 μM RR; whole-cell record from a cell held at −80 mV (Liu *et al*., 2006). TRP, transient receptor potential; RR, ruthenium red.

channels in *Drosophila* (Chyb *et al*., 1999; Hardie, 2003). Arachidonic acid and the non-metabolizable ETYA activate *Drosophila* TRPγ channels expressed in HEK-293 cells, inducing a rise in $[Ca^{2+}]_i$ (Jörs *et al*., 2006). Arachidonic acid potentiates the responses of TRPV3 channels to 2-aminoethoxydiphenyl borate and this effect is also mimicked by non-metabolizable analogues of AA (Hu *et al*., 2006). In the case of TRPV1 channels, by contrast, AA acts through its lipoxygenase products, and in the case of TRPV4 channels through epoxygenase products. As shown by the dose-response curves in Figure 5b, the lipoxygenase products 12-(S)-HPETE, 15-(S)-HPETE, 5-(S)-HETE and leukotriene B_4 activate the TRPV1 channel with the fairly high half-maximal concentrations of 8.8, 8.7, 9.2 and 11.7 μM; AA itself has the same effect (Hwang *et al*., 2000; see also Nilius and Voets, 2005; various authors have expressed doubts whether such high concentrations of metabolites could be produced *in vivo*, for example, Takahashi *et al*., 1999). By contrast, the epoxygenase metabolites 5′,6′-epoxyeicosatrienoic acid (EET) and 8′,9′-EET (but not the lipoxygenase products) are effective on TRPV4 channels expressed in HEK-293 cells (Figure 5c) and on TRPV4-like non-selective cation channels (Figure 5d). Hypotonic cell swelling induces the activation of PLA_2; the released AA is metabolized to 5′,6′-EET, which in turn activates TRPV4 channels (Vriens *et al*., 2004). In smooth muscle cells of cerebral arteries, 300 nM 11,12-EET suffice to induce an inward current similar to the current recorded from cloned TRPV4 channels (Earley *et al*., 2005). 5,6-EET is a second messenger that activates Ca^{2+} entry in endothelial cells (Graier *et al*., 1995) by opening the Ca^{2+}-permeable TRPV4 channels, which are broadly expressed in endothelial cells (Vriens *et al*., 2005).

Apart from channels of the TRPV family, other TRP channels are either activated (TRPA1 Bandell *et al*., 2004; TRPM2 (earlier called LTRPC2) Hara *et al*., 2002; Togashi *et al*., 2006; TRPM5 Oike *et al*., 2006) or inhibited (TRPM8, Andersson *et al*., 2007) by AA and other PUFAs. TRPC6 channels are opened by remarkably small concentrations of the P-450-epoxygenase product 20-HETE ($EC_{50} = 0.8$ μM) (Basora *et al*., 2003; Cloutier *et al*., 2003; see page 8).

SOCE and non-SOCE

'TRP proteins have attracted almost exponentially growing attention as exceptionally unique Ca^{2+}-entry channels' (quoted from Inoue *et al*., 2006). A good example is the TRPV4 channel expressed in HEK-293 cells as studied by Watanabe *et al*. (2003) (see Figure 5c). Arachidonic acid and 5,6-EET cause a robust increase of $[Ca^{2+}]_i$ with $EC_{50} = 130$ nM for 5,6-EET. The effect depends on extracellular Ca^{2+} and is also observed in endothelial cells. TRP channels, particularly members of the canonical TRP family TRPC, are generally debated as possible molecular candidates for store-operated Ca^{2+} entry (SOCE) and the Ca^{2+} release-activated Ca^{2+} current I_{CRAC}, the most studied and best characterized SOCE current. Smyth *et al*. (2006) summarized the discussion by saying: 'As of yet, no TRPC channel has passed the ultimate test—that is, the ability to fully recapitulate the electrophysiological and pharmacological properties of I_{CRAC}'.

As pointed out by Smyth *et al.* (2006), the literature also provides controversial evidence for TRPV6 and TRPM3, either in favour of or refuting a role as SOCE. More recent publications, however, favour the view that TRP channels are molecular candidates for SOCE. A review by Leung *et al.*, 2007 argues that members of the TRPC family, particularly TRPC1 and TRPC5, are involved in SOCE. Ong *et al.*, 2007 and Cheng *et al.*, 2008 report that the association of TRPC1, STIM1 and Orai1 (see page 6) is involved in the activation of SOCE in salivary glands and HEK-293 cells. The same view has been expressed by Alicia *et al.*, 2008 and Bréchard *et al.*, 2008.

