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Differences between cation-chloride co-transporter functions in the visual cortex of pigmented and albino rats

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Abstract

Albinism in mammals is accompanied by specific morphological and functional alterations of the visual system. To understand their cellular basis we studied the physiological characteristics and transmembrane currents of pyramidal neurons in 350-μm-thick slices of visual cortex from pigmented and albino rats using whole-cell and gramicidin perforated patch-clamp recordings. The resting membrane potential was significantly more positive and the rheobase was significantly lower in neurons of layers II/III and V in albinos as compared with pigmented rats. No significant differences were found in the input resistance, time constant and chronaxy. Whereas the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor-mediated currents were not significantly different, the maximum γ-aminobutyric acid $(GABA)_A$ receptor ($GABA_AR$)-mediated currents and miniature inhibitory postsynaptic currents showed significantly lower amplitudes in neurons of layer V in visual cortex of albinos as compared with pigmented rats. The reversal potential of the $GABA_AR$-mediated currents (E_{GABA}) was significantly shifted to more positive values in albinos. Pharmacological experiments showed that this shift could be caused by an increased action of the inward chloride co-transporter NKCC1 and reduced action of the outward chloride co-transporter KCC2 in albino rats. This difference seems to be restricted to the visual cortex because in pyramidal neurons from frontal cortex E_{GABA} was not significantly different in albinos as compared with pigmented rats. These results are discussed in relation to functional alterations in the albino visual system.

Introduction

In addition to the well-known features of albinism, such as pigment deficiency of the skin, hair and ocular tissues, a lot of studies indicate profound differences in the organization of the visual system between albinos and pigmented mammals. It is probably the reduction of dihydroxyphenylalanine in the retina that causes spatiotemporal alterations of neurogenesis, and in turn leads to reduced rod and ganglion cell densities, as well as to the abnormal crossing of retinofugal fibres originating from the temporal retina (e.g. Jeffery, 1997; Ilia & Jeffery, 2000; Donatien *et al*., 2002; Rachel *et al*., 2002). Ipsilateral retinal projections to superior colliculus, pretectum and visual thalamus are reduced (Morgan *et al*., 1987; Zhang & Hoffmann, 1993). This results in reduced and abnormal binocular representations at higher levels of the visual system, and an abnormal retinotopic map in the visual cortex (Guillery, 1986; Akerman *et al*., 2003) but not the superior colliculus (Quevedo *et al*., 1996). Albino mammals often are unable to perform regular optokinetic eye movements to stabilize the visual environment (for a recent review, see Hoffmann *et al*., 2004). In rats and ferrets this optokinetic defect could be directly linked to a loss of direction selectivity in the nucleus of the optic tract and dorsal terminal nucleus (NOT-DTN), the sensorimotor interface in the pathway subserving the optokinetic reflex (Lannou *et al*., 1982; Hoffmann *et al*., 2004). As direction selectivity in the NOT-DTN arises from direction-selective retinal ganglion cells (turtle: Rosenberg & Ariel, 1991; rabbit: Oyster *et al*., 1972; cat: Hoffmann & Stone, 1985) and from direction-selective pyramidal cells in motion-sensitive cortical areas (cat: Schoppmann, 1985; monkey: Hoffmann *et al*., 2002), one can hypothesize that direction selectivity must be generally disturbed in the visual system of albino mammals.

There is growing evidence that direction selectivity in the retina and visual cortex critically depends on γ-aminobutyric acid (GABA)ergic mechanisms and cation-chloride co-transporters (e.g. Caldwell *et al*., 1978; Kittila & Massey, 1997; Taylor *et al*., 2000; Gavrikov *et al*., 2003; Thiele *et al*., 2004). However, little is known about the effect of albinism on these mechanisms (Cransac *et al*., 1997). Using a biochemical approach we recently demonstrated that in the retina the ratio of glutamate to GABA is altered in albino when compared with pigmented rats (Blaszczyk *et al*., 2004). To directly investigate whether excitatory and inhibitory mechanisms are altered in the visual system of albino mammals, we compared the physiological properties of visual cortical pyramidal cells in pigmented and albino rats. We characterized their electrophysiological properties and transmembrane currents using whole-cell patch-clamp and gramicidin perforated patch-clamp techniques. As a result of our observation that excitatory currents were equal but $GABA_A$ receptor ($GABA_AR$)-mediated inhibitory currents were different in albinos as compared with pigmented rats, we then investigated the functional involvement of the main cation-chloride co-transporters in neocortical neurons: Na^+-K^+-$2Cl^-$ co-transporter (NKCC1, Cl^- uptake) and K^+-Cl^- co-transporter (KCC2, Cl^- extrusion) (Kaila, 1994).

