Rapid Changes in Gustatory Function Induced by Contralateral Nerve Injury and Sodium Depletion

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Abstract

The combination of dietary sodium depletion and unilateral chorda tympani (CT) nerve section decreases sodium taste function in the intact CT nerve. However, functional changes have not been examined prior to day 4 postsectioning, even though degenerative and inflammatory responses are robust during that period. Rats received unilateral CT section and/or dietary sodium depletion, accomplished by 2 injections of furosemide and a sodium-restricted diet, on day 0. Surgical controls received sham nerve sectioning. At days 1, 2, 3, or 4, taste responses were recorded from the intact nerve. Functional changes were rapid and unexpected. At day 1 postsectioning, neural responses from the uninjured CT of both control-fed and sodium-depleted animals were reduced. By day 2, however, normal function was restored in control-fed rats, whereas functional deficits persisted in depleted animals. Sodium depletion alone also induced a transient decrease in sodium responses at days 2–3 after furosemide injection. These results demonstrate that distant neural injury can elicit gustatory plasticity regardless of the dietary environment, but normal responses can be restored. We suggest that neutrophils mediate the initial postinjury deficits in taste function, whereas macrophages promote the recovery of normal function.

Key words: amiloride, chorda tympani nerve, neural degeneration, neural plasticity, neurophysiology

Introduction

Taste buds on the anterior region of the tongue are innervated by the chorda tympani (CT) nerve, which maintains taste bud integrity and transmits gustatory signals to the central nervous system. Upon CT nerve sectioning, taste buds degenerate and taste function is lost on the ipsilateral side of the tongue (Olmsted 1921; Guth 1971; Cheal and Oakley 1977). Once regeneration occurs, new taste buds are formed and taste function is restored (Cheal et al. 1977).

Newly formed taste receptor cells are sensitive to dietary manipulation, as demonstrated in models of development (Hill 2004) and neural injury (Hill and Phillips 1994; Phillips and Hill 1996; Hendricks et al. 2002; McCluskey and Hill 2002). During postnatal development, sodium responses gradually increase until they reach adult-like levels (Cheal and Oakley 1977; Hill and Almli 1980; Ferrell et al. 1981; Hill et al. 1982). However, maternal dietary sodium restriction prevents the emergence of normal sodium responses as long as the offsprings are maintained on a low-sodium diet (Hill 2004). Neurophysiological responses to sodium are also subnormal in adult rats when denervated taste buds and the CT regenerate under conditions of sodium restriction (Hill and Phillips 1994). Surprisingly, the intact CT initially exhibits subnormal responses to sodium as well. Responses then increase linearly over the next 50 days until they reach hypersensitive levels. Both the low-sodium diet and unilateral nerve section were required to elicit functional changes in these studies (Hill and Phillips 1994; McCluskey and Hill 2002).

Dietary sodium unmasks a functional, apparently nonneural interaction (Kinnman and Aldskogius 1988) between the injured and intact lingual fields (Hill and Phillips 1994; Phillips and Hill 1996; Hendricks et al. 2002; McCluskey and Hill 2002). However, sodium sensitivity in the intact CT has not been examined during the early postinjury period when a number of important events take place. On the sectioned side of the tongue, CT fibers retract from taste buds within 12–24 h after CT and lingual sectioning and denervated taste receptor cells subsequently degenerate (Farbman 1969). CT sectioning also modulates immune activity within hours to days. For example, there are rapid increases in

lingual levels of adhesion molecules and chemokines that recruit leukocytes to injured sites (Cavallin and McCluskey 2007a, 2007b). Activated macrophages also respond bilaterally to nerve injury within 2 days (McCluskey 2004; Cavallin and McCluskey 2005). It is unknown whether the function of the intact CT changes concomitantly because the earliest point examined in previous work was day 4 after section (Hill and Phillips 1994; Phillips and Hill 1996; Hendricks et al. 2002).

In the current study, we determined the effects of dietary sodium depletion on the function of the intact CT during the early postsectioning period. Knowing when functional changes first occur in the uninjured nerve will contribute to an understanding of underlying mechanisms. Furosemide, a natriuretic/diuretic, was injected to ensure rapid sodium depletion of rats in the appropriate groups. This method of sodium depletion (i.e., furosemide injection and a low-sodium diet) replicates that used in previous work focused on the function of the intact CT after contralateral injury (Hill and Phillips 1994; Phillips and Hill 1996; Hendricks et al. 2002; McCluskey and Hill 2002). Our findings demonstrate that the functional plasticity exhibited by the uninjured CT is even more dynamic than previously appreciated.

