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SUMMARY

In this study, we evaluated the goldfish model of hemilabyrinthectomy for investigating potential recovery-promoting drugs. In this lesion model, the unilateral removal of the labyrinth induces a postural imbalance in response to light (Dorsal Light Reflex), from which the animals can recover over time. The behavioral effects of two neuropeptides were tested—namely, of substance P and ACTH4-10, both of which are known to promote functional recovery in several other lesion models. Furthermore, the effect of MK-801, an antagonist of the glutamatergic NMDA-receptor subtype, was tested because this substance has also been shown to exert a neuroprotective effect. After lesion of the right labyrinth, the animals (n=12) were treated intraperitoneally daily either with vehicle (n=12), substance P (n=11), ACTH4-10 (n=12), or MK-801 (n=12). Another group (n=11), which served as a non-lesion control, did not receive hemilabyrinthectomy or systemic injections. The lesion group, treated post-operatively with vehicle, did not recover from the postural deviation over the 24-d testing period. In contrast, all three test substances accelerated the functional recovery after unilateral labyrinthectomy. The decrease of the dorsal light reflex persisted even after cessation of drug treatment after 20 d. The results indicate that using the dorsal light reflex in the model of hemilabyrinthectomy in goldfish provides a useful approach to studying the ability of potential new neurotrophic or neuroprotective drugs to promote functional recovery.

KEYWORDS

goldfish, MK-801, learning, Substance P, ACTH4-10, functional recovery

INTRODUCTION

Hemilabyrinthectomy is a lesion model that has the important characteristic of lesioning the CNS without directly damaging tissue in the brain.

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The main behavioral consequence of this unilateral vestibular removal is a postural imbalance from which the animals can recover over time. Therefore, this model has been used in various species to study functional recovery and its possible physiological determinants (Schaefer & Meyer, 1974; Dieringer, 1995; Deliagina, 1997; Vidal et al., 1998).

In goldfish, behavioral deficits and potential recovery after hemilabyrinthectomy can elegantly be studied by measuring the dorsal light reflex (DLR) (Ott & Platt, 1988a; 1988b): When illuminated from one side, non-lesioned fish slightly tilt toward the light source, which indicates a role of vision in postural maintenance. Vestibular-lesioned fish, on the other hand, tilt very strongly toward the light, and some of them even align themselves fully with the light, indicating the loss of influence of the gravitational component on postural maintenance. With time after lesion, the degree of light-induced tilt can decrease, which is taken as the index of functional recovery. Apparently, after the loss of vestibular input, fish initially adjust posture, mainly using the visual system, whereas during the development of functional recovery, the impact of the gravitational component gradually increases again. Such recovery after hemilabyrinthectomy is thought to be due to compensatory mechanisms, including the following:

- bilateral adjustments in the activity of vestibular nuclei (Flohr & Beinhold, 1981; Sans et al., 1997),
- modulation of the lesion side via commissural interconnections (Dieringer & Precht, 1979),
- cerebellar input to the vestibular neurons (Dieringer & Precht, 1979), and
- neurochemical modulation via cholinergic systems (Beinhold & Flohr, 1980).

The lesion- and stimulus-dependent postural deficit and its potential to recover after hemilabyrinthectomy in goldfish might be useful for investigating the effectiveness of drugs for therapeutic means. To test this hypothesis, we used two neuropeptides—namely, substance P (SP) and the adrenocorticotropic hormone ACTH4-10, which have been shown to promote functional recovery and to have neurotrophic and/or neuroprotective effects in other species. With respect to the neurokinin SP, this substance is known to be present in the brain of mammals and fish (Schaefer & Meyer, 1974) to promote functional recovery after brain lesions (Mattioli et al., 1992; Bannon et al., 1995) and to act in a neurotrophic and neuroprotective way (Jonsson & Hallman, 1982; Iwasaki et al., 1989; Kowall et al., 1991; Mattioli et al., 1992; Nikolaus et al., 1999). ACTH4-10 can also accelerate recovery after hemilabyrithectomy in frogs (Flohr & Lüneburg, 1982) and monkeys (Igarashi et al., 1985) and after lesions of the CNS (Antonawich et al., 1993; for review see van Rijzingen et al., 1996). Furthermore, we tested the non-competitive NMDA receptor antagonist MK-801 (dizolcipine), for which a positive effect on recovery after brain lesions is disputed. It has been suggested that MK-801 might be able to act neuro-protectively (Grigg & Anderson, 1990; Robinson & Mair, 1992; Yanase et al., 1995), an action that may be due to decreases of secondary mechanisms affecting neuronal death, especially edema (Yanase et al., 1995) and calcium channel blocking (Schurr et al., 1995). Contradictory data exist, however, because Holtz & Gerdin (1991) did not find any improvement of recovery with MK-801 treatment after spinal cord injury. Additionally, NMDA receptor imbalance has been reported after unilateral vestibular lesion (Li et al., 1997); such imbalance could be reduced by MK-801 treatment.