Materials and methods

All experimental procedures were approved by the local ethics committee and were performed in accordance with the European Communities Council directive of 24 November 1986 (S6609 EEC)

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and National Institutes of Health guidelines for care and use of animals for experimental procedures.

Pigmented Long–Evans and albino Wistar rats of either sex (4–5 weeks old) were anaesthetized with halothane and decapitated. The brain was removed and immersed in ice-cold artificial cerebrospinal fluid [ACSF (in mM): NaCl, 123; KCl, 2.5; NaH_2PO_4, 1; $NaHCO_3$, 26; D-glucose, 11; $CaCl_2$, 1.8; $MgCl_2$, 1.3; bubbled with 95% O_2 and 5% CO_2, pH 7.4]. Five–six 350-μm-thick coronal slices of visual cortex were cut on a vibratome (RHG, Rhema Labortechnik, Hofheim, Germany). Slices were incubated for at least 1 h in ACSF at room temperature and then transferred to a submerged recording chamber that was mounted on an upright microscope (OLYMPUS-BX51WI, Olympus, Japan) equipped with a 40 × water immersion objective (N.A. = 0.8; Olympus). The recording chamber was perfused at 3 mL/min with oxygenated ACSF at room temperature.

Whole-cell and gramicidin perforated patch-clamp recordings were performed under visual control. Borosilicate patch electrodes (5–9 MΩ) were filled with a solution containing (in mM): K-gluconate, 130; Na-gluconate, 0.5; HEPES, 20; $MgCl_2$, 4; Na_2ATP, 4; Na_3GTP, 0.4; EGTA, 0.5 (pH 7.2), to which gramicidin (25 μg/mL, dissolved in dimethylsulphoxide (Sigma, St. Louis, MO, USA) was added as the membrane-perforating agent in perforated patch recordings and lidocaine N-ethyl bromide (QX-314, 5 mM, Tocris Cookson, Bristol, UK) to verify the integrity of perforation. The measured membrane potentials were corrected for the junction potential of −10 mV (Mienville & Pesold, 1999).

The neurons were voltage- or current-clamped by means of a RK-300 patch-clamp amplifier (Biologic, Grenoble, France) connected via AD/DA-converters (CED 1401+, Cambridge Electronic Design, UK) to a personal computer. Physiological membrane properties were estimated in current-clamp mode by applying depolarizing and hyperpolarizing current steps (100–600 ms duration). In other experiments, postsynaptic currents (PSCs) were evoked through a concentric bipolar electrode placed approximately 50–100 μm lateral to the recorded neuron with stimuli (20–100 μA, 50 μs duration, 0.1 Hz) in voltage-clamp mode. Holding potentials were systematically varied

