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cAMP-induced expression of ABCA1 is associated with MAP-kinase-pathway activation

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Abstract

Several lines of evidence suggest that the ATP binding cassette A1 (ABCA1) is also involved in other degenerative processes such as brain neurodegeneration. Cholesterol and cAMP activate ABCA1 in a cell-specific manner. We employed a cell culture model of murine monocytes (P388) and neuroblastoma cells (N2A) and studied the differential induction of the ABCA1-gene product by modifying the cholesterol acceptor and by inhibition of the MAP-kinase pathway. Our study reveals a rise of ABCA1-expression in both N2A and P388 by cAMP. This increase is accompanied by a higher activation of the MAP-kinase-pathway. The inhibition of the MAP-kinase activation disrupts the stimulating effect of cAMP but increases the base line expression of ABCA1. Our data suggest a negative feedback between the MAP-kinase-system and ABCA1. We conclude that the interaction of the MAP-kinase pathway and the ABCA1 system might affect the function of neuronal and microglial cells in the brain.

Keywords: ABCA1; cAMP; MAP-kinase; Microglia; Nerve cells

The ATP-binding-cassette transporter A1 (ABCA1) is a member of a family of highly conserved transmembrane transport proteins with a large range of substrates such as drugs (multidrug-resistance-gene products, transported by MDR), ions (cystic-fibrosis-transmembrane-conductance regulator gene products, transported by CFTR), peptides (apolipoproteins, transported by ABCA1), and lipids (cholesterol and phospholipids, transported by ABCA1) [1–4]. Mutations in the ABCA1-gene locus cause dyslipoproteinaemia such as the Tangier disease [5,6], leading to sterol deposits in tissues and to premature atherosclerosis. By its role in macrophage lipid transport ABCA1 is an important target for the prevention and treatment of atherosclerosis [7].

ABCA1 is a protein of 240 kDa with two transmembrane domains and two ATP-binding cassettes, both located either in one (''full-size transporter'') or two polypeptides (''half size transporter'') [7]. Full-size transporters are located in the outer cellular membrane, while half size transporters are mainly located in intracellular membranes like peroxisomes, the Golgi compartment and the endoplasmatic reticulum [8]. Its regulation is cAMP and sterol-depending. The RXR/LXR-motif is important for sterol-depending activation of expression [9,10], cAMP is necessary for either functional activation of ABCA1 in stock [11,12] or for the increase of expression [13–15].

Growing evidence indicates that dysfunctions in the lipid metabolism in the brain can cause neurodegenerative diseases such as Alzheimer's disease (AD) [16–18]. Therefore, the ABCA1 function and regulation in the brain were studied and, in fact, ABCA1-RNA was detected in human brain [19] and agonists of the liver X receptor not only increase ABCA1 expression but also increase secreted $A\beta_{40}$ and $A\beta_{42}$, both known risk factors for AD [20]. In hippocampal cells, ApoE4, another risk factor for AD, increases the ABCA1 expression via the MAP-kinase pathway [21].

A number of kinases, among them the MAP-kinase pathway, play a key role in AD pathology; e.g. the

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activated MAP-kinase pathway is associated with an inflammatory response of glia and monocytes on amyloid fibrils [22], the neurotoxicity of Aß [23], Tau-deposits in the brain of AD-patients [24], and an abnormal phosphorylation in response to oxidative stress [25]. The ERK-activation of astroglia correlates with clinical and neuropathological findings in early AD [25].

Aim of our study was to study the interaction of ABCA1 and the MAP-kinase pathway. In a cell culture model of murine monocytes and neuroblastoma cells (P388 and N2A), this study shall address the effects of different lipids and lipoproteins on ABCA1. In addition, the effects of inhibition of the MAP-kinase pathway and stimulation of ABCA1 by cAMP should also be tested in these cells.

Among the different kinases of the MAP-kinase pathway, we focused on the activation status of ERK1/2, two isoforms with 83% homology [26]. The activation requires double-phosphorylation both on Thr^{183} and Tyr^{185} by specific upstream-MEKs, the down-regulation of the signal occurs by single or double dephosphorylation [27]. The main target motifs for ERKs are Ser/Thr-residues followed by Pro-residues [26]. The function and the localization of the targets vary, including membrane proteins, proteins of the cytosol, cytoskeleton or mitochondria, transcription factors and downstream-protein kinases. Because of the

