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Recovery of metabolic activity in retinofugal targets after traumatic optic nerve injury is independent of retinofugal input

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Abstract

Traumatic injury of the adult optic nerve causes a progressive degeneration of retinal ganglion cells. Despite this ongoing degeneration, a partial recovery of visual behavioral function and of local cerebral glucose use (LCGU) has been observed. To evaluate whether this partial recovery of LCGU is due to a recovery of visual conductance (extrinsic) or intrinsic neuronal activity, visual stimulation alone and combined with physostigmine, an acetylcholinesterase inhibitor, were used to activate the retinofugal pathway. LCGU was determined in 30 male adult rats with or without physostigmine treatment 2 or 9 days after crush or 8 days after cut of the right optic nerve. Analysis of LCGU in contralateral first-order projection areas revealed no differences 8 days after cut and 9 days after optic nerve crush. Furthermore, LCGU in the contralateral areas could not be stimulated by the treatment with physostigmine. We therefore conclude that the increase in LCGU from 2 to 9 days after crush is not due to a recovery in the conductance of visual input. We hypothesize a relief of an injury-dependent active suppression (diaschisis) of LCGU. This reversal of diaschisis may, in part, account for the return of visual functions after mild optic nerve injury.

Keywords: diaschisis, lateral geniculate nucleus, metabolic activity, neuroplasticity, recovery of function, superior colliculus, vision

1. Introduction

Graded crush of the adult rat optic nerve causes a progressive degeneration of retinal ganglion cells (RGC). RGC-counts two days after mild optic nerve crush revealed only 28 % and by postoperative day 14 only 11 % of RGC were still connected with their target areas. In contrast to this progressive retrograde loss of RGCs, visual behavioral function is partially restored within 2–3 weeks after mild optic nerve crush, i.e., a major improvement of performance occurred in a visual discrimination task [7,21,22]. This recovery of visual functions occurs independent of how the lesion was created, i.e. by pharmacological or by traumatic methods [19,20, 24]. The behavioral changes are furthermore paralleled by changes in local cerebral glucose use (LCGU) in primary visual target structures, the superior colliculus (SC) and the lateral geniculate nucleus of the thalamus (LGN) [23]. This suggests that the target structures might play an important role in recovery of vision [23,24].

Activation of the visual target structures could be achieved by either visual stimulation via the retina or by pharmacological activation. It is known that enhanced activation of nicotinic retinal cells by acetylcholinesterase inhibitors such as physostigmine increases LCGU in the retinocollicular pathways [1,2,11,13,14,15,17]. Both strategies, vi-

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sual and pharmacological activation, require at least a partially intact optic nerve.

The present investigation was designed to further delineate the mechanisms responsible for the recovery of LCGU [23]. Specifically, we wanted to ascertain if the partial recovery of metabolic activity in visual first-order projection areas after mild optic nerve crush is due to a recovery of visual conductance from the retina to the brain or whether it is due to the relief of active injury-dependent suppression of metabolic activity (diaschisis). Therefore, rats were visually stimulated by light alone or in combination with physostigmine. Physostigmine in combination with visual stimulation should result in a further increase in LCGU in first order projection areas which will lead to a further characterization of the kind of metabolic activity in these areas. Evaluation of LCGU was performed 2 days post lesion because at this point the rats showed no recovery in behavior. Furthermore, LCGU was determined one week after optic nerve crush, at a time point were the major increase in recovery of behavioral performance was observed [21]. In addition, LCGU was checked after the optic nerve was transected.

2. Material and methods

Animals

Adult Long Evans rats weighing 275–300 g were obtained from Harlan Sprague Dawley, Inc. (Indianapolis, IN). Food and water were provided ad libitum and a 12-hour light/dark cycle was maintained. Experiments were conducted in accordance with the guidelines of the National Research Council DHEW publications No. (NIH) 80–23 (1980).

Experimental design

Dependent on lesion and stimulation-treatment, rats were randomly assigned to each of the following groups:

postlesion days / lesion	*without physostigmine*	*with physostigmine (300 µg/kg)*
2 days / crush	n = 5	n = 6
9 days / crush	n = 6	n = 6
8 days / cut	n = 3	n = 4

Optic nerve surgery

Optic nerve crush was performed according to Duvdevani et al. [7]. Briefly, rats were anesthetized with chloralhydrate (7 % solution; 420 mg/kg, intraperitoneally, (i.p.)). To expose the optic nerve, an incision of the conjunctiva lateral to the cornea was performed using microscissors. The optic nerve was identified and exposed near the eyeball by blunt dissection. The right optic nerve was then either cut or crushed unilaterally for 30 s, 2–4 mm distal to the eye ball. After completion of either the cut or the crush an antibiotic eye ointment (Aureomycin®) was applied and the animals were allowed to recover from surgery. The animal's left eye was sham operated in a similar procedure without applying the pressure to the optic nerve.

Physostigmine (300 µg/kg ESERINE; SIGMA St. Louis) was injected intramuscularly (i.m.) 5 min prior to the initiation of the LCGU procedure.