The store-operated calcium entry is activated by the release of Ca^{2+} from intracellular stores, whereas non-SOCE is triggered by lipid metabolites and entirely independent of store depletion. The best characterized non-SOCE activator is AA (for review, see Shuttleworth *et al.*, 2004). Arachidonate-regulated Ca^{2+} (ARC) channels can be readily activated in cells whose Ca^{2+} stores have been maximally depleted (for example, by treatment with thapsigargin). This has first been observed on avian nasal glands (Shuttleworth, 1996), HEk-293 cells (Shuttleworth and Thompson, 1998) and smooth muscle cells (Broad *et al.*, 1999). More recently, SOCE and non-SOCE were studied on smooth muscle cells (Moneer *et al.*, 2003), astrocytes (Sergeeva *et al.*, 2003; Yang *et al.*, 2005; Alloisio *et al.*, 2006), parotid and pancreatic acini (Watson *et al.*, 2004; Mignen *et al.*, 2005), endothelial cells (Mottola *et al.*, 2005; Tomatis *et al.*, 2007)), pancreatic β cells (Woolcott *et al.*, 2006), liver cells (Rychkov *et al.*, 2005) and HEK-293 and Saos-2 cells (Peppiatt *et al.*, 2004; Luo *et al.*, 2005; Holmes *et al.*, 2007). Tomatis *et al.* (2007) showed that low concentrations of AA (5 μM) activate calcium-permeable store-independent channels in bovine aortic endothelial cells, whereas higher AA concentrations trigger calcium release from intracellular stores. The STIM1 protein (stromal interacting protein) influences the magnitude of both SOCE and non-SOCE (Mignen *et al.*, 2006; Shuttleworth *et al.*, 2007). The protein Orai1 and the closely related Orai3 are essential components of the arachidonate-regulated non-SOCE channels, whereas only Orai1 is required for the activation of SOCE channels (Mignen *et al.*, 2008).

Figure 6 illustrates the Ca^{2+} responses evoked by thapsigargin and AA in HEK-293 (a–c) and Saos-2 cells (d). Stimulation of the cells with 2 μM thapsigargin in Ca^{2+}-free medium evoked a rapid transient mobilization of Ca^{2+} from intracellular stores (Figure 6a). Subsequent superfusion with Ca^{2+}-containing medium led to a sustained cytosolic Ca^{2+} increase, indicative of SOCE. A similar pattern of response was observed, if AA (30 μM) was used instead of thapsigargin (Figure 6b). Pharmacologically, however, the Ca^{2+} responses evoked by thapsigargin and AA were distinct. They differed significantly in their sensitivity to 2-APB, Gd^{3+} and LOE-908. The Ca^{2+} entry stimulated by thapsigargin was substantially inhibited by the Ca^{2+} entry inhibitors 2-APB (2-aminoethoxydiphenyl borate) and Gd^{3+}, whereas the non-selective cation channel inhibitor LOE-908 produced only a modest reduction in SOCE. With AA-stimulated Ca^{2+} entry, the sensitivity to these blockers was reversed. In Figures 6c and d, cells were treated with 2 μM thapsigargin in the presence of extracellular Ca^{2+}. Thapsigargin caused a rapid initial increase in cytosolic Ca^{2+} (due to release from