Materials and methods

Animals

All protocols were approved by the Institutional Animal Care and Use Committee of the Medical College of Georgia and followed guidelines set by the National Institutes of Health. Female specified pathogen-free Sprague–Dawley rats ($n = 112$; Charles River, Wilmington, MA) were 150–290 g at the time of nerve recording. CT responses did not vary with body weight. Rats were housed in cages with barrier tops and received autoclaved food, bedding, and water.

Groups

Separate groups of rats ($n = 8$ each) were given the following dietary and surgical treatments: 1) unilateral CT section and dietary sodium depletion, 2) dietary sodium depletion alone, or 3) CT section alone. Distinct groups of rats were examined on days 1, 2, 3, and 4 following furosemide injection and initiation of the low-sodium diet and/or CT sectioning (day 0). In addition, we recorded from a separate group of unmanimulated "controls" ($n = 8$) and from a group at day 1 after sham sectioning ($n = 8$) to control for the effects of anesthesia and the surgical approach to the CT nerve.

Nerve sectioning procedure

Rats receiving nerve section were injected with atropine sulfate (0.5 mg/ml, intraperitoneal [i.p.]) followed by anesthesia with a mixture of ketamine (40 mg/kg, i.p.) and xylazine (10 mg/kg, i.p.). Body temperature was maintained between 36 °C and 38 °C with a hot water pad. The right CT nerve was aseptically exposed by a mandibular approach and transected after its bifurcation from the lingual nerve, as described in previous work (Hill and Phillips 1994; Phillips and Hill 1996). The sutured incision was swabbed with Bactine after the surgical procedure.

Dietary manipulations

Rats in the unoperated and sectioned low-sodium groups received 2 injections of furosemide (10 mg each within 24 h, i.p.; Sigma, St Louis, MO), low-sodium chow (0.03% NaCl, MP Biomedicals, Solon, OH), and distilled water ad libitum. For convenience, we refer to these groups as "sodium depleted" below. Rats in control-fed groups were maintained on a control diet (0.25% NaCl) and tap water.

Neurophysiology

CT recordings were performed from day 1 to day 4 postsectioning to determine when functional changes occur in the contralateral, intact CT nerve. Rats were anesthetized with chloral hydrate (525 mg/kg, i.p.). Additional injections were given as needed to maintain a surgical level of anesthesia. The dissection and recordings proceeded as in previous work (Hill and Phillips 1994). Briefly, animals were tracheotomized and placed in a nontraumatic head holder. Body temperature was maintained between 36 °C and 38 °C. The head was laterally dissected and the left CT exposed, cut near its exit from the tympani bulla, and placed on a platinum electrode. Multifiber activity from the entire nerve was amplified, displayed on an oscilloscope, and monitored with an audio amplifier. For data analysis, the amplified signal was passed through an integrator with a time constant of 1.0–2.0 s, and the summated electrical activity was viewed using PowerLab software (ADI, Colorado Springs, CO). This measure of the neural response reflects the sum of single-fiber responses (Beidler 1953).

Stimulation procedures

Responses were recorded during stimulation of the anterior tongue with concentration series (0.05–0.5 M) of NaCl, sodium acetate (NaAc), and KCl. Responses to 1 M sucrose, 0.01 M quinine, 0.01 N HCl, and 0.3 M monosodium glutamate (MSG) were also determined. All chemicals were reagent grade, dissolved in distilled water, and kept at room temperature during recording. Three milliliters of each stimulus were applied to the anterior part of the tongue over a period of ~5 s using a syringe. After 25 s, the tongue was rinsed with distilled water for at least 1 min. The stability of each series was determined by analyzing the height of the integrated response to 0.5 M ammonium chloride (NH_4Cl) at the beginning and end of each concentration series. Only stable series with NH_4Cl responses that differ by ≤10% were used for data analysis (Hill and Phillips 1994; Phillips and Hill 1996). NH_4Cl (0.5 M) was also used as the standard

stimulus for calculating relative response magnitudes. Specifically, we measured the steady-state height of the integrated neural response at 20 s after stimulus application to the tongue. At the end of the experiment, responses to a NaCl concentration series were recorded after lingual application of the epithelial sodium channel (ENaC) blocker, amiloride hydrochloride (MP Biomedicals, Solon, OH). The solvent and rinse for each stimulus consisted of 50 μM amiloride. Following the conclusion of each recording, rats were euthanized with an overdose of sodium pentobarbital (80 mg/kg, i.p.).