Surgical preparation for LCGU procedure

After animals were anesthetized with halothane, lidocaine was infiltrated around the incision sites. The femoral vein was cannulated with a 3 cm section of Intramedic PE 50 polyethylene tubing inserted into a 3 cm piece of Dow silastic tubing (0.03" I.D.) attached to a 24 cm section of S-54-HL formulation tygon tubing (0.034" I.D.). By a seven inch stainless steel needle, the venous cannula was threaded subdermally from the hind leg to exit between the ears. The femoral artery was cannulated with a 5 cm section of Intramedic PE 10 polyethylene tubing connected to a 15 cm section of S-54-HL formulation tygon tubing (0.02" I.D.). The arterial cannula reached the aorta and could be cleared by two or three drops of blood. The arterial cannula was passed subdermally behind the leg to exit just rostral to the tail. Each cannula was anchored to the skin with a sleeve of PE 205 intramedic polyethylene tubing. About 4 cm of each cannula was left protruding and plugged. The rats were allowed to recover from halothane over night before the 2-DG-experiments were begun. Just before the initiation of the 2-DG procedure, 150 units of heparin were injected i.v., control blood samples were taken and placed on ice.

LCGU procedure

The method for regional glucose use was based on that of Sokoloff et al. [26] as reported by Pazdernik et al. [15]. 2-deoxy[14C]glucose (American Radiolabeled Chemicals Inc., St. Louis, MO) was injected i.v. (100 µCi/kg) as a pulse in a 0.9 % saline solution through the venous cannula which was immediately flushed with saline (see Experimental design section for time of injection). During the first minute immediately following the pulse, six timed serial arterial blood samples (0.05–0.07 ml) were collected in heparinized hematocrit tubes. Rats were released from the cage after the one minute blood sampling and placed into the stimulation chamber. Blood samples were taken again every 5 min for plasma glucose determinations and [14C] scintillation counting. At the end of the experiment, the rats were decapitated and the brain quickly removed, frozen in methylbutane kept at −70 °C, and bagged in plastic air tight bags for storage at −70 °C. Five microliters of each plasma sample were pipetted into 4 ml of scintillation cocktail and counted in a Hewlett-Packard Tri-Carb Scintillation Counter. Ten microliters of plasma were used to determine plasma glucose level with a Yellow Springs Instrument model 23A glucose analyzer (Yellow Springs, OH). The brains were sectioned at 20 µm at −20 °C and immediately dried on a 55–60 °C slide warmer. These sections, along with [14C]methyl methacrylate standards, were exposed to Kodak Ectascan EM-L

X-ray film for 21 days. The optical density (O.D.) of selected brain structure was determined by video-computer-assisted analysis. For each subject, the average of several O.D. readings of representative sections per brain structure was determined. These readings, together with the plasma glucose levels and [14C] concentrations were used to calculate the rate of brain glucose use according to the Sokoloff equation [26].

Visual stimulation procedure

Visual stimulation was based on Schmitt et al. [23]. Briefly, 1 min. after the 2DG-injection the rat was placed in a glass cylinder cage (26 cm × 25 cm) which was surrounded by a rotating (0.08 Hz) white sleeve with black bars of varying spatial frequencies. In addition, the rat was stimulated simultaneously by a strobe-light placed 40 cm above the cage. The strobe provided 10 µs flashes at 5 Hz. This visual stimulation will be referred to as a "strobe-light pattern" hereafter.

Analysis of autoradiographs

Analysis was done in accordance to Schmitt et al. [23]. Briefly, nine different brain areas in each brain hemisphere were analyzed with three visual structures and two auditory structures (reference structures). O.D. readings were taken from three consecutive sections for each of these structures using a spot densitometer (Model TBX, Tobias Assoc., Inc., Ivyland, PA). The SC superficial layer was divided into 4 regions: a rostral area was divided into a medial (mSCr) and a lateral (lSCr) part, and a caudal area was also divided into these two parts (mSCc; lSCc). Similarly, the lateral geniculate nucleus was analyzed in a rostral and a caudal part (LGNr; LGNc) and area 17 of the visual cortex (VC). LCGU was also determined in the medial geniculate nucleus (MGN) and in the inferior colliculus (IC), to determine the impact of the lesion on non-visual sensory structures. "LCGU relative rates" (LCGU of right or left brain structure divided by the average LCGU of auditory structures × 100) were calculated to allow comparison of visual structures between the two sides and across animal groups. This intraindividual comparison was considered to be the proper control to minimize LCGU variability. Here, each animal served as its own control by comparing the contralateral activity to the ipsilateral activity. As the ipsilateral input from the lesioned side is only minor (in the order of 6 %), it is adequate to control for stimulation-dependent activation in the target.

It should be noted that the auditory structures are altered by optic nerve injury. However, they remain unaffected by visual stimulation and are therefore used to normalize for the glucose activity that depends on visual information transfer.

Statistics

Statistical analysis has been done for each brain area separately. A two-way analysis of variance (ANOVA) was calculated for treatment effects (factor A) and lesion effects (factor B). In addition a one-way ANOVA was used with a post hoc Fisher's PLSD test for the various group comparisons.

3. Results

LCGU (µmoles/100 g/min.) was determined in both the ipsilateral and contralateral sides of seven discrete visual structures and two auditory structures. This was done under conditions of strobe-light pattern stimulation with and without physostigmine i.m. injection (300 mg/kg) at 2, 8 and 9 days after optic nerve lesion. Actual LCGU rates are given in Tables and "LCGU relative rates" are shown in bargraphs.

two-way-ANOVA for the main effects revealed:

	SC		*LGN*		*VC*	
factor	F-test	p value	F-test	p value	F-test	p value
A treatment	11.124	0.0001	4.587	0.0017	2.3	0.0594
B lesion	372.743	0.0001	201.605	0.0001	9.215	0.0039
A × B interaction	9.103	0.0001	2.145	0.076	0.436	0.8211

Superior colliculus (SC)