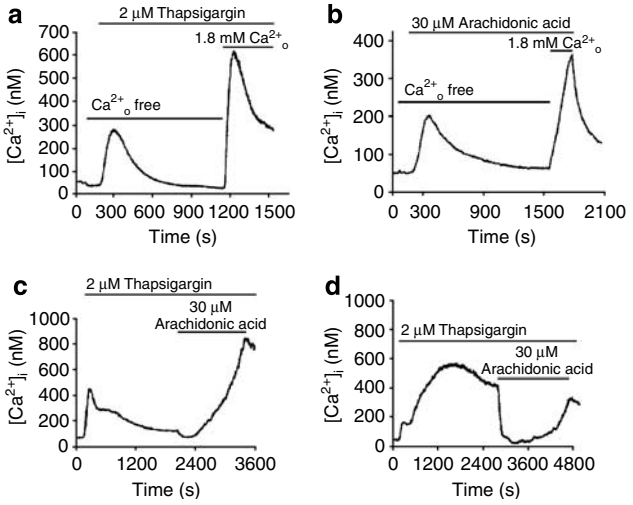

Figure 6 Store-operated Ca^{2+} entry (SOCE) and arachidonate-activated Ca^{2+} entry (non-SOCE) in HEK-293 and Saos-2 cells. (**a** and **b**) In the absence of extracellular Ca^{2+} thapsigargin (**a**) and AA (**b**) evoke in HEK-293 cells a transient increase in $[Ca^{2+}]_i$; restoration of extracellular Ca^{2+} results in Ca^{2+} entry. (**c** and **d**) HEK-293 (**c**) and Saos-2 cells (**d**) were treated with thapsigargin in the presence of extracellular Ca^{2+}; this resulted in Ca^{2+} release followed by a sustained plateau of $[Ca^{2+}]_i$ (SOCE); the subsequent addition of AA evoked a rapid inhibition of SOCE and the gradual activation of an alternative form of Ca^{2+} entry (non-SOCE). (Holmes *et al.*, 2007). AA, arachidonic acid.

stores), followed by a prolonged phase of Ca^{2+} entry (SOCE). For both cell types, the addition of AA immediately reduced cytosolic Ca^{2+}, consistent with a rapid inhibition of SOCE. Following this decline in $[Ca^{2+}]_i$, there was a gradual re-emergence of a Ca^{2+} influx, which had the pharmacological characteristics of non-SOCE. The experiment demonstrates that the two pathways, SOCE and non-SOCE, cannot operate simultaneously; they are reciprocally regulated. The reciprocal regulation of SOCE and non-SOCE was first reported by Mignen *et al.* (2001) and Luo *et al.* (2001). As pointed out by Taylor (2002), coordinating SOCE and non-SOCE is important if cells are not to be swamped with Ca^{2+}.

In some cells, AA regulates the two Ca^{2+} entry paths through nitric oxide (NO). This has been reported for vascular smooth muscle (Moneer *et al.*, 2003), parotid acini (Watson *et al.*, 2004) and endothelial cells (Mottola *et al.*, 2005). It should be noted that in general, the effects of AA do not require its metabolism but are effects of AA itself. Inhibiting pathways responsible for AA metabolism does not prevent the effect of AA (Sergeeva *et al.*, 2003; Peppiatt *et al.*, 2004; Shuttleworth *et al.*, 2004; Luo *et al.*, 2005; Woolcott *et al.*, 2006). In B lymphocytes, however, Zhu *et al.* (2005) have described AA sensitive channels that are biophysically and pharmacologically different from the arachidonate-regulated Ca^{2+} channels in other cell types. They resemble the TRPV4 channels mentioned above. As in TRPV4 channels, Ca^{2+} entry is triggered by 5,6-EET.

Other channels

Compared with I_K, I_{Na} and I_{Ca} have smaller AA sensitivity. In Na^+ channels of rat skeletal muscle, half inhibition occurs

at 4 μM AA (Bendahhou *et al*., 1997). For sympathetic neurons, inhibition of L-type and N-type Ca^{2+} channels by 5 μM AA at positive test potentials and enhancement of these currents at negative potentials have been reported by Liu and Rittenhouse (2000) and Liu *et al*. (2001a). More recently, Liu and Rittenhouse (2003) and Liu *et al*. (2006) found that AA also mediates the inhibition of N- and L-currents by muscarinic agonists. In addition, AA inhibits the L-type Ca^{2+} channel in cardiac myocytes ($IC_{50} = 8.5\,\mu M$) (Liu, 2007). Arachidonic acid attenuates currents through human T-type Ca^{2+} channels; 10 μM AA shifts their inactivation curve by −25 mV (Zhang *et al*., 2000). Talavera *et al*. (2004) described half inhibition of T-type Ca^{2+} channels expressed in HEK-2903 cells with 3.9 μM AA. Arachidonic acid and other PUFAs inhibit T-type Ca^{2+} current in bovine adrenal zona fasciculata cells (Danthi *et al*., 2005). Arachidonic acid does not alter the unitary current through Ca^{2+} channels (Liu and Rittenhouse, 2000; Talavera *et al*., 2004). Arachidonic acid (1 μM) also directly inhibits 46% of the carbachol-induced current in gastric myocytes (Cui *et al*., 2003).