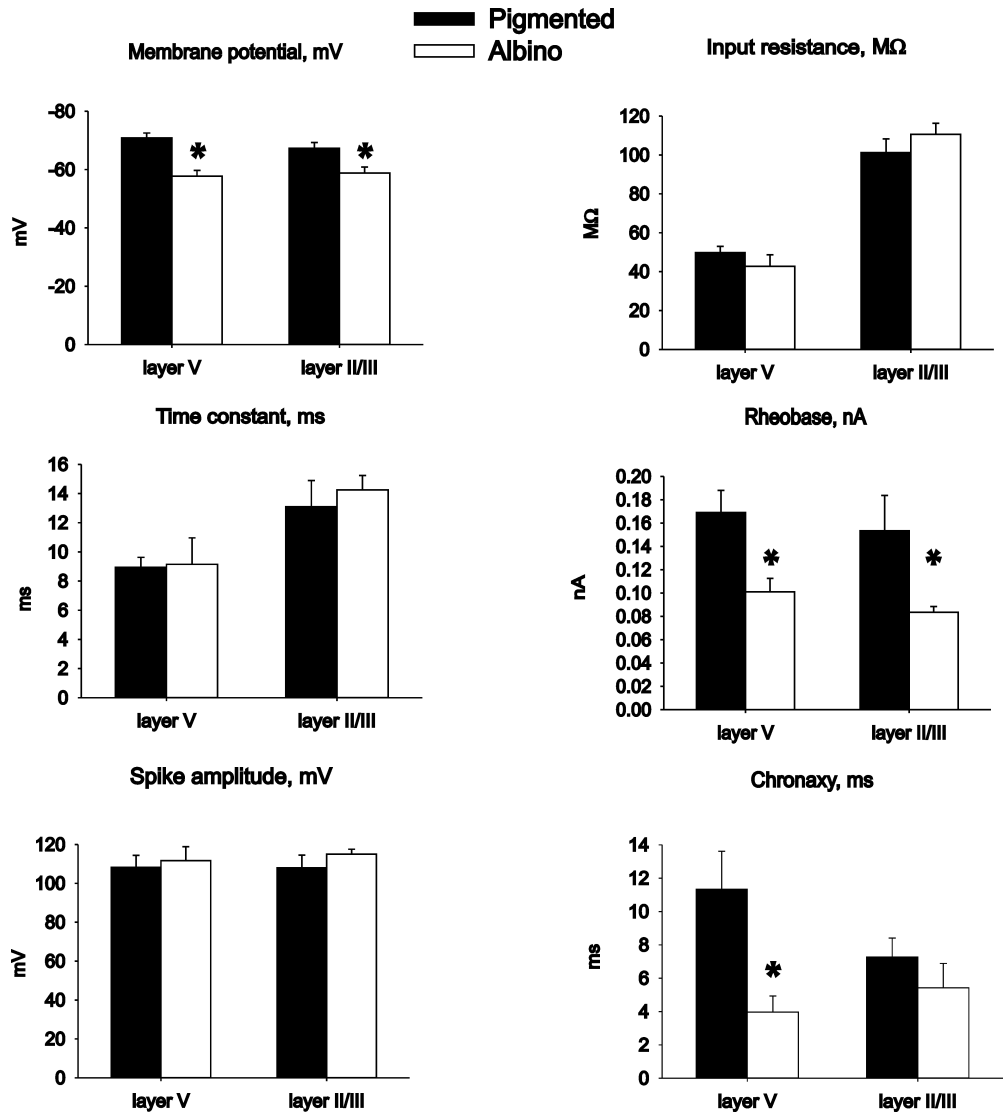

FIG. 1. Physiological properties of pyramidal neurons of layer V and layer II/III in the visual cortex from pigmented (black bars) and albino (white bars) rats. For most of the properties analysed, no significant difference between albino and pigmented rats was found. However, albinos show a significantly more positive resting membrane potential and significantly smaller rheobase compared with pigmented rats. Also, in layer V neurons from albino rats, chronaxy was significantly smaller than in the cells from pigmented rats. *$P < 0.05$.

from −100 to +30 mV in 10-mV steps (Fig. 2). Recordings underwent low-pass filtering at 3 kHz and were sampled at 10 kHz. WinWCP software (John Dempster, University of Strathclyde, Glasgow, UK) was used for recording and analysis.

The drugs applied were kynurenic acid, bicuculline, bumetanide, furosemide (Sigma), 2-amino-5-phosphonopentanoic acid (APV) and tetrodotoxin citrate (TTX, Tocris). Substances were prepared as stock solutions and frozen, then added to ACSF to reach the desired final concentration. Kynurenic acid was added directly to the bath solution.

Data are presented as mean ± SEM and tested for significant differences with the Student's unpaired *t*-test ($P < 0.05$) using SigmaStat software.

Results

The visual cortex slices were derived from Bregma −5.8 mm to Bregma −7.5 mm (Paxinos *et al*., 1985), where the visual cortical areas 18, 17 and 18a extend 7–8 mm from the midline laterally to the temporal cortex. Slices of frontal cortex were taken from Bregma −1.8 mm to Bregma −3.2 mm. All recorded cells are pyramidal neurons from layer V or layer II/III of either visual or frontal cortex. In the first set of experiments we compared the passive electrophysiological properties and threshold parameters of pyramidal neurons from pigmented and albino rats (Fig. 1). The average resting membrane potential was significantly more positive in albinos (−57.7 ± 2.0 mV) than in pigmented rats (−70.9 ± 1.7 mV). Input resistance, time constant and, consequently, cell capacitance, spike amplitudes, frequency and spiking pattern were not significantly different between neurons from pigmented and albino rats. Rheobase (the current threshold to release a spike by long depolarizing pulses) and chronaxy (the minimal duration of a current pulse of twice the rheobase amplitude to release a spike) were measured by depolarizing current injections from resting potential. The rheobase was significantly lower in neurons from albino (0.10 ± 0.01 mV) compared with pigmented rats (0.17 ± 0.02 mV). The chronaxy was significantly smaller in layer V neurons from albino rats (4.0 ± 1.0 ms) compared with pigmented animals (11.3 ± 2.3 ms; Fig. 1).

In the second set of experiments we compared the maximum amplitudes of electrically evoked excitatory and inhibitory postsynaptic currents (EPSC and IPSC), and miniature excitatory and inhibitory postsynaptic currents (mEPSC and mIPSC) in layer V pyramidal neurons of the visual cortex in pigmented and albino rats. α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor (AMPAR)-mediated currents were recorded in voltage-clamp mode at holding potentials between −100 and +30 mV by electrical stimulation with the stimulation electrode positioned approximately 50–100 μm lateral to the recorded neuron. Bicuculline (30 μM) and APV (25 μM) were added to the bath solution in order to block $GABA_A$ and *N*-methyl-D-aspartate receptors, respectively (Fig. 3A). The mEPSCs were measured in the whole-cell mode of the patch-clamp technique at −70 mV holding potential after adding TTX (1 μM) to the bath solution, which already contained bicuculline (30 μM) and APV (25 μM). No significant differences in AMPAR-mediated currents or the mEPSC were observed between pigmented and albino animals (Fig. 3B, 15.8 ± 1.9 pA, $n = 4$ albino and 15.8 ± 1.6 pA, $n = 5$ pigmented).