LCGU of the SC was calculated in 4 regions: a rostral section divided into a medial (mSCr) and a lateral (lSCr) part and a caudal section also divided in the same manner (mSCc, lSCc). Given "LCGU relative rates" were calculated for the entire SC based on averages from the regional subdivisions. One-way ANOVA revealed statistical significance between groups with $F_{(5,29)} = 5.482$ $p = 0.0017$. The following significant effects were based on the post-hoc t-test ($p < 0.05$). Two days after mild optic nerve crush LCGU was statistically significant decreased in the contralateral SC (Figs. 1a,b). Nine days after optic nerve crush there was a significant increase in "LCGU relative rates" from day 2 in the contralateral SC, but these values were still significantly lower compared to the ipsilateral side. Optic nerve cut reduced "LCGU relative rates" in the contralateral SC but there was no significant difference to either 2 days or 9 days after crush. "LCGU relative rates" after the cut were significantly higher than 2 days after the crush in the case of physostigmine treatment (Figs. 1a,1b).

Lateral geniculate nucleus (LGN)

"LCGU relative rates" were calculated for the rostral and caudal areas of the LGN (LGNr; LGNc) without distinguishing between anatomical substructures. One-way ANOVA revealed statistical significance between groups with $F_{(5,29)} = 2.672$ $p = 0.0131$. The following significant effects were based on the post-hoc t-test ($p < 0.05$). As shown in Figure 2a,b there was a significant decrease at post-lesion day 2, followed by a significant increase in "LCGU relative rates" in contralateral LGN at post-lesion day 9. After cut of the optic nerve, the reduction of "LCGU relative rates" in

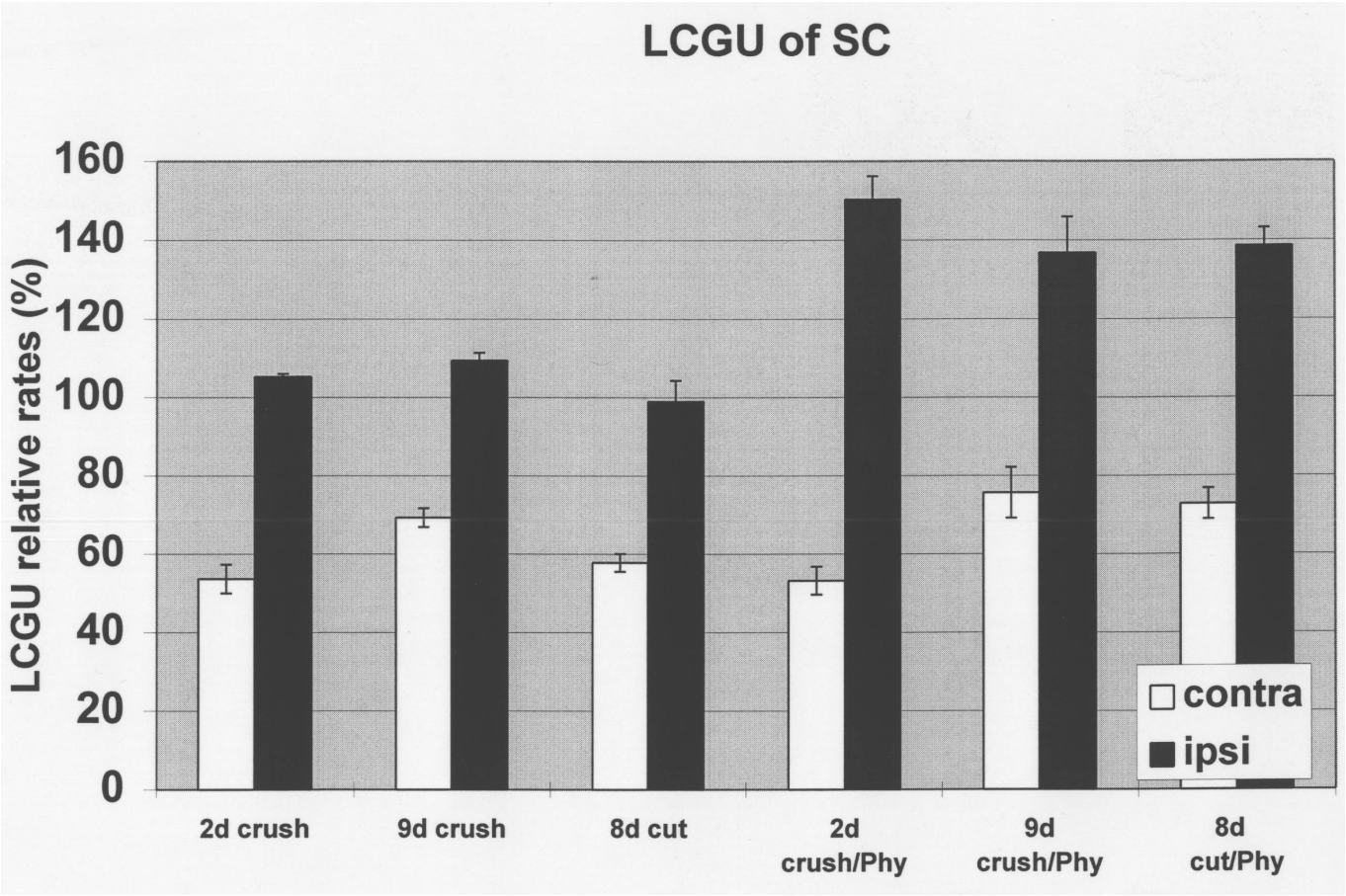

Fig. 1a. Bargraphs showing relative rates of LCGU in the ipsilateral and contralateral superficial layer of the SC. "LCGU relative rates" are expressed as percentage of auditory control structures and displayed at the different time points either with or without physostigmine (Phy) treatment; Mean ± S.E.M. Statistical differences ($p < 0.05$) between the different time points of LCGU determination are indicated by an asterisk based on post-hoc Fischer's PLSD test. Furthermore significant but not indicated is the difference between ipsilateral and contralateral "LCGU relative rates" at any time point and the increase in ipsilateral "LCGU relative rates" after stimulation with physostigmine ($p < 0.05$).