Arachidonic acid potentiates acid-sensing ion channels in rat cerebellar and sensory neurons by a direct mechanism, thereby enhancing acid-mediated pain (Allen and Attwell, 2002; Smith *et al*., 2007). Arachidonic acid at 3 μM or higher activates proton channels in human neutrophils and eosinophils (Susztak *et al*., 1997; Cherny *et al*., 2001). Arachidonic acid (10–100 μM) and other PUFAs activate non-selective cation currents associated with the dopamine transporter (Ingram and Amara, 2000).

Currents flowing through synaptic channels of the NMDA family are potentiated by AA ($EC_{50} = 2.2\,\mu M$) (Casado and Ascher, 1998; Yelshanskaya *et al*., 2002). In the hippocampus, AA facilitates long-term potentiation. According to Ramakers and Storm (2002), AA suppresses the postsynaptic transient K^+ current I_A (Kv4) (see Figures 1e–f) and thereby enhances the amplitude of excitatory postsynaptic responses. Arachidonic acid and other PUFAS also affect synaptic transmission in other ways, namely by potentiating vesicle fusion and exocytosis (Darios *et al*., 2007; Davletov *et al*., 2007; Latham *et al*., 2007).

Does AA act on K^+ channels from the outer or from the inner side of the membrane?

Arachidonic acid and other PUFAs can flip across the bilayer (Kamp *et al*., 2003). Therefore, the question whether AA acts from the outer or inner side of the membrane is difficult to decide. Liu and Rittenhouse (2003) suggested that AA-induced enhancement of Ca^{2+} currents results from AA binding to an extracellular site, whereas AA-mediated inhibition of Ca^{2+} currents is mediated intracellularly. In agreement with this hypothesis, Barrett *et al*. (2001) found that AA enhances N-type Ca^{2+} current at an extracellular site. Bittner and Müller (1999) reported inhibition of I_A by the intracellular application of 1 pM AA, whereas extracellular application required a 10^6-fold higher concentration. Liu *et al*. (2001b) showed that the excitatory effect of AA on the inward rectifying K^+ channel Kir2.3 is caused by an action of AA at an extracellular site. Clarke *et al*. (2003) and Gavrilova-Ruch *et al*. (2007) likewise postulate an extracellular site of action for fatty acids activating BK channels and EAG channels, respectively.

In other studies, however, activation of channels from an intracellular site and inhibition from an extracellular site were seen. Denson *et al*. (2000) report that AA and other PUFAS enhance BK currents by acting from the cytosolic surface of the BK channel protein; arachidonyl-CoA, a membrane impermeable analogue of AA, activates BK channels when applied to the cytosolic surface of excised patches. Studies using arachidonyl-CoA also showed that the activation of non-SOCE channels by AA reflects an action specifically at the internal site of the plasma membrane (Mignen *et al*., 2003). For fatty acids activating small-conductance K^+ channels in toad stomach smooth muscle, the site of action also appears to be located on the inner membrane surface (Petrou *et al*., 1994). In cardiac myocytes, AA inhibits L-type Ca^{2+} currents from an extracellular site (Liu, 2007).

Arachidonic acid often produces a left-shift in the voltage dependence of channel activation or inactivation, leading respectively to an increase or decrease of the current. This has been observed for Na^+ channels (Bendahhou *et al*., 1997), Ca^{2+} channels (Schmitt and Meves, 1995; Zhang *et al*., 2000; Talavera *et al*., 2004; Liu, 2007), BK channels (Denson *et al*., 2000), EAG channels (Gavrilova-Ruch *et al*., 2007), ERG channels (Guizy *et al*., 2005) and H^+ currents (Cherny *et al*., 2001). Binding of AA anions to the outer side of the membrane would explain this left-shift. By contrast, AA right-shifts the conductance vs voltage curve of the inwardly rectifying K^+ channel Kir2.3 (Liu *et al*., 2002).

AA metabolites

In many cases, AA acts directly on ion channels, but in some cases its effects are mediated by AA metabolites. Twenty years ago, Piomelli *et al*. (1987) found that inhibition of synaptic transmission in Aplysia sensory neurons induced by the neuroactive peptide FMRFamide is mediated by 12-lipoxygenase metabolites, specifically 12-HPETE (see also Piomelli and Greengard, 1990). Subsequently, AA was reported to activate cardiac muscarinic channels K_{ACh} through 5-lipoxygenase products (Kim *et al*., 1989; Kurachi *et al*., 1989; later work showed unambiguously that AA is not an activator of K_{Ach} activity but that it inhibits it under more normal conditions when GTP and ATP are present; see Kim and Pleumsamran, 2000, page 3). In the following years, several other effects of cyclo-, epoxy- and lipoxygenase metabolites on various ion channels were reported.