Data presentation and analysis

Mean relative CT response ratios were compared among treatment groups (Hill and Phillips 1994; Phillips and Hill 1996; Hendricks et al. 2002; McCluskey and Hill 2002). Responses from normal control animals were compared with those from sham-sectioned surgical controls using *t*-tests. To examine the effects of diet and/or CT section, responses from each treatment group at each day postsectioning were compared with those from pooled controls. Comparisons were made with analyses of variance followed by Dunnett's posttests where appropriate using Prism 3.0 (GraphPad Software, San Diego, CA). The α-level was set at $P < 0.05$, and the resulting P values are reported in Results.

Results

Control groups

Mean relative responses from untreated, normal control rats were similar to those from sham-sectioned rats. This was true for all concentrations of each stimulus tested ($P > 0.05$), except for the responses to 0.1 M KCl ($P < 0.017$). Because the surgical approach and/or anesthesia (i.e., without nerve section) did not substantially change neural responses, data from these groups were pooled for further analyses and are subsequently referred to as "controls." Thus, mean relative CT responses from controls were compared with those from separate treatment groups, obtained from acute recordings, at days 1–4 after treatment. Functional changes in the intact CT of sectioned and/or depleted rats compared with controls are summarized in Table 1 and reported below.

Effects of CT sectioning and dietary sodium depletion

Representative whole nerve recordings from the intact CT of animals receiving contralateral nerve section and sodium depletion (cut + diet) are shown in Figure 1. Mean responses to both 0.25 and 0.5 M NaCl were reduced at each time point in rats receiving both dietary and surgical treatments ($n = 8$) compared with controls (control, $n = 16$; Figure 2; $P < 0.001$–0.05). In addition, reduced responses to 0.05 and 0.1 M NaCl were observed at day 3 and to 0.1 M NaCl at day 4 ($P < 0.001$–0.05; Figure 2C,D). Sodium responses

Table 1 Summary of changes in neural response to sodium

Treatment	Days posttreatment				
	0	1	2	3	4
Control	Normal	N/A[a]	N/A	N/A	N/A
Cut	N/D[b]	Reduced	Normal	Normal	Normal
Diet	N/D	Normal	Reduced	Reduced	Normal
Cut + diet[c]	N/D	Reduced	Reduced	Reduced	Reduced

[a]Not applicable.
[b]Not determined.
[c]Furosemide injection (×2) followed by a low-sodium diet.

rapidly decreased within 24 h after CT section, and dietary sodium depletion then continued to diminish gradually until reaching a minimum at day 4 postsection. The intact CT responses to another sodium stimulus, 0.5 M NaAc, were also significantly reduced in depleted rats at days 1–4 postsectioning compared with controls ($P < 0.001$; Figure 3). Mean responses to 0.25 M NaAc from this group were also significantly lower versus controls at days 3–4 after contralateral sectioning ($P < 0.05$; Figure 3C,D). At day 1, the response to 0.05 M NaAc was slightly, though significantly, increased ($P < 0.05$; Figure 3A).

CT responses to nonsodium stimuli were largely unaffected by sodium depletion and nerve injury, with a few exceptions. Responses to 0.1 and 0.5 M KCl at day 2 postsection ($P < 0.05$) and to 0.10–0.5 M KCl ($P < 0.05$) at day 3 were significantly lower than mean control responses (Figure 4B,C). In addition, responses to 0.05–0.25 M KCl were slightly, though significantly, diminished by contralateral sectioning and depletion at day 4 postsection ($P < 0.05$; Figure 4D). Altered KCl responses have not been observed previously in animals treated with CT section and dietary sodium depletion (Phillips and Hill 1996; Hendricks et al. 2002; McCluskey and Hill 2002). However, the combination of dietary and surgical treatments may have some impact upon the transduction of potassium by amiloride-sensitive (Lundy and Contreras 1997; Lundy et al. 1997) or amiloride-insensitive pathways in noninjured taste receptor cells (DeSimone and Lyall 2006). The intact CT nerve from cut + diet rats also exhibited reduced sensitivity to MSG from day 2 to day 4 postsectioning compared with controls ($P < 0.001$–0.05) (Figure 5). Although MSG stimulates the umami transduction pathway, this stimulus also contains a sodium component.

