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Short communication

Methylprednisolone reduces spontaneous nystagmus following unilateral labyrinthectomy in guinea pig

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Abstract

The present study investigated the effects of methylprednisolone on the vestibular compensation process following unilateral labyrinthectomy in guinea pigs. A single injection of methylprednisolone (15, 30 or 60 mg/kg s.c.), 15 min pre-labyrinthectomy, had no significant effect on either the severity or the rate of compensation of spontaneous ocular nystagmus or yaw head tilt; roll head tilt showed a significant change in the rate of compensation ($P < 0.005$), due to increased roll head tilt in the 60 mg/kg group. However, a pre-labyrinthectomy injection of 30 mg/kg s.c. methylprednisolone followed by a second 30 mg/kg injection at 4 h post-labyrinthectomy resulted in a significant reduction in spontaneous nystagmus frequency ($P < 0.005$) and a significant change in the rate of spontaneous nystagmus compensation ($P < 0.005$). The additional 30 mg/kg injection had no significant effect on the magnitude or compensation of the postural symptoms. These results indicate that, at the optimal dose of 30 mg/kg, 2 injections of methylprednisolone (15 min pre-labyrinthectomy and 4 h post-labyrinthectomy) result in a significant reduction in spontaneous nystagmus frequency.

Keywords: Vestibular compensation; Methylprednisolone; Steroid; Labyrinthectomy, unilateral

1. Introduction

Unilateral labyrinthectomy results in a syndrome of ocular motor and postural disorders which gradually subsides over time in a process of behavioral recovery known as vestibular compensation. Unilateral labyrinthectomy results in a loss of resting activity in many neurons in the ipsilateral vestibular nucleus complex, which is believed to be responsible for the behavioral effects which follow. However, the development of vestibular compensation correlates with a gradual, partial recovery of resting activity in the ipsilateral vestibular nucleus. Since there is no substantial recovery of function in the ipsilateral vestibular nerve, the recovery which takes place in the vestibular nucleus is assumed to be due to central nervous system (CNS) plasticity (see Smith and Curthoys, 1989; Curthoys and Halmagyi, 1992 for reviews).

Many studies have addressed the question of whether the vestibular compensation process can be facilitated by drug treatment (see Smith and Darlington, 1994 for a review). This objective is relevant both from the viewpoint of investigating potential drug treatments which may benefit patients suffering from vestibular disorders and from the viewpoint of understanding the basic mechanisms of vestibular compensation. Methylprednisolone is a steroid which is widely used in the treatment of acute spinal cord trauma in humans (e.g. Bracken et al., 1990). Although its mechanism of action is poorly understood (e.g. Anderson et al., 1994), methylprednisolone has been demonstrated to reliably improve recovery from acute spinal trauma, provided that it is administered during the first 8 h following the insult (e.g. Bracken et al., 1990).

The aim of this study was to evaluate whether methylprednisolone treatment can facilitate the process of vestibular compensation in guinea pigs, either by reducing the severity of the initial symptoms or by accelerating the vestibular compensation process. To our knowledge, this is the first experimental study of

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the effects of methylprednisolone on vestibular compensation in animals. There is, however, evidence that methylprednisolone can alleviate acute vestibular vertigo in humans due to conditions such as peripheral vestibular neuritis (Ariyasu et al., 1990).

2. Materials and methods

Twenty guinea pigs (160–800 g) were divided into 5 groups: group 1 ($n = 4$) received a single injection of 15 mg/kg methylprednisolone (6α-methylprednisolone 21-hemisuccinate, sodium salt; Sigma) approximately 15 min before a unilateral labyrinthectomy; group 2 ($n = 4$), a single 30 mg/kg methylprednisolone injection 15 min pre-unilateral labyrinthectomy; group 3 ($n = 4$), a single 60 mg/kg methylprednisolone injection 15 min pre-unilateral labyrinthectomy; group 4 ($n = 4$), a 30 mg/kg methylprednisolone injection 15 min pre-unilateral labyrinthectomy followed by a second 30 mg/kg injection 4 h post-labyrinthectomy; group 5 ($n = 4$), a 1 ml/kg saline injection 15 min pre-unilateral labyrinthectomy. In all cases the drugs were delivered s.c. in 1 ml/kg saline. The methylprednisolone doses for groups 1–3 were chosen on the basis of previous studies which have shown that 30 mg/kg is the optimal methylprednisolone dose (Hall et al., 1984); since, in the present study, the largest effect was obtained with 30 mg/kg, a second injection of this dose was used in group 4.

Prior to surgery, animals were anesthetized with Fentazin (0.4 ml/kg i.m.; containing 0.4 mg/ml fentanyl citrate, 58.3 mg/ml xylazine HCl and 3.2 mg/ml azaperone; Parnell, New Zealand). Wound margins and pressure points were infused with 2% procaine and heart rate was monitored using ECG electrodes inserted in the forelimb muscles. A right surgical unilateral labyrinthectomy was performed under microscopic control as described in detail previously (Gilchrist et al., 1994). Following surgery, the wound was sutured and the animal allowed to recover in light.