$GABA_A$R-mediated currents were monitored using whole-cell and gramicidin perforated patch at holding potentials between −100 and +30 mV (Fig. 2) by the electrical stimulation with the stimulation electrode positioned approx. 50–100 μm lateral to the recorded neuron. Kynurenic acid (2 mM) was added to the ACSF to block

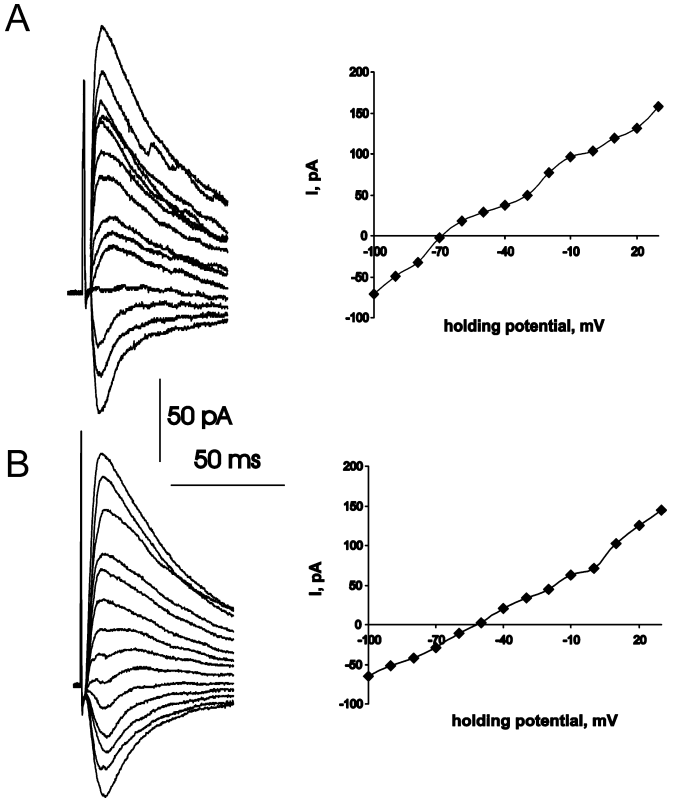

FIG. 2. Sample traces and corresponding current–voltage curves of the electrically evoked $GABA_A$R-mediated postsynaptic currents in neurons from pigmented (A) and albino (B) rats. Holding potentials were systematically varied from −100 to +30 mV in 10-mV steps. Note the E_{GABA} shift in positive direction in albino rats.

glutamate receptor currents. By application of the $GABA_A$R antagonist bicuculline (30 μM), all PSCs disappeared (not shown). The mIPSCs were recorded at +10 mV holding potential after addition of 1 μM TTX to ACSF containing kynurenic acid and were significantly lower in neurons from albinos compared with pigmented rats (whole-cell recording: Fig. 3D, 25.9 ± 1.9 pA, $n = 10$ albino and 35.4 ± 3.6 pA, $n = 8$ pigmented; gramicidin perforated patch: Fig. 3F, 24.8 ± 1.6 pA, $n = 20$ albino and 34.6 ± 1.6 pA, $n = 20$ pigmented). At holding potentials between −50 and +30 mV the maximum $GABA_A$R current amplitude was significantly decreased in albinos (Fig. 3C and E). The reversal potential of the $GABA_A$R-mediated currents (E_{GABA}) was significantly shifted to more positive values in albinos than in pigmented rats by gramicidin perforated patch (Figs 3E and 4).

To investigate whether the observed differences in $GABA_A$R-mediated currents were also present in non-visual areas, we repeated the above experiments on 24 layer V neurons from frontal cortex from albino and on 48 cells from pigmented rats. In frontal cortex, $GABA_A$R currents, E_{GABA} and mIPSCs were almost identical in both animal groups (Figs 3G and H and 4A, mIPSPs: 36.2 ± 3.6 pA, $n = 6$ albino and 30.3.8 ± 3.5 pA, $n = 7$ pigmented).