Thus, we tested the effects of post-operative treatment with SP, ACTH4-10, or MK-801 in the model of hemilabyrinthectomy in goldfish, with the expectation that SP and ACTH4-10 should promote recovery, whereas MK-801, if at all, should only weakly be effective.

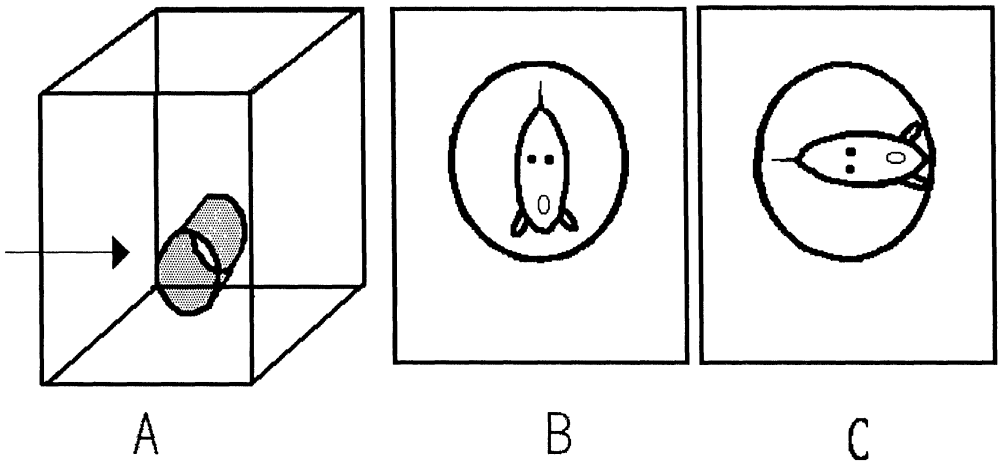

Fig. 1: **A**, Schematic representation of the testing chamber being illuminated from the right side. **B**, Fish represented with no tilt or 0° and **C**, fish represented with maximum tilt or 90°, as seen on TV screen.

METHODS

Animals

Fifty-eight unsexed, experimentally naive comet goldfish (*Carassius auratus*), weighing between 3.5 to 7.0 g each, were maintained in groups of 12 or less in continuously filtered and aerated 60-L aquaria, under natural temperature and a light cycle of 14 h light/10 h dark. They were fed 5 d per week with goldfish pellets (Wardley, USA).

Test chamber

For the DLR test, a black aquarium (15 cm high, 20 cm long, 10.5 cm wide) was placed in a small room that could be darkened completely. This aquarium had a small transparent window on the right side that allowed light to enter from a lamp placed at that side. Another transparent window at the front wall allowed video recording of the animals' behavior. Inside the aquarium, a translucent tube (2.5 cm diameter) was attached to the front wall. The tube was used to keep the animal facing forward, allowing the fish to tilt, but not to turn away from the front wall (Fig. 1).

