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RESEARCH ARTICLE

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Effects of intra-vestibular nucleus injection of the Group I metabotropic glutamate receptor antagonist AIDA on vestibular compensation in guinea pigs

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Abstract Removal of the peripheral vestibular receptor cells in one inner ear (unilateral vestibular deafferentation, UVD) results in a syndrome of ocular motor and postural disorders, many of which disappear over time in a process of behavioural recovery known as vestibular compensation. Excitatory amino acid receptors, in particular the *N*-methyl-D-aspartate (NMDA) receptor, have been implicated in vestibular compensation; however, the metabotropic glutamate receptors (mGluRs) have not been studied in this context. The aim of this study was to determine whether group I mGluRs in the brainstem vestibular nucleus complex (VNC) ipsilateral to the UVD are involved in vestibular compensation of the static symptoms of UVD in guinea pig. The selective group I mGluR antagonist (*RS*)-1-aminoindan-1,5,dicarboxylic acid (AIDA) was continuously infused into the ipsilateral VNC for 30-min pre-UVD and 30-min post-UVD by cannula, at a rate of 1 µl/h, using one of four doses: 0.1 fg, 0.1 pg, 0.1 ng or 0.1 µg (n=5 animals in each case). In control conditions, a 0.1-fg (n=4) or 0.1-µg (n=5) NaOH vehicle was infused into the ipsilateral VNC using the same protocol. In order to control for the possibility that AIDA disrupted spontaneous neuronal activity in the VNC in normal animals, 0.1 µg AIDA (n=4) or 0.1 µg NaOH (n=2) was infused into the VNC in labyrinthine-intact animals. In both groups, static symptoms of UVD (i.e. spontaneous nystagmus, SN, yaw head tilt, YHT and roll head tilt, RHT) were measured at 8, 10, 12, 15, 20, 25, 30, 35, 45 and 50 h post-UVD. In addition, the righting reflex latency (RRL) was measured in labyrinthine-intact animals in order to assess whether AIDA impaired motor coordination in labyrinthine-intact animals. In UVD animals, the highest dose of AIDA significantly reduced SN frequency and changed its rate of compensation (P<0.001 and P<0.0001, respectively). This dose of AIDA also caused a significant reduction in YHT (P<0.005) as well as a significant change in its rate of compensation (P<0.0001). However, RHT was not significantly affected. In the labyrinthine-intact animals, AIDA infusion did not induce a UVD syndrome, nor did it significantly affect RRL. These results suggest that group I mGluRs in the ipsilateral VNC may be involved in the expression of ocular motor and some postural symptoms following UVD. Furthermore, group I mGluRs may not contribute to the resting activity of vestibular nucleus neurons.

Key words Group I metabotropic glutamate receptors · AIDA · Vestibular compensation · Unilateral labyrinthectomy · Vestibular nucleus · Guinea pig

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Introduction

In the last decade, it has become apparent that excitatory amino acid (EAA) receptors are critically involved in every stage of synaptic transmission in the vestibulo-ocular and vestibulo-spinal reflex pathways (see de Waele et al. 1995; Smith and Darlington 1996, 1997 for reviews). Although it is now well established that the kainate/alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionate (AMPA) and *N*-methyl-D-aspartate (NMDA) EAA receptor subtypes are involved in synaptic transmission between the vestibular receptor hair cells and the vestibular nerve, and between the vestibular nerve and brainstem vestibular nucleus complex (VNC) neurons, there is less information available on the metabotropic glutamate receptors (mGluRs; see Smith and Darlington 1997 for a recent review).

NMDA receptors have been implicated in lesion-induced plasticity in the VNC following damage to the peripheral vestibular receptor cells (unilateral vestibular deafferentation, UVD). When administered prior to or at