In search of the mechanisms responsible for the observed differences in $GABA_A$R currents and E_{GABA} in visual cortex, we repeated the same measurements in the presence of antagonists to the most important chloride-transporters: furosemide (20 μM), a selective blocker for the outward transporter KCC2, and bumetanide (10 μM), a selective blocker for the inward transporter NKCC1 (Russell, 2000) were used. Thirty-four visual cortical neurons from albino rats and 30

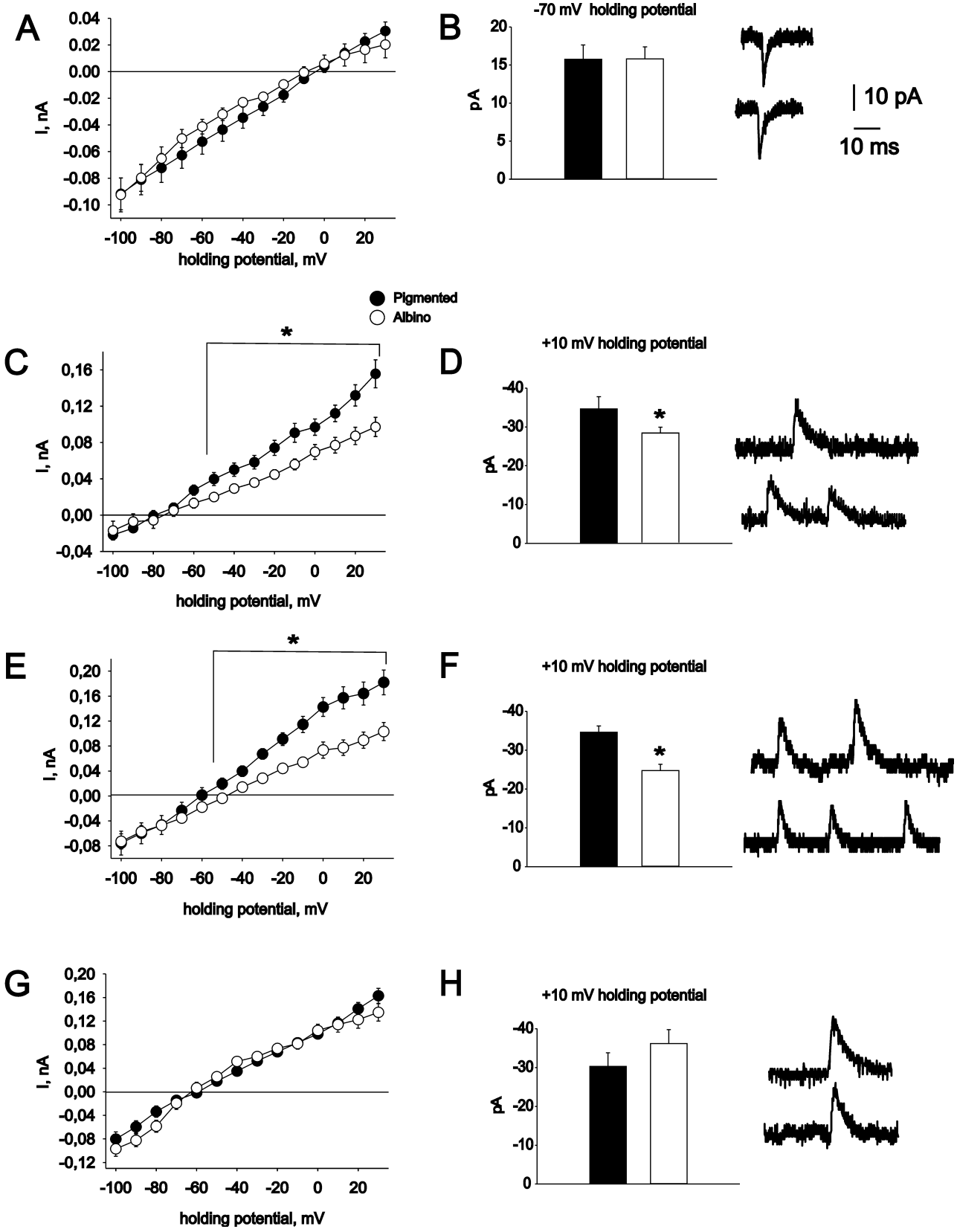

FIG. 3. Electrically evoked and miniature AMPAR- and $GABA_AR$-mediated currents in neurons from pigmented (filled symbols) and albino (open symbols) rats. Electrically evoked (A) and miniature (B) AMPAR-mediated currents were similar in the two experimental groups. Electrically evoked (C) and miniature (D) $GABA_AR$-mediated currents were significantly smaller in albinos compared with pigmented rats both in whole-cell (C and D) and gramicidin perforated (E and F) patch-clamp recordings. In albinos, E_{GABA} was shifted in a positive direction (E). Electrically evoked (G) and miniature (H) $GABA_AR$-mediated currents in neurons of the frontal cortex from pigmented and albino rats. No significant differences were observed between the two experimental groups. $*P < 0.05$.