Drugs and treatmensts

Substance P acetate and ACTH4-10 (Sigma Chemical Co., St Louis, Missouri, USA); and MK-801 (RBI, Natick, Massachusetts, USA) were dissolved in distilled water to concentrations of 25 μg/mL (SP), 125 μg/mL (ACTH4-10), and 50 μg/mL (MK-801). All substances were placed immediately in a freezer (–40°C) in aliquots of 250 μL. Fresh aliquots were thawed on each injection day. All substances were administered in a volume of 2 mL/kg body weight using a 1-mL syringe and a 27-gage needle. The final doses used were 50 μg/kg

for SP, 250 μg/kg for ACTH4-10, and 100 μg/kg for MK-801. These doses were derived from previous studies (Flohr & Lüneburg, 1982; Mattioli et al., 1995, 1996; 1997). Because this was an initial study to examine the suitability of the goldfish hemi-labyrinthectomy model for functional recovery rather than a study of drug efficacy, the dose response of the drugs were not evaluated. Vehicle-injected fish received distilled water of the same volume. The animals were injected 5 d per wk for 3 wk, beginning after the first DLR test, which was performed 24 h after surgery. Treatment was discontinued on day 20, and two additional tests were performed, on days 22 and 24 after the lesion.

Surgery

Fish were anesthetized by placing them in a solution of tricaine methanesulphonate (TMS) (0.6 g/L) until gill movements stopped. The fish were then wrapped in wet gauze and placed on a stand that stabilized the body by laterally placed adjustable holders. Anesthesia and artificial ventilation were maintained by perfusing the animals through the mouth continuously with an aerated solution of TMS (0.3 g/L).

A small triangular opening was cut in the skull just behind and above the right eye. The utricle was localized and gently pulled out; attached portions of the pars superior (e.g. semicircular canals) were also removed (Ott & Platt, 1988a, 1988b). The space was then filled with sterile gel foam (Upjohn Co., Kalamazoo, Michigan, USA), and the skull hole was closed with dental acrylic (Motloid Co., Chicago, Illinois, USA). Little, if any, bleeding was observed during successful surgery. After the skull was closed, the anesthetic solution was replaced by fresh water until the fish began moving. The fish were then placed in the maintenance aquarium and were observed for immediate ataxia, a sign that was used to evaluate surgical success and served as a necessary condition for including the animal in the experiment.

Another group (n=5) was anesthetized, the skull was opened and closed the same way; but without otolith removal. These animals did not differ in body tilt from seven other non-operated animals. Therefore, they were pooled with the non-operated animals into one non-lesion, control group. Altogether, the following groups were tested:

- Group SP, n=11, lesion and injected with Substance P (50 μg/kg body wt.),
- Group ACTH, n=12, lesion and injected with ACTH4-10 (250 μg/kg body wt.),
- Group MK, n=12, lesion and injected with MK-801 (100 μg/kg body wt.),
- Group VEH, n=12, lesion and injected with vehicle (2 mL/kg body wt.),
- Group NON, n=11, no-lesion, not injected.

Testing procedure

Twenty-four hours after surgery, the animals were placed in the experimental chamber, which was held at ambient room temperature (24±2°C). Then, the room was completely darkened, and the light on the right side of the experimental chamber was turned on. The animals' behavior was recorded on videotape for 5 min with the recording time (in seconds) displayed on-screen at recording and videotape playback. This test was repeated on days 3, 8, 10, 15, 17, 22, and 24 after surgery. The tilt angle was determined after testing by stopping the tape during playback at each full minute, and by measuring the angle formed between a line traced through the eyes and a horizontal line. Five measures were taken from each animal per test, and the angle used for each day was the mean of these five measures.

Statistical analysis

A two-way analysis of variance (ANOVA) with repeated measures was made to determine

whether a treatment regimen or postoperative time or an interaction between these factors affected tilt angles. For multiple comparisons between means, the Student-Newman-Keuls analysis was used; the significance level was established at 5%.

RESULTS

After recovering from anesthesia, the labyrinthectomized animals showed immediate ataxia that lasted between 30 and 40 min; a few animals that did not recover from this ataxia were not used further in the study. On the first test, performed on the first day after surgery and before any treatment was administered, the lesion groups showed a body tilt toward the light side of about 50 degrees, whereas the no-lesion control group had a tilt of about 7 degrees to the same side. The degree of tilt was significantly higher in the lesion groups than in the no-lesion group (Table 1).