the time of the UVD, NMDA receptor antagonists have been shown to reduce the expression of the vestibular symptoms, suggesting that VNC NMDA receptors are important in the mechanisms by which UVD symptoms are expressed (Sansom et al. 1992, 2000; see Smith and Darlington 1997 for a review). Furthermore, a large body of evidence indicates that NMDA receptor antagonists disrupt the development of the behavioural recovery process ("vestibular compensation") when the drugs are delivered following the lesion (see Smith and Darlington 1997 for a review). However, to date, the possible role of mGluRs in vestibular compensation has not been investigated. mGluRs are of interest in this context because in situ hybridization (Shigemoto et al. 1992; Li et al. 1997; see de Waele et al. 1994 for conflicting evidence) and electrophysiological studies (Vibert et al. 1992; Kinney et al. 1993; Darlington and Smith 1995; Peterson et al. 1995) have suggested their existence in the VNC. In addition, vestibular compensation is a model of central nervous system (CNS) plasticity and mGluRs have been implicated in other forms of plasticity in the VNC such as long-term potentiation (LTP; Kinney et al. 1993; Peterson et al. 1995; Grassi et al. 1998). Peterson and colleagues reported that application of (1*S*,3*R*)-1-aminocyclopentane-1,3-dicarboxylic acid (1S,3R-ACPD) to medial vestibular nucleus (MVN) neurons produced a long-lasting potentiation of excitatory postsynaptic potentials (EPSPs) induced by electrical stimulation of the vestibular nerve (Kinney et al. 1993; Peterson et al. 1995). More recently, Grassi et al. (1998) have reported that the non-selective mGluR antagonist (*RS*)alpha-methyl-carboxyphenylglycine (MCPG) enhanced LTP induced in the MVN by tetanization of the vestibular nerve. However, it is not clear which mGluR subtype mediates these effects because of the use of non-selective mGluR ligands.

The aim of the present study was to investigate the effects of the "selective" group I mGluR antagonist (*RS*)-1-aminoindan-1,5,dicarboxylic acid (AIDA; Pellicciari et al. 1995; Moroni et al. 1997; Contractor et al. 1998), delivered into the ipsilateral VNC, on the static symptoms of UVD (spontaneous nystagmus, yaw head tilt and roll head tilt) in guinea pig. Group I mGluRs were chosen for investigation because their transduction pathway involves the release of intracellular Ca^{2+} and the activation of protein kinase C, both of which have been implicated in the mechanisms of vestibular compensation (see Smith and Darlington 1997 for a review).

Materials and methods

Subjects

Thirty-five male or female pigmented guinea pigs were used in these experiments (270–380 g). Food and water were available ad libitum. Animals were allocated to one of the following 8 groups: (1) 0.1 fg (0.5 pM) NaOH vehicle + UVD (*n*=4 animals); (2) 0.1 µg (0.5 mM) NaOH vehicle + UVD (*n*=5); (3) 0.1 fg (0.5 pM) AIDA + UVD (*n*=5); (4) 0.1 pg (0.5 nM) AIDA + UVD (*n*=5); (5) 0.1 ng (0.5 µM) AIDA + UVD (*n*=5); (6) 0.1 µg (0.5 mM) AIDA + UVD (*n*=5); (7) 0.1 µg (0.5 mM) NaOH vehicle + labyrinths intact (*n*=2); (8) 0.1 µg (0.5 mM) AIDA + labyrinths intact (*n*=4). Two different vehicle control groups were used (groups 1, 2 and 7 above). Concentrations of AIDA from 0.5 pM to 0.5 mM were used in the UVD conditions because, at the beginning of this study, the majority of studies that had used AIDA were in vitro (Pellicciari et al. 1995; Moroni et al. 1997) and therefore it was necessary to conduct a dose-response analysis of its effects in the context of the VNC. The highest dose used in this study is in accordance with subsequent in vivo studies that have used AIDA (Kearney et al. 1998; Chapman et al. 1999). Furthermore, in vitro studies (Moroni et al. 1997) suggest that at high concentrations (more than 1 mM) AIDA is a modest group II agonist; to reduce this possibility, the highest concentration used in the present study was 0.5 mM. Nonetheless, AIDA is regarded as one of the most selective group I mGluR antagonists and has been demonstrated to act as such in vivo (Chapman et al. 1999). MCPG was not used because of evidence that it can act as an mGluR agonist in some circumstances (Keele et al. 1995). Following the results obtained in UVD animals using 0.5 mM AIDA, this concentration was also used in labyrinthine-intact animals.