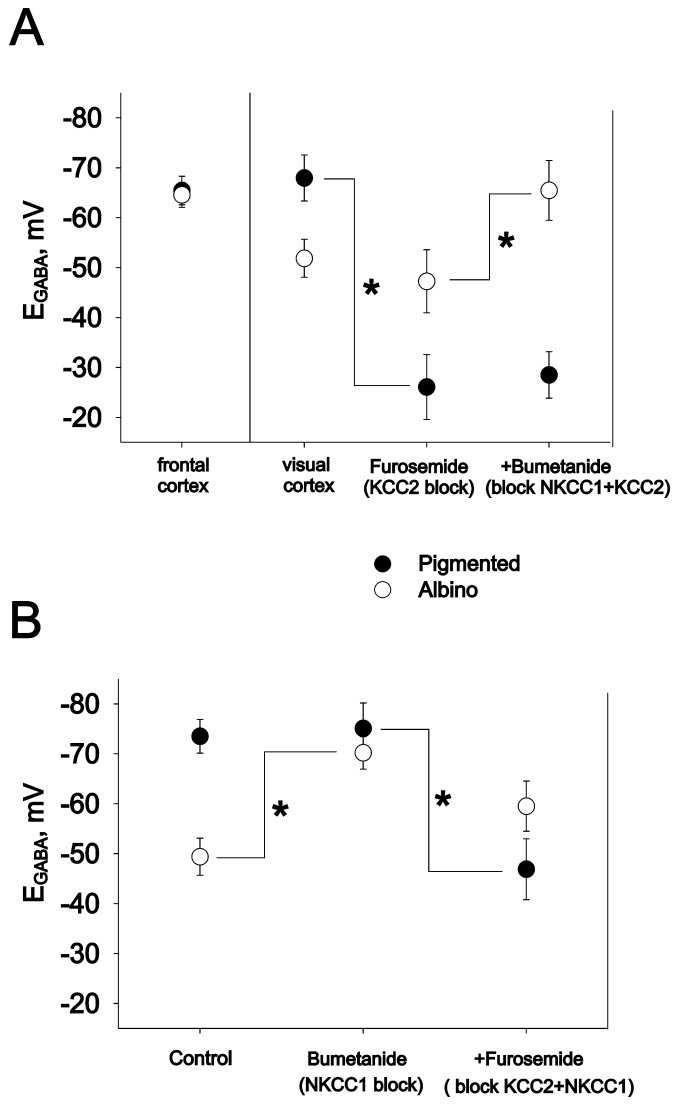

FIG. 4. (A) Summary diagram showing changes in E_{GABA} in frontal cortex (no significant differences between two groups) and in visual cortex during the inhibition of KCC2 and NKCC1. In visual cortex, E_{GABA} is significantly more positive in albinos compared with neurons of pigmented rats. In pigmented animals, the KCC2-inhibitor furosemide (20 μM) leads to a significant shift of E_{GABA} to more positive values. Co-application of the NKCC1-inhibitor bumetanide (10 μM) has no significant effect on E_{GABA}. In albinos the inhibition of KCC2 shows no effect on E_{GABA}, but the additional block of NKCC1 induces a significant shift of E_{GABA} to more negative values. (B) The same effects can be observed by inhibition of the cation-chloride co-transporters in the opposite order. *$P < 0.05$.

from pigmented rats were voltage-clamped at holding potentials between −100 and +30 mV, and $GABA_A$R-mediated currents were measured in normal ACSF containing 2 mM kynurenic acid, and in the presence of the KCC2-inhibitor furosemide. Afterwards, the NKCC1-blocker bumetanide was added and the same protocol was repeated (for 18 neurons from albinos and 14 from pigmented rats). For 16 neurons from albino and 16 from pigmented rats we blocked the cation-chloride co-transporters in the opposite order.

Figure 4 shows the averaged E_{GABA} in pigmented and albino rats estimated for each single neuron measured. In frontal cortex both estimates were not significantly different (−65.4 ± 2.9 mV in pigmented and −64.5 ± 2.5 mV in albinos). E_{GABA} in frontal cortex was also not significantly different from E_{GABA} in visual cortex (−67.9 ± 4.6 mV) in pigmented rats. In albinos, however, E_{GABA} was significantly more positive (−51.8 ± 3.8 mV) in visual than in frontal cortical neurons. In addition, E_{GABA} in visual cortical neurons of albino and pigmented rats differed significantly.

The presence of the KCC2 blocker did not alter E_{GABA} in albino rats (−47.2 ± 6.3 mV) but it shifted E_{GABA} significantly to more positive values (−26.1 ± 6.5 mV) in pigmented rats. The additional application of the NKCC1 blocker shifted E_{GABA} significantly to more negative values in albino rats (−65.4 ± 6.0 mV) and had no effect in neurons of pigmented animals (−28.5 ± 4.7 mV).