Throughout the postoperative testing period, the statistical analysis of DRL (two-way ANOVA with repeated measures, Fig. 2) yielded significant differences between treatments ($F=12.54$, $p<0.0001$), a significant effect of post-operative time ($F=17.81$, $p<0.0001$), and an interaction effect between treatments and time ($F=2.39$, $p=0.0001$). Further multiple comparisons indicated that on the first day after surgery, the four hemilabyrithectomized groups (SP, ACTH, MK, VEH) differed from the no-lesion group (NON), whereas at 22 d after surgery, only the VEH group remained different from the no-lesion control group (Table 1).

TABLE 1

Means (± S.E.M) of the body tilt on different test days after surgery

Days	Non	Vehicle	$ACTH_{4-14}$	SP	MK–801
1	7.17 (±1.99)	48.55† (±7.36)	52.00† (±8.24)	49.10† (±7.64)	47.53† (±7.41)
3	8.91 (±1.65)	46.67† (±7.27)	31.39‡ (±3.37)	37.33† (±8.73)	30.60 (±5.13)
8	8.50 (±1.86)	49.14† (±6.87)	30.09‡ (±4.55)	29.27‡ (±8.14)	33.57 (±6.81)
10	9.42 (±1.77)	41.97† (±5.80)	26.31‡ (±3.59)	29.27‡ (±8.31)	11.50‡ (±2.06)
15	7.83 (±1.56)	35.66† (±7.22)	15.28‡ (±2.31)	28.85‡ (±5.14)	16.43‡ (±2.05)
17	8.74 (±2.20)	45.13† (±8.52)	18.80‡ (±3.03)	21.81‡ (±4.93)	15.63‡ (±3.25)
22	5.17 (±2.07)	34.78† (±9.20)	14.41‡ (±2.72)	17.43‡ (±2.82)	14.18‡ (±3.33)
24	5.90 (±2.22)	29.35 (±7.15)	16.18‡ (±3.17)	14.09‡ (±3.45)	15.13‡ (±1.57)

†$p<0.05$ Student–Newman–Keuls multiple comparison test group *versus* non group.
‡$p<0.05$ Student–Newman–Keuls multiple comparison test, day *versus* first day after surgery.