Drug administration

AIDA (Tocris Cookson, UK) was dissolved in a 1:1 solution of 10 mM NaOH, pipetted into 20-µl aliquots, then frozen at –30°C. AIDA was diluted to the required concentration using pH-corrected (pH 7), modified artificial cerebrospinal fluid (mACSF), containing: 1.0 mM NaCl, 1.0 mM KCl, 0.5 mM KH_2PO_4, 0.5 mM $MgSO_4.7H_2O$, and 0.5 mM $NaHCO_3$ (Sansom et al. 1993a, 1993b; Gilchrist et al. 1996).

In the UVD animals, AIDA was infused by cannula (see Surgery) into the ipsilateral VNC for a period of 1 h, starting at the time of anaesthetic administration and finishing approx. 30 min after the completion of the UVD. AIDA was infused using a Harvard syringe pump connected to a 20-µl Hamilton syringe, with an infusion rate of 1 µl/h. A single-lumen polyethylene tube (95 cm long) connected the Hamilton syringe to a 35-gauge needle, which was inserted inside the cannula. The tubing was filled with water with an air bubble separating the water from the drug solution, so that the movement of the drug solution down the tubing could be monitored (Sansom et al. 1993a). The infusion rate was based on previous studies which have shown that this rate of infusion does not cause damage to the VNC (Sansom et al. 1993b).

Surgery

For all surgical procedures, animals were anaesthetised with 0.4 ml/kg fentazin i.m. (0.4 mg/ml fentanyl citrate, 3.2 mg/ml azaperone, 58.3 mg/ml xylazine hydrochloride; Sansom et al. 1996). A 0.8-mm stainless steel cannula was implanted stereotaxically into the right (ipsilateral) VNC, using the procedures we have described in detail previously (Sansom et al. 1993a, 1993b, 2000; Gilchrist et al. 1996; Bolger et al. 1999). Any animal showing behavioural evidence of severe brainstem or cerebellar damage, indicated by vigorous spontaneous nystagmus and postural asymmetry or ataxia, was excluded from the study. None of the 35 animals described here was excluded on this basis. Animals were allowed to recover for at least 1 week before inner ear surgery. For animals in the UVD conditions, a right surgical UVD was performed under fentazin anesthesia (as above), using the methods we have described previously (Gilchrist et al. 1994, 1996; Sansom et al. 1993a, 1993b, 2000; Bolger et al. 1999). Histological examination has shown that this UVD procedure results in complete destruction of the labyrinthine receptors (Curthoys et al. 1988).

Behavioural measurements

Three static symptoms of UVD were quantified: spontaneous ocular nystagmus (SN), yaw head tilt (YHT) and roll head tilt (RHT;

Gilchrist et al. 1994). Measurements were made at 8, 10, 12, 15, 20, 25, 30, 35, 45 and 50 h post-UVD using video techniques and the procedures we have described in detail previously (Gilchrist et al. 1994, 1996; Sansom et al. 1993a, 1993b, 2000; Bolger et al. 1999).

The effects of AIDA (0.1 µg, 0.5 mM) infused into the right VNC of labyrinthine-intact animals was also investigated, in order to determine whether AIDA, at the highest concentration used, caused an asymmetry in neuronal activity between the bilateral VNCs when both labyrinths were intact. Exactly the same anaesthesia and drug administration protocols were used for these animals, except that no UVD was performed. SN, YHT and RHT were measured at the same time points post-operatively (post-op.) as for the UVD groups and the results were compared with the effects of infusing the NaOH vehicle alone (0.1 µg, 0.5 mM) in labyrinthine-intact animals.

Righting reflex latency (RRL) measurements were also made in labyrinthine-intact animals receiving AIDA or vehicle in order to determine whether AIDA significantly impaired the righting reflex in normal animals and therefore impaired motor control in a non-specific way. This was not done in UVD animals, because it was considered to be unethical. RRL, defined as the latency (in seconds) for the animal to right itself from the supine position to the prone position, was measured between 8 and 50 h post-op., using an automated measurement system consisting of a semi-cylindrical, felt-covered platform (10×6 cm) positioned on a 2-kg load cell connected to a strain gauge amplifier (Radio Spares Components) and a MacLab data acquisition system (Analog Digital Instruments) and Macintosh computer (see Dingwall et al. 1993 for detailed methods).