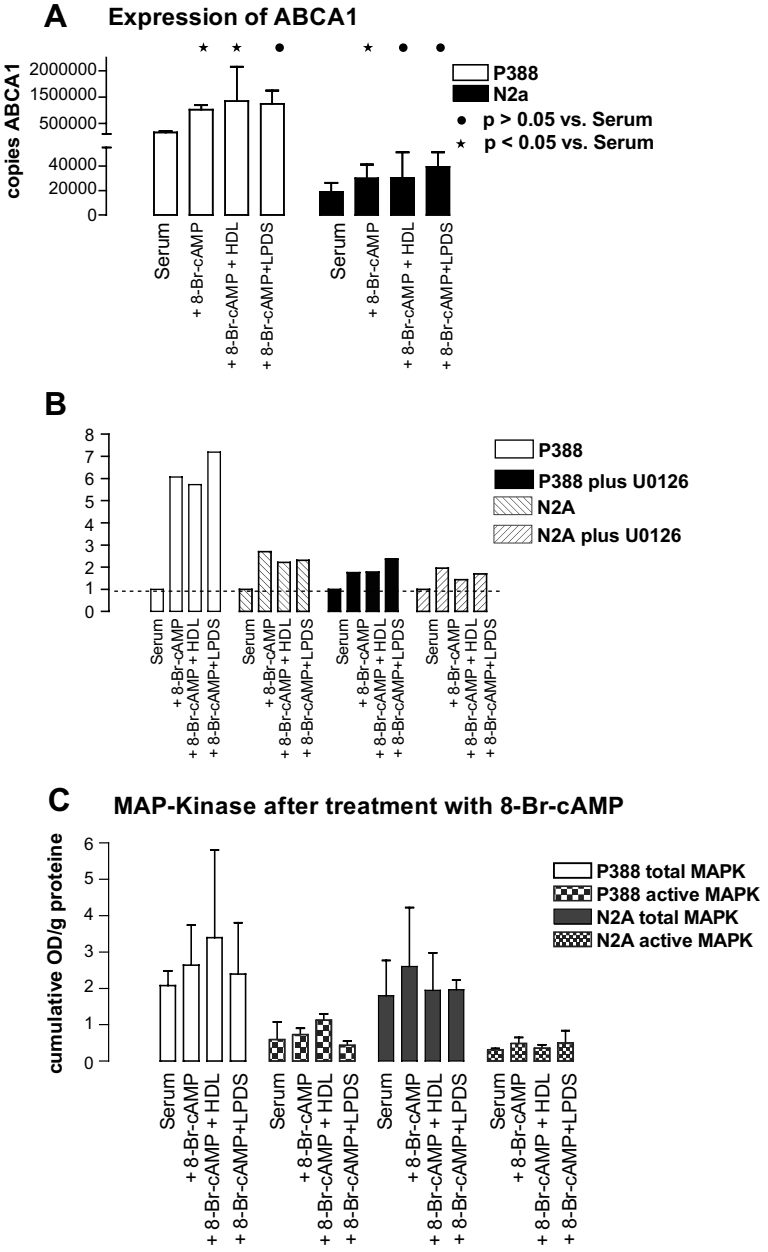

Fig. 1. Effects of 8-Br-cAMP ± HDL or LPDS on the expression of ABCA1 without (A) and with inhibition by U0126 (B) and on the MAP-Kinase activation in P388 and N2A (C). Data are mean ± standard deviation from three independent experiments.

ability of cAMP to activate the MAP-kinase via protein kinase A [28] and to stimulate ABCA1 expression our interest was to examine the role of active MAP-kinases in P388 and N2A cells.

Materials and methods

Cell culture. Neuro2A-cells (N2A) and monocytes (P388) were grown for 3 days in pre-culture. For N2A, 0.6×10^6 cells were seeded on 175 cm^2 culture bottles and grown in Dulbecco's modified Eagle medium (DMEM, GibcoBRL) with 10% fetal calf serum, 1% non-essential amino acids and 1% penicillin–streptomycin. For P388, 0.6×10^6 cells were seeded on 175 cm^2 culture bottles and grown in RPMI with 10% fetal calf serum (Biochrom), 1% L-glutamine and 1% penicillin-streptomycin. To each cell type, 750 μg acetylated human LDL was added. LDL was isolated by ultracentrifugation from plasma obtained from the local blood bank.

MAP-kinase stimulation started on day 4. First, the cells were rinsed with PBS containing 1 mg/ml BSA. After this, DMEM containing 1% non-essential amino acids, 1% penicillin-streptomycin and 1 mg/ml BSA was added. In this medium, stimulating supplements in following combinations were added:

- no supplements ± 10 μM U0126 (Promega) and 0.1% DMSO;
- 0.3 mM 8-Br-cAMP (Sigma) ± 10 μM U0126 and 0.1% DMSO;
- 0.3 mM 8-Br-cAMP, 50 μg/ml HDL ± 10 μM U0126 and 0.1% DMSO;
- 0.3 mM 8-Br-cAMP, 50 μg/ml LPDS ± 10 μM U0126 and 0.1% DMSO.