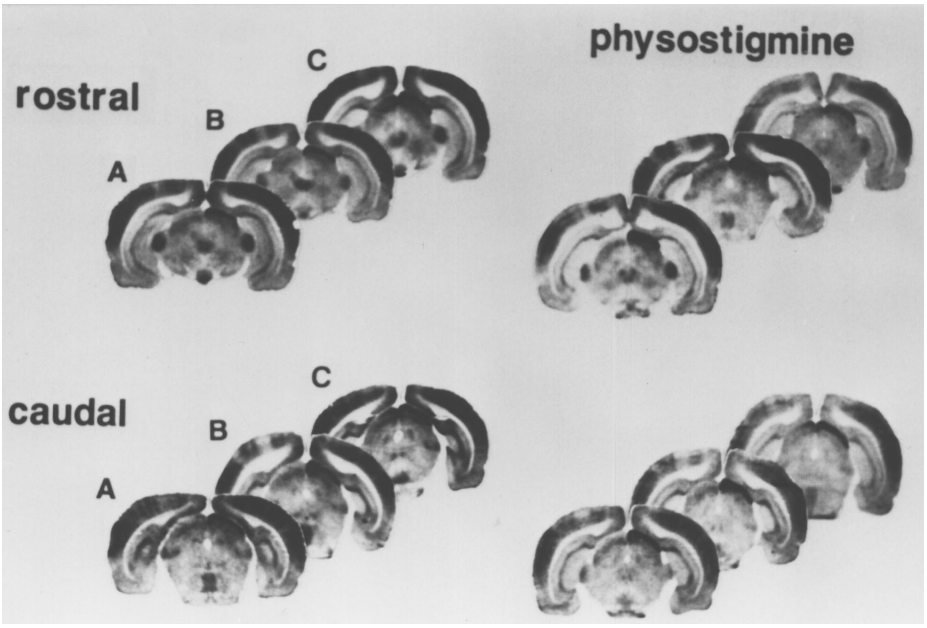

Fig. 1b. Representative autoradiographs illustrate LCGU response in SC after strobe light-pattern stimulation with and without physostigmine treatment in rats with optic nerve damage: A = 2 days after mild crush, B = 9 days after mild crush, and C = 8 days after cut of the optic nerve. The sections correspond to the different regions in SC where the LCGU has been determined.