Three static symptoms of unilateral labyrinthectomy were quantified in this study: spontaneous ocular nystagmus, yaw head tilt and roll head tilt. Spontaneous nystagmus frequency, yaw head tilt and roll head tilt were videotaped using a video camera (Panasonic NV-M7) with a zoom lens, a video recorder (Mitsubishi E7 Black Diamond) and a colour monitor (Sony Trinitron) (see Gilchrist et al., 1994 for detailed methods). Mean spontaneous nystagmus frequency, yaw head tilt and roll head tilt were calculated for each measurement time and analysed using a 2-factor analysis of variance (ANOVA) with repeated measures on time (Gilchrist et al., 1994). A linear regression analysis was also performed on the spontaneous nystagmus data (Fig. 1).

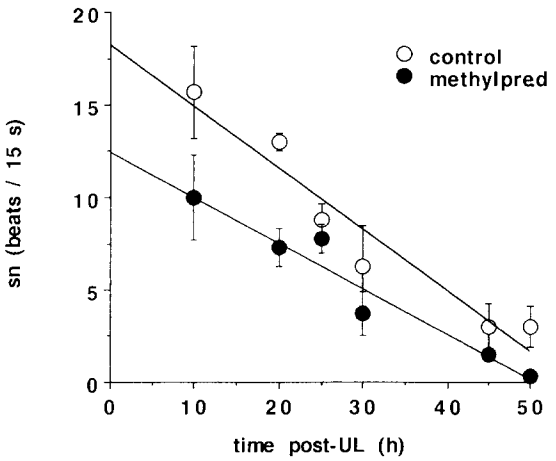

Fig. 1. Effect of an s.c. 30 mg/kg methylprednisolone injection approximately 15 min before unilateral labyrinthectomy (UL) followed by a second s.c. 30 mg/kg methylprednisolone injection 4 h post-labyrinthectomy, on spontaneous ocular nystagmus frequency (sn) in 'beats/15 s'. Symbols represent means ± 1 standard deviation. Open symbols: vehicle controls ($n = 4$). Closed symbols: methylprednisolone group ($n = 4$). h: hours. Lines of best fit were derived from linear regression analyses.

3. Results

A single pre-labyrinthectomy injection of methylprednisolone had no significant effect on either the severity or the rate of compensation of spontaneous nystagmus or yaw head tilt. Although analysis of roll head tilt showed a significant interaction ($P < 0.005$), this was due to increased roll head tilt in the 60 mg/kg group.

By contrast, a second 30 mg/kg injection of methylprednisolone at 4 h post-labyrinthectomy resulted in a significant reduction in spontaneous nystagmus frequency ($P < 0.005$) and a significant change in its rate of compensation ($P < 0.005$) (see Fig. 1). However, the additional 30 mg/kg injection had no significant effect on the magnitude or compensation of the postural symptoms, yaw head tilt and roll head tilt.

4. Discussion

The results of the present study demonstrate that methylprednisolone treatment significantly reduces spontaneous nystagmus frequency when a 30 mg/kg s.c. injection is administered 15 min before a unilateral labyrinthectomy and 4 h post-labyrinthectomy. By contrast, even a high dose (i.e. 60 mg/kg s.c.) of methylprednisolone had no significant effect on spontaneous nystagmus when given as a single injection before the labyrinthectomy.

It is unclear why two 30 mg/kg injections of methylprednisolone caused a significant decrease in sponta-

neous nystagmus frequency but no significant reduction in either yaw head tilt or roll head tilt. However, there is considerable evidence to support the view that ocular motor symptoms such as spontaneous nystagmus are controlled mainly by the medial vestibular nucleus, whereas postural symptoms such as yaw head tilt and roll head tilt are controlled mainly by the lateral vestibular nucleus. Following unilateral labyrinthectomy, resting activity returns to neurons in the ipsilateral medial vestibular nucleus rapidly over 2–3 days, whereas in the ipsilateral lateral vestibular nucleus the restoration of resting activity is a slower process (see Smith and Curthoys, 1989; Curthoys and Halmagyi, 1992 for reviews). Short fragments of the adenocorticotrophic hormone (ACTH) have also been shown to facilitate vestibular compensation of spontaneous nystagmus without significant effect on yaw head tilt or roll head tilt (e.g. Gilchrist et al., 1994).

The mechanism by which methylprednisolone treatment reduces spontaneous nystagmus frequency is unknown. Because the injections were systemic, the drug could have been acting on many parts of the CNS other than the vestibular nucleus. However, if the vestibular nucleus ipsilateral to the unilateral labyrinthectomy is the site of action, it is possible that methylprednisolone reduces the acute detrimental effects of labyrinthectomy on vestibular nucleus neuron function. Since methylprednisolone normalizes calcium levels following spinal trauma (e.g. Young and Flamm, 1982), one possibility is that it reduces calcium influx in ipsilateral vestibular nucleus neurons at the time of the unilateral labyrinthectomy (Darlington and Smith, 1992). This hypothesis would be consistent with the evidence that calcium antagonists and calcium-dependent enzyme inhibitors reduce the symptoms of unilateral labyrinthectomy (see Smith and Darlington, 1994 for a review). Further studies will be needed to determine whether methylprednisolone exerts its effects on vestibular compensation by acting directly on the ipsilateral vestibular nucleus. This possibility is supported by our preliminary evidence that methylprednisolone can act directly on medial vestibular nucleus neurons in brainstem slices maintained in vitro (Darlington, Smith and Jerram, unpublished observations).

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