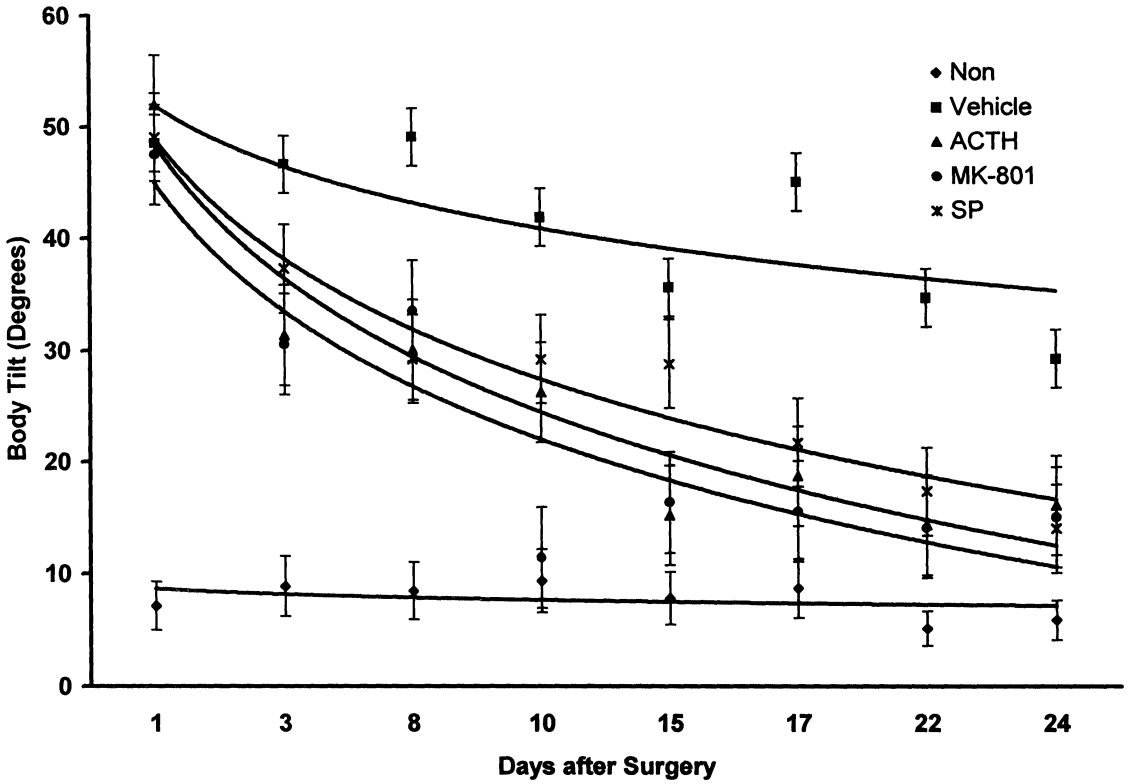

Fig. 2: Means (± S.E.M) of the body tilt of goldfish after unilateral lesion of the labyrinth. Logarithmic trend–lines were added for visualization purposes only. The trend–lines, from top to bottom represent the best fitting curve for the results of the NON, VEH, ACTH, MK and SP groups respectively.

Within-group comparisons showed no difference between days in the lesion group treated with vehicle (VEH) and in the non-lesion group (NON; Table 1). The results of DLR testing after treatment indicate that the degree of body tilt significantly recovered by the 3rd day for the group treated with ACTH4-10, by the 8th day for the group treated with SP, and by the 10th day for the group treated with MK-801. The within-group comparison did not indicate a significant recovery of body tilt in the lesion-group treated with vehicle until the last day of testing, when the degree of tilt no longer differed from that of the no-lesion control.

After this experiment, we found in vitro evidence suggesting a suppression of optic field potentials by MK-801 in goldfish (van Deusen & Meyer, 1990). To test a possible effect of MK-801 on the visual system of goldfish, we tested no-lesion animals for DLR after chronic treatment with MK-801 for 10 d. The results of these animals did not differ from those of non-lesioned, vehicle-treated animals (Mann Whitney U-test, p=0.0997; Vehicle: 12.1±2.18, MK-801: 17.6±2.95; mean±SEM).

DISCUSSION

This study shows that hemilabyrinthectomy in goldfish is suitable for analyzing lesion-induced functional deficits and the effectiveness of drug treatments to improve recovery therefrom. The method used to lesion the labyrinth was the removal of the right utricle and remaining pars superior. The difference between lesion and no-lesion animals in tilt on the first day after surgery confirms that pars superior removal results in a measurable postural imbalance, and that the DLR test is suitable for detecting postural deficits after hemilabyrinthectomy in goldfish, as proposed by Ott and Platt (1988a, 1988b). Curiously, Ott and Platt reported substantially lower tilt angles 1-day post-hemilabyrinthectomy than those noted in this study (mean 19.2° versus 48.6°). The reason for this difference is not clear but is presumably due to some methodological differences between the two studies (namely, light levels in the test apparatus) and warrants further study.

The results with the three drug treatments in this study indicate that not only the neuropeptides SP and ACTH4-10 but also the NMDA receptor blocker MK-801 accelerated functional recovery of body tilt induced by DLR in the goldfish model of hemilabyrinthectomy. The absence of rebound increase in body tilt on the tests performed after the termination of drug treatments indicates that the postural improvement was not due to a temporary drug effect but may have occurred through a process of reorganization.

The two neuropeptides tested, that is, SP and ACTH4-10, have previously been shown to improve functional recovery in different lesion models and species (Flohr & Lüneburg, 1982; Igarashi et al., 1985; Mattioli et al., 1992; Antonawich et al., 1993; Bannon et al., 1995; Sprick et al., 1996). Such promotive effects might be due to their known neurotrophic effects (Jonsson & Hallman, 1982; Nyakas et al., 1985; van der Neut et al., 1988; Iwasaki et al., 1989; Kowall et al., 1991). Nevertheless, neuronal regeneration usually takes weeks to months to occur (Antonawich et al., 1993; Zottoli et al., 1994; for review see Marshall, 1985); therefore, such a mechanism is rather unlikely to have been critical in the present experiment because the peptidergic treatments led to functional recovery within days. Alternatively, they may have acted neurochemically by inducing short term changes that compensated for the lesion-induced loss; in this case, however, cessation of drug treatment should have led to a reappearence of deficits (Flohr & Lüneburg, 1982), which did not occur, at least during the subsequent 4 days.