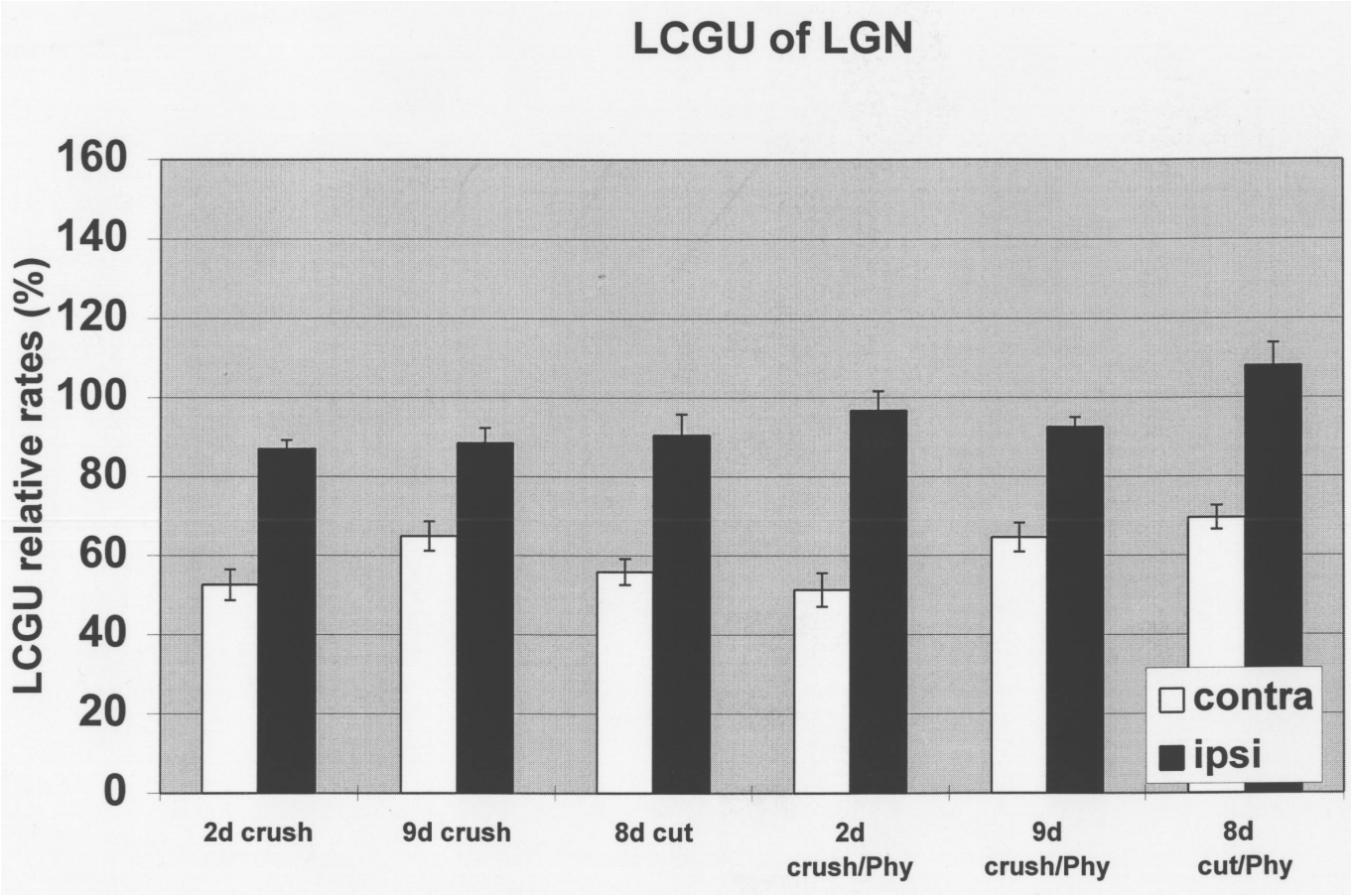

Fig. 2a. Bargraphs showing relative rates of LCGU in the ipsilateral and contralateral LGN. "LCGU relative rates" are expressed as percentage of auditory control structures and displayed at the different time points either with or without physostigmine (Phy) treatment; Mean ± S.E.M. Statistical differences ($p < 0.05$) between the different time points of LCGU determination are indicated by an asterisk, based on post-hoc Fischer's PLSD test. Furthermore significant but not indicated is the difference between ipsilateral and contralateral "LCGU relative rates" at any time point ($p < 0.05$).

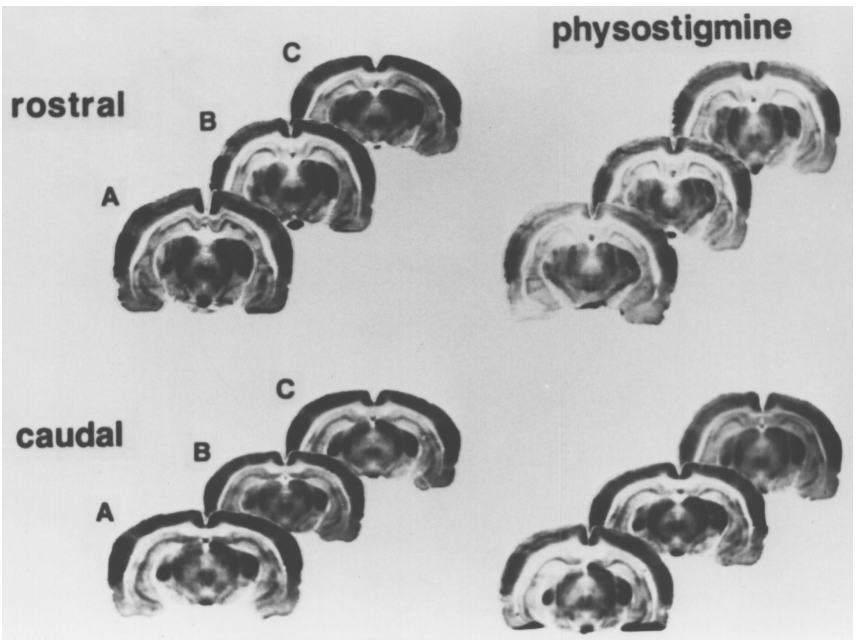

Fig. 2b. Representative autoradiographs illustrate LCGU response in LGN after strobe light-pattern stimulation with and without physostigmine treatment in rats with optic nerve damage: A = 2 days after mild crush, B = 9 days after mild crush, and C = 8 days after cut of the optic nerve. The sections correspond to the different regions where the LCGU has been determined.

contralateral LGN was also significant. "LCGU relative rates" were not statistically different to those either 2 or 9 days after crush. In rats treated with physostigmine, the reduction of "LCGU relative rates" 2 days after the crush was comparable to the reduction seen without physostigmine treatment. Nine days as well as 8 days after the respective lesion there was a significantly higher level of "LCGU relative rates" with physostigmine treatment compared to the respective 2 day values (Figs. 2a,b).

Visual cortex (VC)

"LCGU relative rates" in the VC were calculated in the area shown in Figure 3b. This area was also affected by the optic nerve lesions. A significant decrease was observed in the contralateral versus ipsilateral side under all conditions ($p < 0.05$; Figs. 3a,b). But there was no significant difference in "LCGU relative rates" between the various groups either with or without treatment with physostigmine, revealed by one-way ANOVA with $F_{(5,29)} = 0.601$ $p = 0.6995$ (n.s.).

Effects of physostigmine on LCGU

Treatment with physostigmine (i.m.) increased LCGU in all ipsilateral visual areas. The most obvious increase occurred in the superficial layers of the SC ($p < 0.05$; Table Ib). As seen without physostigmine, after both types of lesion of the optic nerve, LCGU in all contralateral areas was significantly reduced at 2 days post-lesion ($p < 0.05$; Table Ib). Eight (cut) and 9 (crush) days after optic nerve lesion, LCGU in SC and LGN was significantly higher compared to 2 days after the crush ($p < 0.05$). Also, physostigmine caused a statistically significant decrease of LCGU in both auditory structures measured ($p < 0.05$).