Statistical analysis

For SN, YHT and RHT, separate 2-factor analyses of variance (ANOVA) with repeated measures on time were performed (Zolman 1993; Gilchrist et al. 1994). Factor A represented the drug effect on SN frequency, YHT or RHT; factor B, the repeated measure, represented time; and the interaction (AB) represented the change in the rate of compensation as a result of treatment (Gilchrist et al. 1994). As factor B, the repeated measure, was always significant (i.e. since vestibular compensation occurred in all cases), it will not be discussed further. Pairwise comparisons to investigate significant differences at particular time points and for particular treatment groups, were conducted only in the case of a significant ANOVA, using the Dunnett test (Zolman 1993). The significance level was set at 0.05 for all comparisons.

Histology for cannula positions

All animals were killed at 50 h post-UVD using a lethal injection of phenobarbitone sodium (0.5 ml i.p; Techvet Laboratory). Alcian blue dye (0.1 µl; Sigma) was injected into the cannula to facilitate confirmation of its location. Once deeply anaesthetised, the animals were transcardially perfused with 10% formalin, the brainstem removed, sectioned coronally (50 µm) and stained with thionin. Only data from animals (i.e. n=35) whose cannulae were located within or on the border of the ipsilateral VNC, i.e. the medial, superior, lateral or inferior vestibular subnuclei, are included in the Results (Fig. 1).

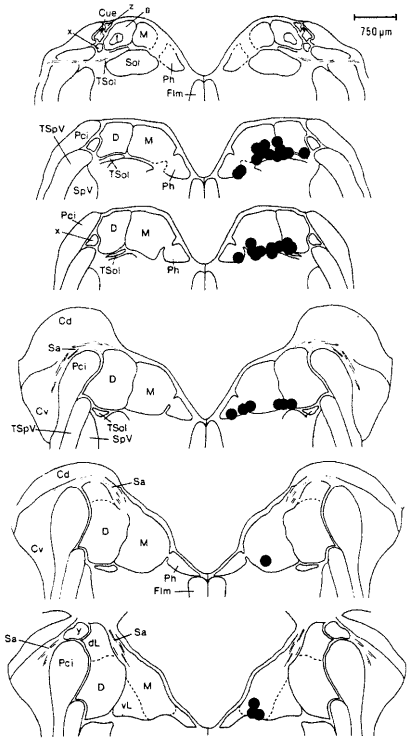

Fig. 1 Schematics of coronal sections through the brainstem, from rostral to caudal, showing the location of cannulae for animals used in this study. (*M* medial vestibular nucleus, *Sol* nucleus tractus solitarii, *Ph* prepositus hypoglossi, *Tsol* tractus solitarius, *Flm* fasciculus longitudinalis medialis, *D* descending vestibular nucleus, *Cue* nucleus cuneatus externus, *Pci* restiform body, *Tspv* tractus nucleus spinalis nervis trigemini, *Spv* nucleus spinalis nervis trigemini, *Cd* nucleus cochlearis dorsalis, *Sa* stria acustica, Cv nucleus cochlearis ventralis, *Dl* dorsal portion caudal most part of the lateral vestibular nucleus, *Vl* ventral portion caudal most part of the lateral vestibular nucleus, *x* cell group x, *y* cell group y, *z* cell group z). (Adapted from Gstoettner and Burian 1987)

Results

UVD animals

The 2-factor ANOVA showed that there was a significant decrease in SN frequency following AIDA administration. Both the drug effect and the drug effect/time interaction were significant (P<0.001 and P<0.0001, respectively), indicating that AIDA not only reduced SN frequency post-UVD but also significantly altered its rate of compensation (Fig. 2). Post-hoc testing at specific time points post-UVD showed that the significant ANOVA was due largely to the effects of the highest (i.e. 0.1 µg) dose of AIDA. Comparisons between the 0.1 µg NaOH group and 0.1 µg AIDA group indicated significant differences at 8 h, 10 h, 12 h and 15 h post-UVD (P<0.05 in all cases). Figure 2 shows that, at 8 h post-UVD, 0.1 µg AIDA reduced SN frequency to less than 5 beats/15 s, which is an approx. 66% decrease in SN frequency compared with the NaOH vehicle control group at this time. However, there were no significant differences between the vehicle and the lower doses of AIDA at any time point (Fig. 2).