After 24 h, the cell medium was removed for the analysis of the pattern of apolipoproteins and the cells were scraped in ice-cold PBS for the isolation of RNA or for lysis [14].

Isolation of RNA. About 10×10^6 cells were treated with 1.5 ml Trizol Reagent and kept at room temperature for 5 min. After incubation with 600 μl chloroform for 3 min the total RNA was centrifuged for 20 min at 12,000*g* and 4 °C. Subsequently, the total RNA was precipitated with 1000 μl isopropanol and after incubation of 10 min at room temperature the RNA was precipitated for 10 min at 16.000*g* and 4 °C. The resulting RNA-pellet was washed with 2000 μl isopropanol and stored at −80 °C. The concentration of RNA was assessed photometrically at 260 nm.

To determine the expression of the murine ABCA1, we applied the TaqMan-method real time PCR with the cyclophilin-gene-product used as house-keeping-gene. Following sequences were used for standards and probes (probes supplied from Eurogentec, primers from MWG Biotech):

ABCA1: upstream primer 5′-GTC CTC GGG CTG ACC CTT TT- 3′
downstream primer 5′-CCA TGG CAA ACA CAG ACA GG-3′
probe 5′FAM-CCC CCA CTT CTG GCA CGG CCT AC-3′TAMRA
Cyclophilin: upstream primer 5′-GGC CGA TGA CGA GCC C-3′
downstream primer 5′-TGC GAT GTA GAT AGC AGT GAC A-3′
probe 5′FAM-CAA CGC CCA CGC AGC AAC A-3′TAMRA

RNA was transcribed into cDNA by random priming. The resulting cDNA was suspended with water at 1:15. To 40 μl of this sample was added for the TaqMan-procedure:

DEPC-water	18.25 μl
$MgCl_2$ (25 mM)	10 μl
10-Fold PCR-buffer (Promega)	5 μl
dNTP-mix (100 mM, Promega)	4 μl
Forward-primer	0.75 μl
Reverse-primer	0.75 μl
TaqMan probe	1 μl
Ampli Taq Gold (Applied Biosysystems)	0.25 μl

The TaqMan-procedure was performed as follows: 50 °C for 2 min, 95 °C for 10 min, 95 °C for 15 s (40 cycles), and 60 °C for 1 min. TaqMan-specific software (Applied Biosystems) was used for analysis. Results are shown as the mean of triplicate analyses.

Expression of MAP-kinase related genes by gene array. The cells were scraped in ice-cold PBS as described above, the RNA was isolated with Trizol reagent (Invitrogen) and the concentration of RNA was measured. The expression was assessed with a DNA array (MAP-kinase Signaling Pathway Nonrad Q Series Kit, SuperArray Inc.) [29,30]. According to the manufacturers manual we performed a non-amplifying PCR converting the RNA into biotin-labeled cDNA. For this, we used a low-thymidine-dNTP-mix (components by Promega) and substituted thymidine with biotin-16-dUTP (Roche). The hybridization of the cDNA with the probe-coated membranes was done according to the manufacturer's instruction. For detection of bound cDNA we used a chemiluminescence system (CDP-Star substrate reacting with AP-strepdavidin). For quantitation, we made a copy of the membranes on Biomax MR (Kodak) and recorded the chemiluminescence with an Alpha-Imager (Alpha Industries). The raw date of the pictures were obtained with the ChemiImager (Alpha Industries) and semiquantitatively analyzed with the GEArray Analyzer (SuperArray Inc.). The results are shown in relation to the expression of GAPDH.

MAP-kinase activation: For lysis we modified the method of Osbourne et al. [31,32] and isolated the cytosolic and the nuclear protein fractions separately. Three different buffers were used:

Buffer A:	
Hepes pH 7.9	10 mM
KCl	10 mM
$MgCl_2$	2 mM
IGEPAL (Sigma)	0.1 % (v/v)
Dithiothreitol (Fluka)	0.5 mM
Pepstatin A (Fluka)	1% (m/v, 0.01 mg/ml)
Leupeptin (Sigma)	1% (m/v, 0.01 mg/ml)
Aqua bidest	ad 100 ml
1 tablet Complete (Roche Diagnostics) in 10 ml	
Buffer B:	
Hepes PH 7.9	20 mM
Glycerol	25 % (v/v)
NaCl	0.42 mM
$MgCl_2$	1.5 mM
EDTA	0.2 mM
Dithiothreitol	0.5 mM
Leupeptin	1% (m/v, 0.01 mg/ml)
Aqua bidest	ad 100 ml
1 tablet Complete in 10 ml	
Buffer C:	
Hepes pH 7.9	20 mM
Glycerol	20 % (v/v)
KCl	0.05 mM
EDTA	0.2 mM
Dithiothreitol	0.5 mM