Effects of contralateral CT section alone

Typical neural responses from control-fed rats receiving contralateral CT section (cut alone) are represented in Figure 1. At day 1 postsection, this group ($n = 8$) demonstrated significantly reduced CT responses to 0.5 M NaCl compared with controls ($P < 0.05$) (Figure 2A). Mean CT responses to 0.5 M NaAc were also significantly lower in animals receiving
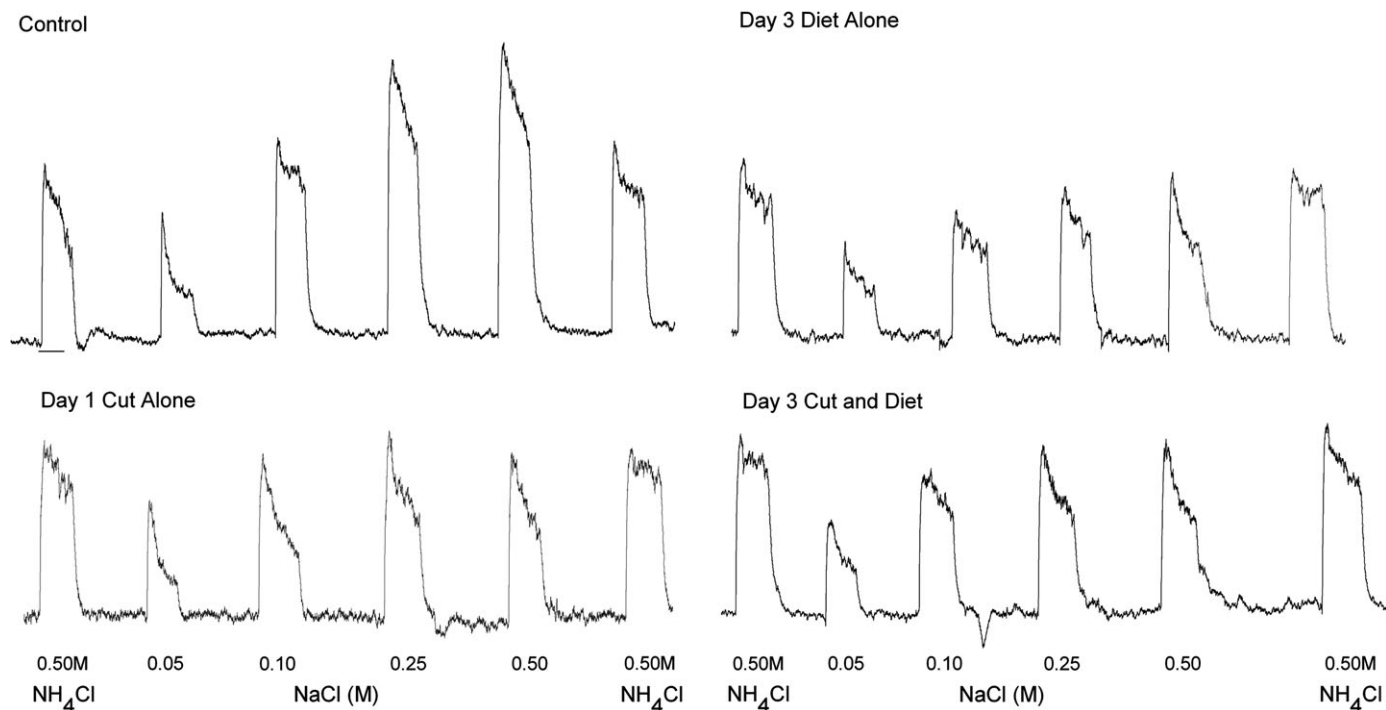
Figure 1 Integrated responses from the intact CT nerve to 0.5 M NH$_4$Cl and a concentration series of NaCl. Groups include unoperated, control-fed animals (control), control-fed rats receiving CT section (day 1 cut alone), sodium-restricted rats (day 3 diet alone), and rats receiving both contralateral CT section and dietary sodium depletion (day 3 cut + diet). Representative responses were chosen to illustrate key findings. Steady-state responses to NaCl, relative to NH$_4$Cl responses, were decreased at day 1 in animals receiving CT section alone compared with controls. Responses to NaCl were also reduced at day 3 in sodium-restricted rats and those receiving both nerve sectioning and sodium depletion versus controls. Time calibration (line under the 0.05 M NaCl response at the top left) = 20 s.