YHT compensation was much more variable than SN (see Fig. 2). However, the 2-factor ANOVA demonstrated that AIDA caused a significant reduction in YHT (P<0.005) as well as a significant change in its rate of compensation (P<0.0001). Post hoc testing showed that there were significant differences between the 0.1 µg

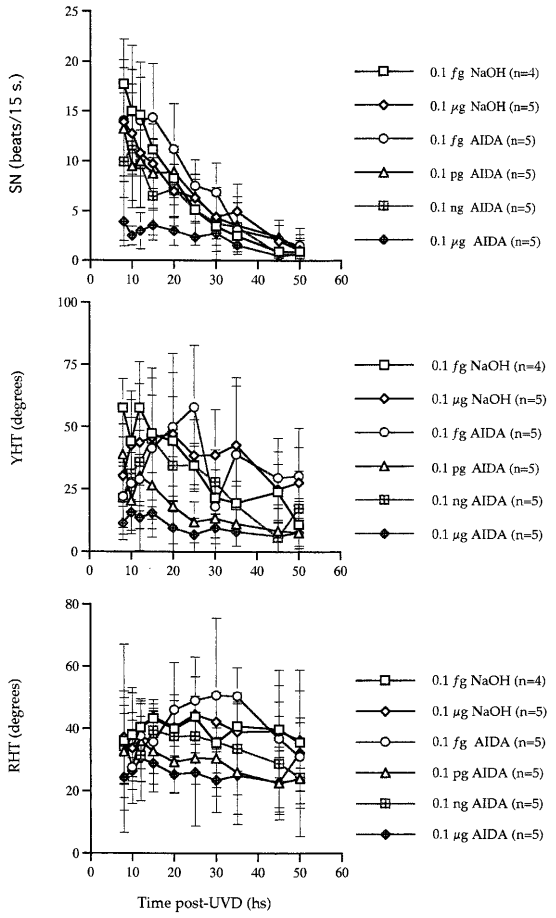

Fig. 2 Effect of various doses of NaOH and (*RS*)-1-aminoindan-1,5,dicarboxylic acid (AIDA) on the compensation of spontaneous nystagmus (*SN*), yaw head tilt (*YHT*) and roll head tilt (*RHT*) following unilateral vestibular deafferentation (*UVD*). Symbols represent means ±1 SD

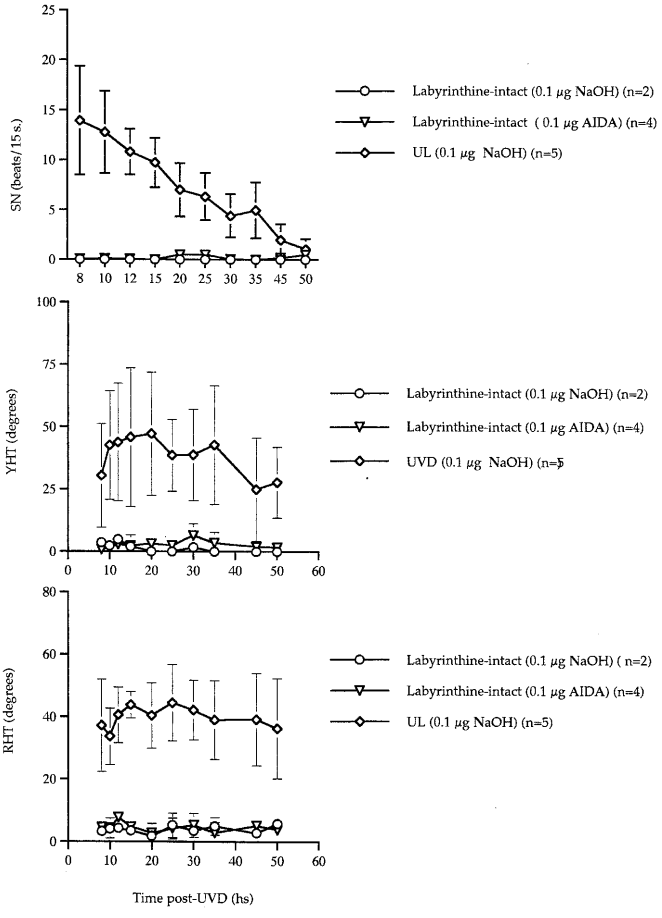

Fig. 3 Effect of NaOH or AIDA on SN, YHT and RHT in labyrinthine-intact animals compared with SN, YHT and RHT in animals receiving a UVD and NaOH treatment. Symbols represent means ±1 SD

AIDA and vehicle control groups at 8 h and 12 h post-UVD ($P<0.01$ for both comparisons); however, there were no significant differences between the vehicle and lower doses of AIDA at any time point post-op. AIDA infusion did not significantly alter the magnitude of RHT or its rate of compensation (see Fig. 2).