4. Discussion

Optic nerve damage caused a marked decrease in LCGU in all contralateral retinofugal targets. This reduction of metabolic activity is followed by a partial restoration of LCGU within the first-order projection areas (i.e., SC and LGN, Figs. 1b, 2b). Furthermore, physostigmine an acetylcholinesterase inhibitor increased LCGU only in ipsilateral SC. Total deafferentation by cut of the optic nerve 8 days after the lesion resulted in similar LCGU levels as those 9 days after crush. These results are in accordance to our own observations [23] and to those reported on LCGU in visual areas and with respect to restoration [4,5,10,27,29,30,31]. Furthermore, the present results confirm also the ability of physostigmine to enhance LCGU in retinofugal targets, most obvious in the superficial layers of the SC [1,2,11,13,14,15]. However, these results indicate that physostigmine inspite its effects on the ipsilateral projection areas, produced no increase in LCGU in contralateral visual areas after the lesion at any time point. Additionally, "LCGU relative rates" in first-order projection areas were similar 8 days after the cut and 9 days after the crush independently of the stimulation. These observations are crucial for the main question whether the restoration of LCGU depends on a partially intact optic nerve.

In principal, the rate of LCGU is closely coupled to the excitatory activity of the brain [25]. This neuronal activity in certain nuclei is dependent on their afferent and efferent connections. In the visual system the primary input comes from the retina through the optic nerve to the SC and the LGN. The LGN projects to the visual cortex which itself has backwards projections to the LGN. Thus, LCGU in the primary visual areas depends on the retina driven activity, on the activity coming from further connections and on the basic cell metabolism [4,10,11,18,23,28,31,32]. Nevertheless, as indicated by our own observations retinal activation is the main factor affecting LCGU [23]. Respectively, it is to assume that metabolic activity is influenced by the degree of retinal deafferentation. Thus, restoration of LCGU should also depend on the degree of deafferentation. However, our results as well as those of several authors showed that metabolic activity is also restored to a certain degree after total deafferentation [5,6,27,31]. In addition, Thurlow and Cooper [27,30] showed that deafferentation is required for restoration of metabolic activity to occur. Thus, the occurrence of restoration of LCGU after total deafferentation must reflect neuronal activity, independent of retinal input. The results of the present work point towards such a retina independent restoration process within the first 9 days after the lesion. This is based on the observation that LCGU after cut and crush were not different and that physostigmine did not increase the LCGU significantly 9 days after optic nerve crush in the contralateral areas. In conclusion, the increase in LCGU in first-order projection areas from 2 to 9 days after the crush is not, or only in a minor part, due to a recovery of retinal input.

This specific restoration of LCGU visual first-order protection areas requires an explanation for the return of neuronal activity independent of the visual input. It is known that following acute, localized lesions of the central nervous system immediate depression of neuronal synaptic functions occurs in other areas of the central nervous system remote from the lesion [8,9,12]. These remote effects result from the deafferentation, a phenomenon known as diaschisis [12,33]. That means, diaschisis is a temporary functional "shock" or deactivation of intact brain regions remote from the area of primary injury. After an interval of time, which correlates directly with the severity of the lesion, recovery of metabolism occurs due to synaptic reactivation of neurons [9,12]. This reactivation of neurons could be responsible for the increase of LCGU from day 2 to 9 after the crush and the measurable LCGU activity 8 days after optic nerve cut. Likewise diaschisis, an active metabolic suppression triggered by the optic nerve lesion itself reduced the metabolic activity in remote areas such as SC, LGN and to a limited extend VC. The relief of this active suppression then might cause the increase seen at day 8 and 9 after the respective lesion. This interpretation would be in line with Cooper and Thurlow [5] which also referred to diaschisis when discussing their findings on LCGU-restoration after enucleation.