unilateral sectioning compared with controls ($P < 0.05$). However, normal sodium taste function was restored at day 2 following nerve injury. This brief drop in sodium taste function was unexpected because nerve injury alone had no effect on the regenerated or intact CT responses from day 4 to day 85 in previous work (Hill and Phillips 1994; Phillips and Hill 1996). Responses to other nonsodium stimuli were generally unaltered by sectioning alone (Figures 4 and 5), although MSG responses were significantly reduced at day 4 compared with controls ($P < 0.001$) (Figure 5D).

Effects of sodium depletion alone

Representative responses to NaCl from sodium-depleted rats (diet alone) are shown in Figure 1. This group ($n = 8$) displayed reduced responses to 0.5 M NaCl at day 2 after treatment compared with controls ($P < 0.05$; Figure 2B). At day 3, responses to 0.10–0.5 M NaCl were also significantly reduced ($P < 0.001$; Figure 2C), but they returned to normal by day 4 after treatment ($P > 0.05$) (Figure 2D). The decreased responses to an additional sodium stimulus, NaAc, occurred one day later than the reduction in NaCl responses. Sodium-deficient rats displayed significantly lower CT responses to 0.25 and 0.5 M NaAc compared with control responses at day 3 ($P < 0.001$; Figure 3C),

although responses again returned to control-like level by day 4 after treatment ($P > 0.05$). Neural responses to nonsodium stimuli were unaffected by sodium depletion (Figures 4 and 5).

Effects of the ENaC antagonist, amiloride

Amiloride decreased sodium responses from each treatment group to similar magnitudes (Figure 6A–D; $P > 0.05$). Two exceptions were the neural responses to 0.10 and 0.50 M NaCl and amiloride, which were significantly lower at day 3 after nerve section and sodium depletion compared with controls ($P < 0.001$ and $P < 0.05$, respectively). The CT response to NaCl in rats is composed of an amiloride-sensitive portion, mediated through ENaC, and an amiloride-insensitive component transduced through a vanilloid receptor 1 variant (Lyall et al. 2004). Because treatment-related disparities in sodium responses are amiloride sensitive (Figure 6), changes in ENaC function likely underlie neural alterations (Hill and Bour 1985; Hill and Phillips 1994).