For lysis, 40 μl buffer A, 4 μl buffer B and 2 μl buffer C were used for 10^6 cells. After scraping and cell count, the cells were spun down at 1500 rpm for 10 min at 4 °C in an Eppendorf centrifuge. The resulting pellet was resuspended with a defined amount of buffer A and kept at 4 °C under continuous agitation (Reax 3, Heidolph). Cells and buffers were vortexed for 15 s and then spun down (14,000 rpm, 4 °C, 5 min). The supernatant resulting from this procedure contained the cytosolic proteins.

The resulting pellet was resuspended with a defined amount of buffer B, vortexed and spun down (14,000 rpm, 10 min, 4 °C). The supernatants were kept and the defined amount of buffer C was added. The resulting supernatant contained the nuclear proteins.

Supernatants were stored at −80 °C. The protein concentration was measured by a BCA-kit (Pierce). Western blotting of the cytosolic and the core protein fractions was performed by SDS-electrophoresis and tank blotting on nitrocellulose membranes (Amersham Pharmacia). After blocking and several washings, membranes were incubated overnight with an antibody binding specifically the total (anti-p44/42) or the active, double phosphorylated form (anti-phospho-p44/42, both antibodies from Cell Signalling Tech.) [33–36]. Second antibody was a HRP-conjugated anti-rabbit-IgG. Antibody binding was detected by Best Western Femto Signalling Substrate (Pierce) and visualized on Biomax MR film (Kodak) with five minutes of exposure. The films were scanned and analyzed with OneD-Scan-software (Scanalytics).

Results

In P388 cells, the combination of 8-Br-cAMP (0.3 mM) and HDL (50 μg/ml) increased the expression of ABCA1 about 4.7 times, 5.2 times for 8-Br-cAMP alone and almost no change for HDL alone versus nonstimulated cells. 8-Br-cAMP and LPDS in combination increased the expression of the ABCA1-gene at the level of 8-Br-cAMP alone (Fig. 1A). ABCA1 was also detected in N2A cells but the level of expression was much lower compared to P388. ABCA1 expression increased 2.2 times after treatment with the combination of 8-Br-cAMP and HDL. Treatment with 8-Br-cAMP alone or with the combination of 8-Br-cAMP and LPDS had a very similar effect (Fig. 1A).

The activation of the MAP-kinase pathway was assessed in parallel to ABCA1 expression. The results are shown in Fig. 1C as the mean of three independent experiments. Maximum activation was observed under 8-Br-cAMP and HDL (about 3.1-fold vs. unstimulated P388). HDL alone lowered the activation by 32% and 8-Br-cAMP doubled the activation. In N2A, maximum activation was achieved with 8-Br-cAMP (1.9-fold increase). The addition of HDL alone had no different effect than the addition of serum, as expected (data not shown).

To rule out the role of activated MAP-kinase, the tests were repeated in the presence of U0126, a specific inhibitor