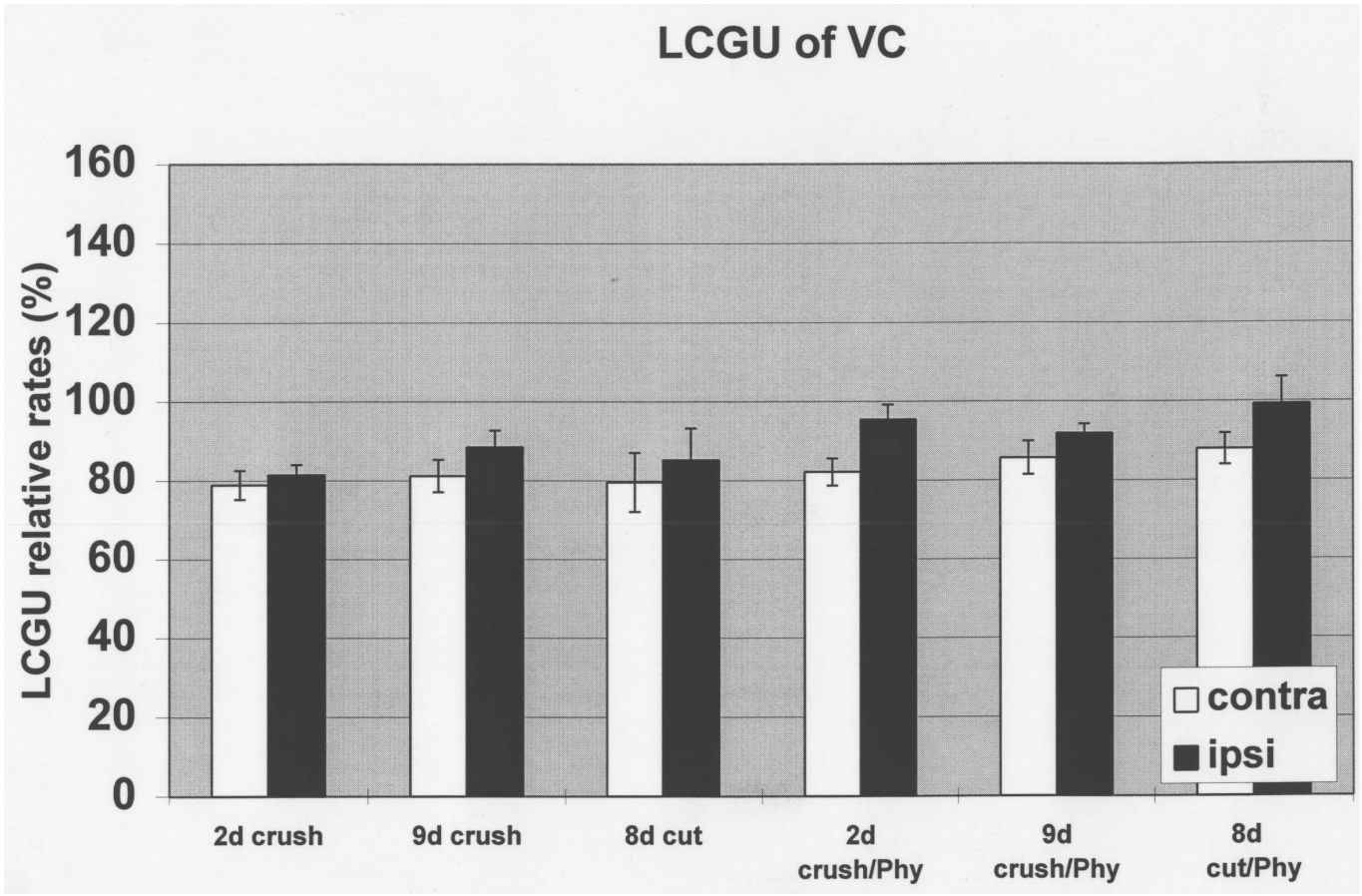

Fig. 3a. Bargraphs showing relative rates of LCGU in the ipsilateral and contralateral VC. "LCGU relative rates" are expressed as percentage of auditory control structures and displayed at the different time points either with or without physostigmine (Phy) treatment; Mean ± S.E.M. Statistical differences ($p < 0.05$) between the different time points of LCGU determination are indicated by an asterisk based on post-hoc Fischer's PLSD test. Furthermore significant but not indicated is the difference between ipsilateral and contralateral "LCGU relative rates" at any time point ($p < 0.05$).

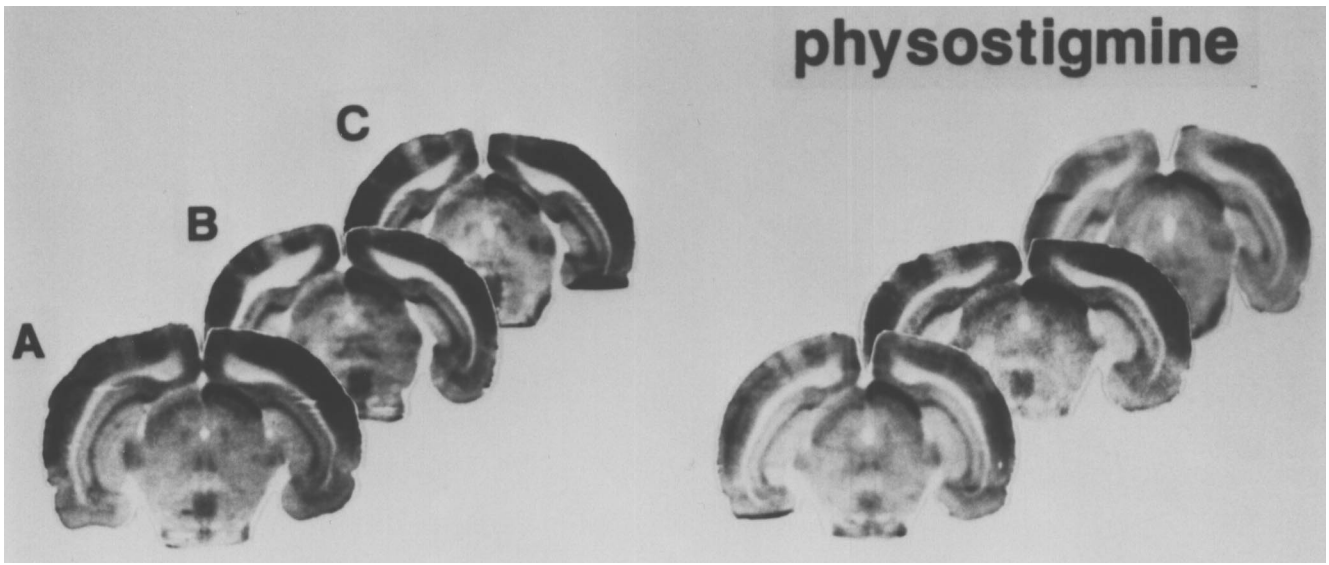

Fig. 3b. Representative autoradiographs illustrate LCGU response in monocular representation area of VC after strobe light-pattern stimulation with and without physostigmine treatment in rats with optic nerve damage: A = 2 days after mild crush, B = 9 days after mild crush, and C = 8 days after cut of the optic nerve. The sections correspond to the different regions where the LCGU has been determined.