Because functional recovery after lesion is also dependent on the organism's ability to re-learn or to compensate behaviorally (Morgan et al., 1983; Mattioli et al., 1988), the role of learning and behavioral compensation must be considered as alternative or additive factors. Both SP and ACTH have been shown to promote learning and memory (Greven & de Wied, 1973; de Wied & Gispen, 1977; Stäubli & Huston, 1980; Wetzel & Matthies, 1982; Tomaz & Huston, 1986; Tomaz et al., 1990; Wan et al., 1992; Huston & Hasenöhrl, 1995; Mattioli et al., 1997), and to have reinforcing effects in rats and goldfish (Huston & Oitzl, 1989; Oitzl et al., 1990; Huston & Hasenöhrl, 1995; Mattioli et al., 1995; 1996), and such effects may facilitate functional recovery, for example, by improving behavioral compensation and re-learning. Effects on learning might also explain why the peptides acted rather rapidly and why their effectiveness outlasted drug discontinuation.

From such a learning hypothesis, one should have expected that the NMDA receptor antagonist MK-801 should not promote recovery because this drug is known to impair learning and memory in several paradigms (Xu & Davies, 1992; Buffalo et al., 1994; Caramanos & Shapiro, 1994; Davis & Klinger, 1994; Paule, 1994; Filliat & Blanchet, 1995; Hudzik & Palmer, 1995; Kesner & Dakis,

1995; Mele et al., 1995; Ylinen et al., 1995; Verma & Moghaddam, 1996). Our results, however, indicate that MK-801 actually improves functional recovery. Apparently, the drug's action on recovery is dependent on a mechanism other than learning. Possibly, MK-801 acted neuroprotectively (Grigg & Anderson, 1990; Robinson & Mair, 1992; Yanase et al., 1995). In the case of hemilabyrinthectomy, a neuroprotective action cannot be ruled out because the removal of the labyrinth can lead to retrograde central degeneration after disruption of the 8th cranial nerve, against which MK-801 might have acted neuroprotectively.

Alternatively, it could be argued that MK-801 did not act in a protective or promotive fashion but rather neurotoxically, for example on the visual system (van Deusen & Meyer, 1990). Such an action could reduce the animal's ability to react to the luminous stimulus, which would then lead to a reduction in DLR. This was probably not the case in the present study, however, because the animals treated with MK-801 presented a stronger body tilt than did non-operated controls. Furthermore, we tested non-lesion animals, treated chronically with MK-801, and that we could not detect a difference in DLR between treated and untreated animals, indicates that the systemic injections of MK-801, at the dose used in this experiment, seem not to be neurotoxic on the visual system (not shown).

The present MK-801-induced facilitation of functional recovery contrasts with previously reported data (Flohr & Lüneburg, 1993), in which MK-801 treatment resulted in an inhibition of the initial phases of recovery in goldfish and frogs. Such different results might reflect important dose dependencies because the former authors administered comparatively high dosages, that is, 0.5 and 2.0 mg/kg, whereas we used 100 µg/kg. Furthermore, it might be possible that even a low dose of MK-801 might disturb behavioral compensation acutely after injection (Kim et al., 1997), whereas such an effect is no longer present after 24 h, the timepoint at which we measured the animal's behavior.

In a recent review (de Waele, 1995), the complex neurochemistry of the vestibular system was summarized. In addition to SP, ACTH, and glutamate, this system has neurons containing somatostatin, enkephaline, GABA, glycine, acetylcholine, noradrenaline, dopamine, serotonine, and histamine; more than 21 receptor types are present. Examining the full range of agonists and antagonists of these receptors on functional recovery is still an incomplete task. The model used in the present study is one of the tools that can help to dissect the vestibular system pharmacologically, as well as, the functional recovery processes after vestibular lesions.

In conclusion, the results of this study show that measuring the dorsal light reflex in the goldfish model of hemilabyrinthectomy provides a suitable approach to studying the effectiveness of drug treatments to promote functional recovery. The data presented here might stimulate further research, for example to investigate other potential drug treatments, like growth factors, or to determine physiological variables that are critical for drug-promoted recovery.

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