We observed the same effects by applying the chloride co-transporter inhibitors in the opposite order. The E_{GABA} was significantly different between pigmented (−73.5 ± 3.4 mV) and albino (−49.4 ± 3.7 mV) rats. The application of the NKCC1 blocker shifted E_{GABA} significantly to more negative values in albino rats (−70.2 ± 3.3 mV) and had no effect in neurons of pigmented animals (−75.1 ± 5.1 mV). The additional application of the KCC2 blocker

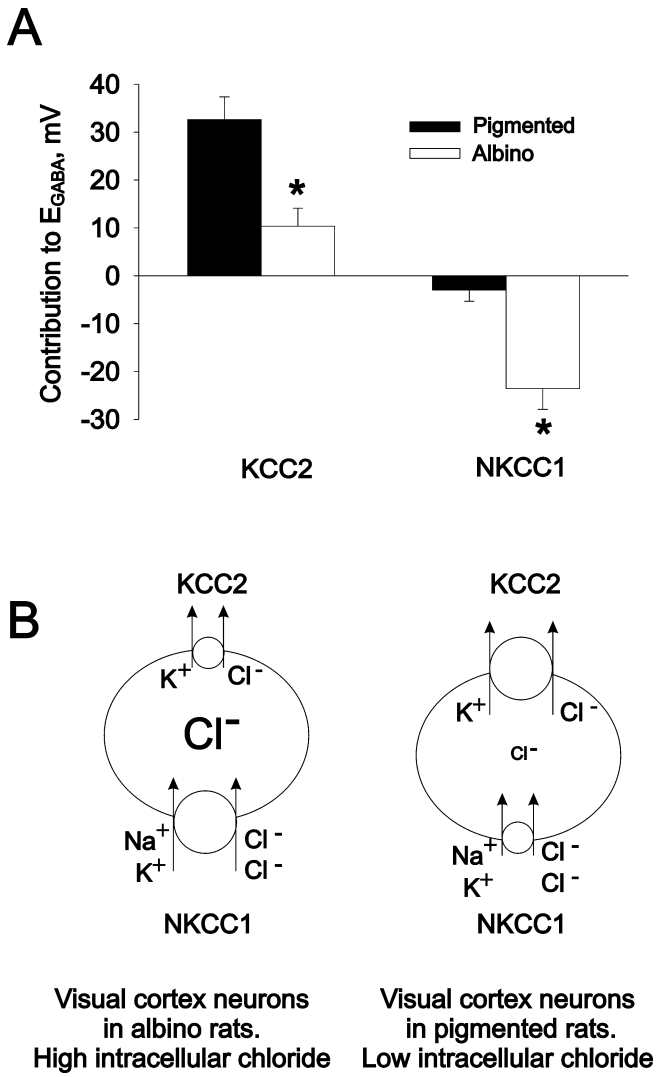

FIG. 5. The contribution to E_{GABA} of KCC2 and NKCC1 in neurons of pigmented and albino rats. The contribution of KCC2 is significantly larger in pigmented rats compared with albinos. In contrast, the contribution of NKCC1 is significantly larger in albinos compared with pigmented rats. (B) The balance between inward and outward chloride co-transporters is altered in neurons of the visual cortex in albino rats. These neurons have a higher intracellular chloride concentration. *$P < 0.05$.

did not alter E_{GABA} in albino rats (−59.5 ± 5.0 mV), but it shifted E_{GABA} significantly to more positive values (−46.9 ± 6.1 mV) in pigmented rats.

For each neuron examined the contribution of both chloride co-transporters to E_{GABA} was calculated as the difference between E_{GABA} before and after the corresponding blockade (Fig. 5A). This contribution did not depend on the order of the chloride transporter inhibition. The contribution of KCC2 was significantly smaller in albinos (10.4 ± 3.8 mV) when compared with pigmented rats (32.6 ± 4.7 mV). In contrast, the contribution of NKCC1 was significantly higher in albinos (−23.6 ± 4.3 mV) when compared with pigmented rats (−3.0 ± 2.3 mV).

Discussion

The present study describes and compares the electrophysiological properties, and EPSCs and IPSCs of pyramidal neurons in slices of visual and frontal cortex from pigmented and albino rats. With our *in vitro* approach we demonstrated significant differences in the membrane potential and rheobase between pigmented and albino rat visual cortical neurons. The positive shift of the membrane potential may lead to the ability of the lower depolarizing current threshold to release a spike (rheobase) in albinos. An altered balance of excitatory and inhibitory currents may cause hyperexcitability or decreased specificity in response properties of visual cortical neurons of albino rats. Maximum amplitudes of AMPAR-mediated currents were similar in both experimental groups.