Labyrinthine-intact animals

Neither 0.1 µg (0.5 mM) AIDA nor the 0.1 µg (0.5 mM) NaOH vehicle produced significant SN, YHT or RHT in labyrinthine-intact animals when they were measured over 50 h post-injection, compared with labyrinthine-intact animals receiving the vehicle injections (Fig. 3). There was also no significant difference in mean RRL between labyrinthine-intact animals receiving AIDA or vehicle (data not shown).

Discussion

This study provides the first evidence that group I mGluRs in the ipsilateral VNC may be involved in the expression of SN and YHT after UVD. Although cannula injection of the selective mGluR antagonist AIDA into the VNC at a dose of 0.1 µg, had no effect in labyrinthine-intact animals, it substantially reduced SN frequency and the magnitude of YHT following UVD, but did not alter the magnitude or compensation of RHT.

Several possible explanations must be considered in evaluating the current data. First, it is possible that, at the dose which reduced SN and YHT (i.e. 0.1 µg), AIDA was less selective for group I mGluRs and began to activate group II mGluRs or to block NMDA receptors. At high concentrations (more than 1 mM), AIDA is a group II mGluR agonist in clonal cell lines transfected with mGluR2 and in hippocampal and striatal slices (Moroni et al. 1997), and therefore the present results could be due to AIDA acting as an agonist at group II mGluRs. However, since the highest concentration used in the present study was 0.5 mM (0.1 µg), it is unlikely that the

results obtained were due to the activation of group II mGluRs. Nonetheless, since AIDA's properties at mGluRs 3, 6, 7 and 8 have not been completely characterised as yet, we cannot exclude the possibility that the results were due to AIDA acting on one or more of these receptors. Furthermore, it is possible that AIDA blocked NMDA receptors. Contractor et al. (1998) have reported that AIDA can inhibit NMDA/glycine-induced currents in *Xenopus* oocytes and HEK 293 cells transfected with the recombinant NR1–1a/NR2A NMDA receptor. In the only in vivo study conducted to date, Krieger et al. (1998) reported that AIDA inhibited NMDA-induced depolarization in the lamprey spinal cord at concentrations of 1 mM or above. However, the suppression of SN by AIDA in the present experiment was completely unlike the effects of NMDA receptor/channel antagonists administered before the UVD, which we have documented previously, where the initial suppression of SN was followed by a recovery of SN frequency towards control levels (Sansom et al. 1992, 2000). We suggest that, even if the effects of 0.1 µg AIDA were due partly to action on VNC NMDA receptors, this cannot be the entire explanation and a substantial group 1 mGluR effect would still be implicated. In addition, it should be noted that, in many areas of the brain, mGluRs can modulate the NMDA receptor complex and therefore the results of the present experiment could be due to the modulation of NMDA receptors by group I mGluRs (see Pin and Duvoisin 1995; Conn and Pin 1997; Michaelis 1998 for reviews).

Second, it is possible that the highest AIDA dose (0.1 µg) combined with lingering effects of the fentazin anaesthesia, was responsible for the observed suppression of UVD symptoms. However, this seems unlikely given that: (1) the anaesthetic effects had worn off in all animals by 8 h post-op. and the labyrinthine-intact animals receiving the highest AIDA dose showed no impairment of the righting reflex latency that might be indicative of sedation; (2) the suppression of SN and YHT lasted for the entire duration of vestibular compensation, i.e. 50 h, not just the first 10–15 h as might be expected if an anaesthetic effect were involved.