Effects of cyclooxygenase metabolites

Cyclooxygenase activity leads to the production of prostaglandins. The multiple actions of prostaglandins on ion channels have recently been reviewed by Meves (2006).

Cyclooxygenase activity is also responsible for the production of reactive oxygen species (for example, hydrogen

peroxide). Sobey *et al*. (1998) showed that dilatation of cerebral arterioles in response to AA is dependent on the endogenous formation of reactive oxygen species through the cyclooxygenase pathway. The oxygen species open large-conductance Ca^{2+}-activated K^+ channels in vascular smooth muscle.

Effects of P-450-epoxygenase metabolites

Five eicosanoids are derived from AA by cytochrome P-450-epoxygenases: 5,6-epoxyeicosatrienoic acid (5,6-EET), 8,9-EET, 11,12-EET, 14,15-EET and 20-hydroxyeicosatetraenoic acid (20-HETE). Ten years ago, the epoxyeicosatrienoic acids were identified as endothelium-derived hyperpolarizing factors. EETs open K_{Ca} channels in smooth muscle cells isolated from coronary arteries, thereby causing hyperpolarization and vasorelaxation (Campbell *et al*., 1996). In rat hippocampal astrocytes, 11,12-EET increases the NP_o of 71 and 161 pS K_{Ca} single-channel currents (Yamaura *et al*., 2006). The role of EETs in endothelium-derived hyperpolarizing factor-mediated responses has been summarized in reviews by Roman (2002) and Fleming and Busse (2006). Another review deals with the multiple effects of EETs on cardiac ion channels (Xiao, 2006). Arachidonic acid (1 μM), and endogenously derived EETs potently activate cardiac and vascular ATP-sensitive K channels (Lu *et al*., 2006). An effect of EETs has also been observed for other types of ion channels. The inhibitory effect of AA on epithelial Na channels in the rat cortical collecting duct ($EC_{50} = 2\,\mu M$) is mediated by 11,12-EET, the three other EETs (5,6-EET, 8,9-EET and 14,15-EET) being without effect (Wei *et al*., 2004). The effect of EETs on TRPV4 channels in HEK-293 cells (Watanabe *et al*., 2003) and on TRPV4-like non-selective cation channels in B lymphocytes (Liu *et al*., 2006) has been mentioned above and illustrated in Figures 5c and d. In addition to their role as vasodilators and their effects on several ion channels, EETs are potent anti-inflammatory and antiatherogenic agents that stimulate lipid metabolism and regulate insulin sensitivity (Larsen *et al*., 2007).

The P-450-epoxygenase metabolite 20-HETE acts either as a vasoconstrictor (for example, in renal or cerebral arteries, see Zou *et al*., 1996; Gebremedhin *et al*., 2000) or as a vasodilator (for example, in adult pig pulmonary arteries, see Fuloria *et al*., 2004). Vasodilation is due to BK_{Ca} channel activation, vasoconstriction to inhibition of Ca^{2+}-activated K^+ channels. 20-HETE has an inotropic effect on airway smooth muscle in guinea pig (Cloutier *et al*., 2003), but relaxes airway smooth muscle in human bronchi (Morin *et al*., 2007). The inotropic effect in guinea pig is caused by the activation of TRPC6 channels (Basora *et al*., 2003; Cloutier *et al*., 2003, see page 5) and the relaxation in human bronchi by BK_{Ca} channel activation (Morin *et al*., 2007).