Our results suggest decreased $GABA_AR$-mediated currents and a shift of E_{GABA} towards more positive values in visual cortex neurons of albino rats. The similar observation of Gulacsi *et al*. (2003) in nigral dopaminergic neurons was caused by their lack of KCC2. Our results may be caused by a change in neuronal expression of the cation-chloride co-transporters in albinos towards levels found in immature neurons. The Na^+-K^+-$2Cl^-$ co-transporter (NKCC1, Cl^- uptake) and the K^+-Cl^- co-transporter (KCC2, Cl^- extrusion) are the most important of the many known chloride regulators in neocortical neurons (Kaila, 1994; Delpire, 2000). While GABA is the main inhibitory transmitter in the adult brain, GABAergic transmission is excitatory during early postnatal development (for review, see Ben-Ari, 2002). The different action of GABA results from a reversed chloride concentration gradient with higher intracellular chloride concentration in immature neurons. The developmental switch to an inhibitory action of GABA is a consequence of a decrease of NKCC1 and concomitant increase of KCC2 expression (Delpire, 2000; Vu *et al*., 2000; Ikeda *et al*., 2003). Vardi *et al*. (2000) demonstrate that the expression of KCC2 or NKCC1 in different cell types in retina leads to opposite effects of GABA on these cell types.

Our results suggest correlation between changes in $GABA_AR$-mediated currents with an altered action of cation-chloride co-transporters in albino rats. The elevated level of intracellular chloride in albinos could be responsible for the differences observed.

The selective blockade of KCC2 by furosemide (at 20 μM) causes a significant positive shift in the E_{GABA} in pigmented rats but not in albinos. Bumetanide, the selective inhibitor of NKCC1 (at 10 μM), induces a significantly negative shift in E_{GABA} in albinos but not in pigmented rats. These results together with the contribution of both co-transporters calculated for each cell (Fig. 5) indicate that the balance between inward and outward chloride co-transporters is altered in visual cortex neurons in albino rats. This alteration is reminiscent of the situation in immature neurons (increased NKCC1 and decreased KCC2 expression compared with mature neurons, Kakazu *et al*., 1999; Mikawa *et al*., 2002; Stein & Nicoll, 2003; Yamada *et al*., 2004).

The difference in currents reported in our study could be caused by a slower maturation of the albino visual system compared with pigmented rats. It is, however, important to note that in frontal cortex no differences in chloride reversal potentials were found between pigmented and albino rats. This strongly suggests that the altered function of the chloride transporters proposed for visual cortex might be a compensatory mechanism triggered by the adjustments necessary to address the differences in neuronal activity caused by the retinal changes and the altered projection pattern from the two eyes. Such activity-dependent changes in KCC2 expression were shown in hippocampal neurons by Rivera *et al*. (2004).

Changes in cation-chloride co-transporter function could profoundly alter the response properties, including direction selectivity, of visual cortex neurons in albino rats and in other albinotic mammals. However, direction selectivity is not completely lost in albino ferret areas 17, 18 and a newly discovered area posterior to the suprasylvian sulcus (PSS) (Philipp *et al*., 2004). In fact, the proportion of direction-selective cells increases from area 17 to 18 and, in particular, to area PSS, with more than 80% of strongly direction-selective cells occurring in the pigmented animals. Decreases were evident in albinos with less than 50% direction-selective cells being present in this area. Thus, the observed hyperexcitability or the decreased GABA-mediated inhibitory currents might degrade direction selectivity from synapse to synapse along the pathway until it is completely lost at the subcortical projection site, such as the NOT-DTN (Hoffmann *et al*., 2004). Further experiments measuring the action of cation-chloride co-transporters in NOT-DTN cells will have to clarify this question.

Also the question as to whether differences between the visual system of albino and pigmented rats are exclusively induced by the altered expression or are due to an altered functional status of the cation-chloride co-transporters in albinos, or whether passive regulatory systems of intracellular chloride ions could also contribute, is still open and demands further investigation.

In conclusion, our results in rats suggest that alterations of cation chloride co-transporter functions, comprising a higher NKCC1 and a lower KCC2 action, may contribute to the pathologies of the visual system in albinos.

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Abbreviations

ACSF, artificial cerebrospinal fluid; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; APV, 2-amino-5-phosphonopentanoic acid; EPSC, excitatory postsynaptic current; GABA, γ-aminobutyric acid; $GABA_AR$, $GABA_A$ receptor; IPSC, inhibitory postsynaptic current; KCC2, K^+-Cl^- co-transporter; mEPSC, miniature excitatory postsynaptic current; mIPSC, miniature inhibitory postsynaptic current; NKCC1, Na^+-K^+-$2Cl^-$ co-transporter; NOT-DTN, nucleus of the optic tract and dorsal terminal nucleus; PSC, postsynaptic current; PSS, posterior to suprasylvian sulcus; TTX, tetrodotoxin citrate.

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