TABLE Ia. LCGU in selected brain structures during strobe-light pattern stimulation 2, 9 (crush) and 8 days (cut) after optic nerve lesion. LCGU was determined in structures ipsilateral and contralateral to the lesion. LCGU is expressed in µmole/100g/min. Abbr.: (lSCr) lateral section of rostral SC; (mSCr) medial section of rostral SC; (lSCc) lateral section of caudal SC; (mSCc) medial section of caudal SC; (r LGN, c LGN) rostral and caudal section of lateral geniculate nucleus; (VC) monocular field of the visual cortex; (IC) inferior colliculus; (MGN) medial geniculate nucleus of the thalamus.

structure	*2d ipsil.*	*2d contral. (crush)*	*9d ipsil.*	*9d contral. (crush)*	*8d ipsil.*	*8d contral. (cut)*
lSC r	119.9±4.2	60.1±4.7	112.0± 9.2	73.4± 9.0	125.0±6.4	78.7±3.2
mSC r	135.5±7,1	66.5±7.6	129.6±10.2	82.0±10.7	135.2±4.8	78.6±5.0
lSC c	128.5±4.9	64.6±3.9	122.9±10.2	73.1± 7.6	135.6±6.9	81.6±4.6
mSC c	150.7±7.6	81.1±9.2	139.7±10.5	94.3± 9.2	155.4±4.3	84.1±4.3
r LGN	112.7±5.2	72.9±6.7	107.1± 8.2	79.2± 9.3	131.3±3.5	83.2±6.2
c LGN	107.7±3.8	60.4±5.2	97.0±10.0	72.9± 9.1	120.4±2.8	72.2±2.9
VC	114.5±4.7	93.7±4.2	106.2± 6.2	85.5± 8.3	124.2±9.0	88.7±8.3
MGN	115.1±5.9	115.4±7.3	106.1± 8.2	107.0± 9.8	120.1±5.6	123.2±2.0
IC	138.1±5.8	138.8±6.6	123.2± 9.4	126.2±11.3	160.7±7.9	155.0±9.7

TABLE Ib. LCGU in selected brain structures during strobe-light pattern stimulation and physostigmine 2, 9 (crush) and 8 days (cut) after optic nerve lesion. LCGU was determined in structures ipsilateral and contralateral to the lesion. LCGU is expressed in µmole/100 g/min. Abbr.: (lSCr) lateral section of rostral SC; (mSCr) medial section of rostral SC; (lSCc) lateral section of caudal SC; (mSCc) medial section of caudal SC; (r LGN, c LGN) rostral and caudal section of lateral geniculate nucleus; (VC) monocular field of the visual cortex; (IC) inferior colliculus; (MGN) medial geniculate nucleus of the thalamus.

structure	*2d ipsil.*	*2d contral. (crush)*	*9d ipsil.*	*9d contral. (crush)*	*8d ipsil.*	*8d contral. (cut)*
lSC r	109.6± 9.0	40.9±1.5	114.0±13.9	65.0± 7.0	146.4±4.5	86.7±4.6
mSC r	123.5± 7.3	46.6±5.6	128.0±18.5	74.2±13.4	157.7±6.2	82.3±5.7
lSC c	124.3±11.4	39.7±3.0	129.3±13.5	63.4± 6.8	176.1±9.9	94.2±2.4
mSC c	152.2±15.0	51.0±4.0	147.1±13.0	84.4± 9.1	207.7±6.2	97.6±5.2
r lGN	79.2± 4.8	47.1±3.6	94.9±10.4	64.1± 6.3	132.8±9.1	93.3±1.9
c lGN	84.6± 8.6	38.8±3.7	83.4±11.1	59.0± 8.2	135.2±5.9	79.0±3.5
VC	87.7± 9.0	55.9±5.7	90.6± 8.7	65.2± 5.4	130.4±5.7	88.0±3.1
MGN	78.1± 5.4	78.6±5.9	87.9± 9.9	93.1± 9.4	118.9±2.1	121.5±1.4
IC	91.5± 4.4	89.8±4.9	101.8± 9.4	98.3± 7.4	129.3±7.7	127.4±9.4

Whether named diaschisis or an active lesion-dependent suppression of neuronal function or metabolic activity, this concept seems a suitable model for the explanation of the discrepancy between restoration and the lack of input. This kind of lesion-dependent suppression could also serve as an underlying mechanism for the results on functional recovery [3]. Sautter and Sabel [21] reported an increase in visual behavioral abilities, while anatomical connectivity decreased during the same time after graded crush of the rat optic nerve. As the recovery of behavior parallels the restoration of LCGU [23], the restored behavioral abilities might also reflect the relief of suppressed neuronal activity. In this case the remaining RGCs after the crush enable the rats, after the relief of suppression in the projection areas (which is the time dependent factor), to perform the behavioral task. At this point the size of the lesion is the critical factor determining behavioral recovery (in accordance to Ramirez and Sabel [16]). In light of the 22 day time period [23] further other possible mechanisms besides the relief of a neuronal suppression such as sprouting, denervation supersensitivity or a change of trophic support can not be ruled out to reflect the increase in LCGU and visual guided behavior [3,23,24].

In summary, we were able to show that the increase in LCGU in retinofugal first-order projection areas from day 2 to day 9 after optic nerve crush is independent of the presence of retinofugal inputs. It is still unclear, however, whether return of LCGU is an active restoration process or if it comprises a relief of injury dependent active suppression of metabolic activity (diaschisis). In any event, our study emphasizes the role of the deafferentated target structure in the process of recovery of function and points our search for the mechanisms of recovery upstream from the lesion site.

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