Third, it is possible that the effects of AIDA were due to action on motoneurons, particularly abducens motoneurons, as a result of the drug solution spreading from the cannula site to other areas of the brainstem. Although this is also conceivable, it is unlikely for several reasons: (1) the effects of the AIDA were similar, irrespective of cannula location, and some of the cannula locations were lateral to the MVN and therefore far from the abducens; (2) YHT was affected as well as SN, and it is unlikely that the drug could spread as far as neck motoneurons; (3) AIDA did not cause UVD symptoms or affect the RRL in labyrinthine-intact animals, suggesting that it does not have an indiscriminate effect on motoneurons. It is therefore likely that the effects of AIDA were mediated at least partially by its actions on group I mGluRs on neurons in the ipsilateral VNC.

The results of this study suggest that group I mGluRs do not contribute to the resting activity of VNC neurons in labyrinthine-intact animals. However, it is conceivable that AIDA could have induced a vestibular syndrome in labyrinthine-intact animals shortly following the cannula injection, in which case it would not have been observed because the animal was anesthetised. Indeed, in vitro studies suggest that mGluRs may contribute to synaptic transmission in the MVN and to the resting activity of MVN neurons (Vibert et al. 1992; Kinney et al. 1993; Darlington and Smith 1995; Grassi et al. 1998). However, because the non-selective ligands MCPG and 1S,3R-ACPD were employed in these brainstem slice studies, it is unclear which mGluR groups mediate these effects. Furthermore, since these studies were conducted in vitro, it is possible that the deafferentation involved in extracting the brainstem slice (i.e. a bilateral UVD) altered the function of the mGluRs in the MVN.

The group I mGluR family, consisting of mGluR1 and mGluR5 receptors, is known to be G protein-coupled to phospholipase C, which splits phosphatidylinositol-4,5-biphosphate (PIP_2) into diacylglycerol (DAG) and inositol (1,4,5)-triphosphate (IP_3). The production of DAG causes activation of the membrane-bound protein kinase C (PKC), which results in phosphorylation of its substrate proteins. The production of IP_3 causes the release of Ca^{2+} from intracellular stores by binding to IP_3 receptors on endoplasmic reticulum (Pin and Duvoisin 1995; Conn and Pin 1997; Michaelis 1998). Given these biochemical effects, what function might group I mGluRs serve in the ipsilateral VNC at the time of the UVD? In the hippocampus, group I mGluRs are thought to potentiate the biochemical effects of NMDA receptor activation during the induction of LTP, and blockade of group I mGluRs has been shown to interfere with LTP induction (Bortolotto et al. 1993, 1994). However, recently Grassi et al. (1998) have reported that the mGluR antagonist MCPG enhanced LTP in the VNC after tetanization of the vestibular nerve, which is also NMDA-receptor-dependent. However, the function of NMDA receptors in the ipsilateral VNC at the time of the UVD is still poorly understood (Smith and Darlington 1997), and therefore it is difficult to speculate on the possible role of mGluRs in this context without further evidence. It has been suggested that an excessive release of glutamate by the vestibular nerve into the ipsilateral VNC at the time of the UVD might, through an overactivation of EAA receptors on type I VNC neurons that receive monosynaptic input from the vestibular nerve, be responsible for the extent of the observed hypoactivity of type I neurons (Darlington and Smith 1996; Smith and Darlington 1997). This hypothesis is supported by the observation that administration of an NMDA receptor/channel antagonist before the UVD reduces the severity of the UVD symptoms (Sansom et al. 1992, 2000; Smith and Darlington 1997). The present evidence might further suggest that mGluRs on ipsilateral type I neurons partially mediate the development of this neuronal hypoactivity and the expression of the UVD symptoms. However,

other interpretations are possible; for example, mGluRs may partially mediate the disynaptic commissural inhibition of type I MVN neurons, and therefore reducing this inhibition following the UVD might be expected to reduce the severity of the UVD symptoms. In either case, it is still not clear why the suppression of SN is so long-lasting. Whatever the validity of the "glutamate" hypothesis, these data suggest that group I mGluRs are important not only in LTP in the VNC (Grassi et al. 1998) but also in lesion-induced plasticity following UVD. The activation of group I mGluRs may be particularly significant for the contribution of PKC-mediated phosphorylation in the VNC to the vestibular compensation process (Sansom et al. 1997; Kerr et al. 2000).

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