Effects of lipoxygenase metabolites

The 5-lipoxygenase pathway of AA metabolism leads to the production of 5-HPETE, 5-HETE and leukotrienes. Leukotrienes (as well as prostaglandins) mediate cardinal signs of inflammation. They have evoked clinical interest because they play an important role in asthma. LTC_4 is released from eosinophils and mast cells in large amounts and converted to LTD_4. Both substances cause a constriction of smooth muscle, thereby producing asthmatic bronchospasm (for reviews, see Soberman and Christmas, 2003; Brock, 2005). Pretreatment with an LTD_4 receptor antagonist blocks the bronchoconstrictive response. LTC_4 and LTD_4 depolarize neurons in the enteric nervous system of the small intestine and enhance their excitability (Liu *et al*., 2003). 5-lipoxygenase products are also known to elicit a short-lasting (ca. 1 min) increase in cytosolic calcium, for example, Mazzetti *et al*. (2003) on smooth muscle cells, Nielsen *et al*. (2005) on intestinal epithelial cells and Andoh and Kuraishi (2005) on cultured dorsal root ganglion neurons. A vast literature deals with the effect of 5-lipoxygenase metabolites (for example, LTC_4) on ion channels. 5-lipoxygenase metabolites activate non-selective cation channels in dorsal root ganglion cells, Ca^{2+} channels in carcinoma cells (Peppelenbosch *et al*., 1992) and TRPV1 channels (Hwang *et al*., 2000; Nilius and Voets, 2005; see Figure 5b). Leukotrienes are further thought to play a role in the pathogenesis of atherosclerosis (Bäck *et al*., 2005) and in immune defence (Flamand *et al*., 2007). Mast cells when stimulated by Ca^{2+} generate and secrete LTC_4 (Peters-Golden *et al*., 2006). In RBL-1 rat basophilic cells, a subplasmalemmal Ca^{2+} rise driven by Ca^{2+} entry through SOCE channels promotes the generation of AA, which is then metabolized to LTC_4, whereas bulk cytoplasmic Ca^{2+} elevation fails to activate this signalling pathway (Chang *et al*., 2008).

The 12-lipoxygenase pathway leads to the production of 12-HPETE. Villarroel (1994) and Yu (1995) found that the M-current (Kv7) of bullfrog sympathetic neurons is enhanced by Ca^{2+} (activating phospholipase A2) and AA, effects blocked by selective 12-lipoxygenase inhibitors at relatively low concentrations, but not by 5-lipoxygenase inhibitors. Overexpression of 12-lipoxygenase in NG108-15 neuroblastoma × glioma hybrid cells dramatically increases the excitability, probably by inhibiting M-current (Takahashi *et al*., 1999). 12-lipoxygenase metabolites have also been proposed as signalling molecules in hippocampal long-term potentiation and long-term depression for more than 15 years (Feinmark *et al*., 2003). Also, 12(S)-HETE and 12(S)-HPETE open calcium-activated K^+ channels and thereby produce membrane hyperpolarization in the vascular muscle of coronary microvessels (Zink *et al*., 2001). Likewise, AA dilates the basilar artery by a lipoxygenase-dependent mechanism, probably by 12-HETE (Faraci *et al*., 2001). The lipoxygenase pathway is also involved in the AA-induced activation of $I_{K(Ca)}$ in gastric myocytes (Zheng *et al*., 2005).

15-HETE, a product of the 15-lipoxygenase pathway, is an anti-inflammatory agent (as opposed to the pro-inflammatory leukotrienes) (Serhan *et al*., 2003). The effect of 15-HETE on TRPV1 channels (Hwang *et al*., 2000) is illustrated in Figure 5b. 11,12,15-trihydroxyeicosatrienoic acid, another 15-lipoxygenase metabolite, activates apamin-sensitive K^+ channels in the rabbit aorta, thereby causing hyperpolarization and vascular relaxation (Gauthier *et al*., 2004).

Two main conclusions

From this short review, two conclusions can be drawn: (1) AA acts on all types of ion channels; it acts in different ways, namely either directly or through its various metabolic products. (2) AA and its products are important in several pathological processes. Arachidonic acid produces the prostaglandins through the cyclooxygenase pathway. They play a key role in inflammation. Arachidonic acid also produces, through the lipoxygenase pathway, the leukotrienes that are involved in the origin of asthma bronchiale. A recent paper by Fang *et al*. (2008) emphasizes an important function of AA itself (rather than its metabolites): the role of AA as 'death pore opener'. During traumatic brain injury, brain ischaemia or convulsions, massive amounts of AA are released (a 10- to to13-fold increase of concentration) and are suggested to be involved in the ischaemic-induced neuronal cell death. Fang *et al*. (2008) show that 10 μM AA induces both cytosolic and mitochondrial Na^+ and Ca^{2+} overload. The authors suggest that AA and other types of fatty acids such as oleic acid or the non-metabolizable ETYA exert their effect by opening a non-selective ion conductance.

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Conflict of interest

The author states no conflict of interest.

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