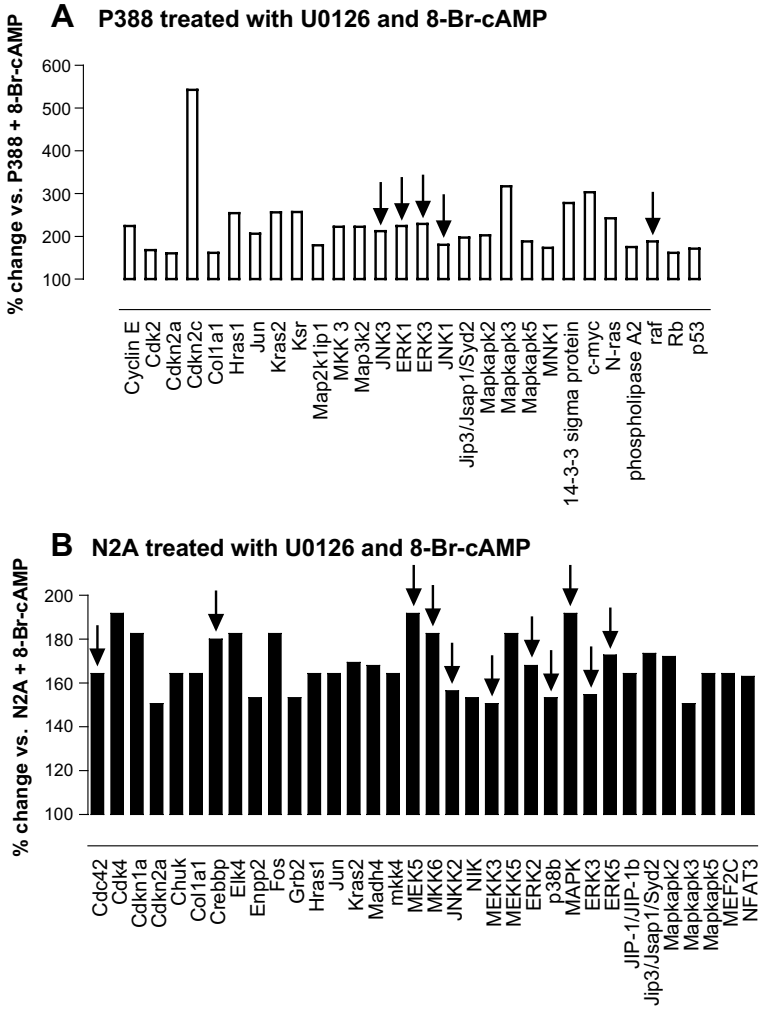

Fig. 2. Expression of of MAPK-related genes: effects of inhibition with U0126 in P388 (A) and N2A (B) cells in the presence of 8-Br-cAMP. Data are obtained by DNA array after RT-PCR,only genes with an expression increase >150% are shown. Data are expressed as percentual change vs. cells treated with 8-Br-cAMP in the absence of U0126. Please note the different scale in (B). Arrows indicate genes that are possibly responsible for the negative feedback under MEK-inhibition.

of MEK 1 and 2 (MEK 1 and 2 are upstream activators of the MAP-kinase). Baseline-level of expression of ABCA 1 increased by MEK1 and MEK2 inhibition, but further activation by 8-Br-cAMP was blunted (Fig. 1B).

For the study of the regulation of MAP-kinase associated genes, the expression of 94 genes was tested with a DNA-array after RT-PCR. Stimulation with 8-Br-cAMP and/or HDL only led to very subtle changes on gene expression of these MAP-kinase associated genes. However, as expected, inhibition of MAP-kinase activation by U0126 increased as well the expression of MAP-kinases as the expression of upstream activators of MAP-kinases (Fig. 2), both in P388 and, to a lower extent, in N2A cells.

Discussion

The novel finding of our study is a linkage between the cAMP-stimulated expression of ABCA1 and the MAP-kinase-pathway in P388 cells. The highest increase of expression of ABCA1 occurs with a concurrent rise in the activation of the MAP-kinase. A similar effect was observed in N2A, but the change was of lower magnitude than in P388. Recent studies have indicated a possible dual mechanism, involving not only the gene expression but also changes in the functional status by phosphorylation of the ABCA1 protein [10,11]. The influence of the MAP-kinase seems to take place in a subtle network of activation between MAP-kinase and protein kinase A. A possible key to a two-way-activation is in this context the HePTP, an inactivator of the MAP-kinase. This kinase becomes inactivated by the protein kinase A which leads to additive amplifying effect of the network of activation [28].

The effect observed of an inhibition of the MAP-kinase-activation revealed in N2A and in P388 was an unexpected result – the base-line-expression of ABCA1 increases in both cell types, but the further increase of ABCA1 expression by cAMP is blunted. To rule out whether this effect is mediated by a single MAP-kinase depending factor or not, we performed a RNA-array of MAP-kinase related genes. Our data can clearly exclude that a single factor is responsible for this finding: The expression array shows a mild but all-over increase of the expression of numerous MAP-kinase-related genes. From out data we conclude that there is a remarkable negative feedback in the system of these genes, counteracting the inhibition the MAP-kinase activation. In a second step, we identified genes with the highest changes in expression (these genes are indicated by arrows in Fig. 2). Some of these genes have been also identified in a comparable setting: Nofer et al. showed a CDC42-induced cholesterol efflux via Apo A-I under participation of JNK and p38 [37].

From our data we conclude that the cAMP-depending expression of ABCA1 depends on the boosting effect directed to functional active system of the MAP-kinases and that the base line expression of ABCA1 is more sensible in an upregulated system of MAP-kinase related genes. A single possible target gene could not be identified. The obvious explanation for this observation is the redundancy of the MAP-kinase systems.

Our data in neuronal cells and macrophages indicate a potential crosstalk of the ABCA1 system and the MAP-kinase system which makes them an interesting target for studies of the neurodegeneration in Alzheimer-type dementia [18,21,23,38–40].

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