Discussion

The adult peripheral taste system is remarkably plastic in the days following distant injury. Within 24 h of CT sectioning,
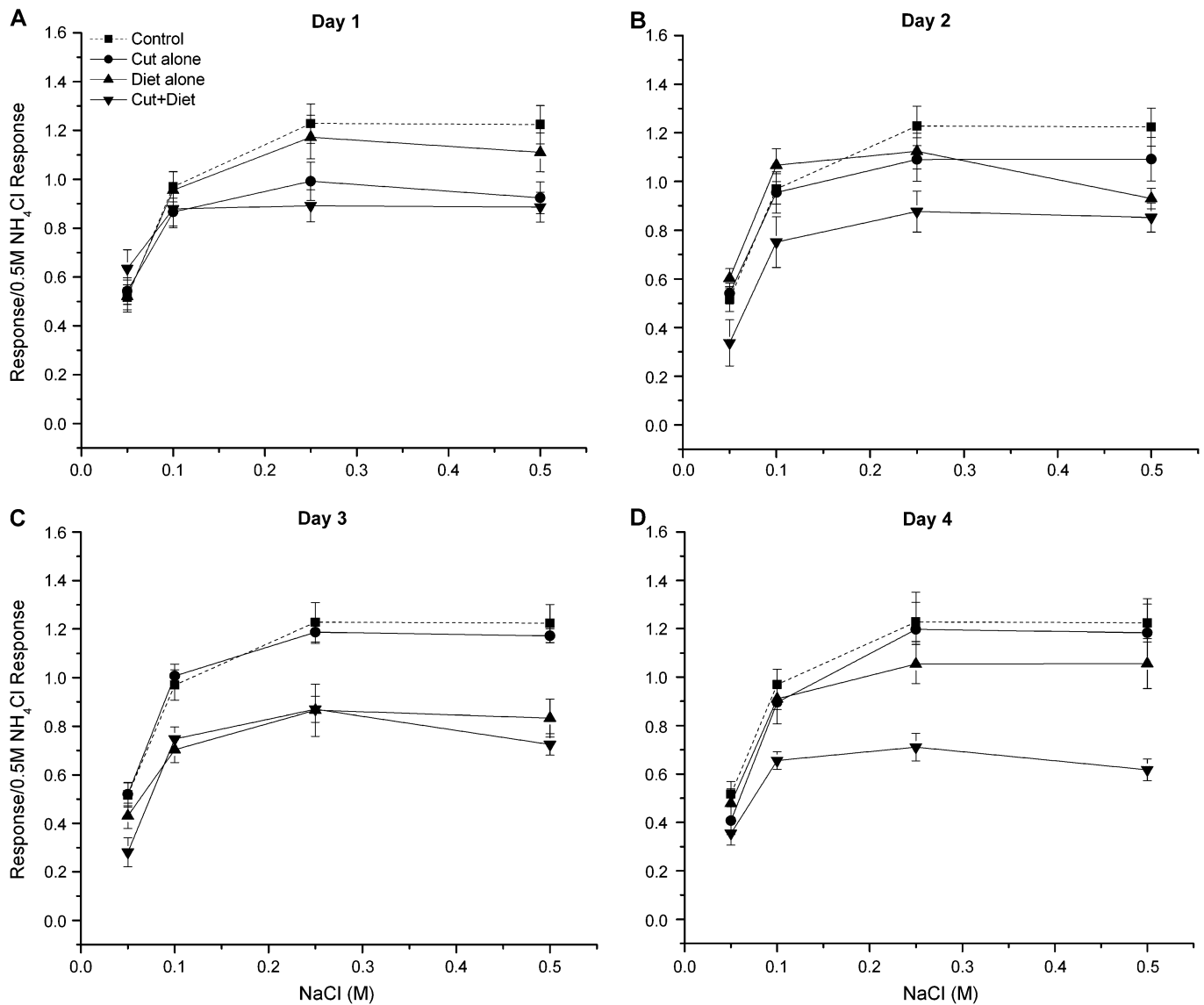
Figure 2   Mean (± standard error of the mean) relative responses to a concentration series of NaCl from the intact CT nerve at day 1 **(A)**, day 2 **(B)**, day 3 **(C)**, and day 4 **(D)** after dietary and surgical treatment. Animals receiving both sodium depletion and nerve section had reduced sodium responses at each day examined after sectioning. At day 1, rats that received CT sectioning alone exhibited diminished NaCl responses compared with controls, but sodium sensitivity recovered by day 2. Responses to higher concentrations of NaCl were also decreased briefly at days 2 and 3 after dietary sodium depletion alone.

neural sensitivity to sodium decreases in the uninjured nerve. This rapid decline in taste function occurs in both control-fed and sodium-depleted rats. Normal taste responses are restored at day 2 postsectioning in animals on a control diet but remain low in animals receiving the dietary manipulation. This study reveals that the uninjured nerve is sensitive to distant injury and that critical events between day 1 and day 2 promote normal neural function. We have thus identified a pivotal period in which injury leads to normal or abnormal function depending on dietary status.

The temporary drop in neural responses after injury—despite a normal diet—has not been previously reported. One possibility is that the dynamic immune response to injury mediates functional recovery in control-fed versus depleted animals. During the first hours after CT sectioning, leukocytes that have adverse effects on the function of innervated taste receptor cells may invade as in other systems (Perry et al. 1987; Jones and Corwin 1996; Taoka et al. 1997; Carlson et al. 1998; Neufeld et al. 2002). For example, within 12 h after neural injury, there is an increase in neutrophils that secrete reactive oxygen species, proteases, and other neuroactive factors (Perry et al. 1987; Carlson et al. 1998). Preliminary evidence suggests that neutrophils also respond to CT section in both depleted and control-fed rats within 12 h.
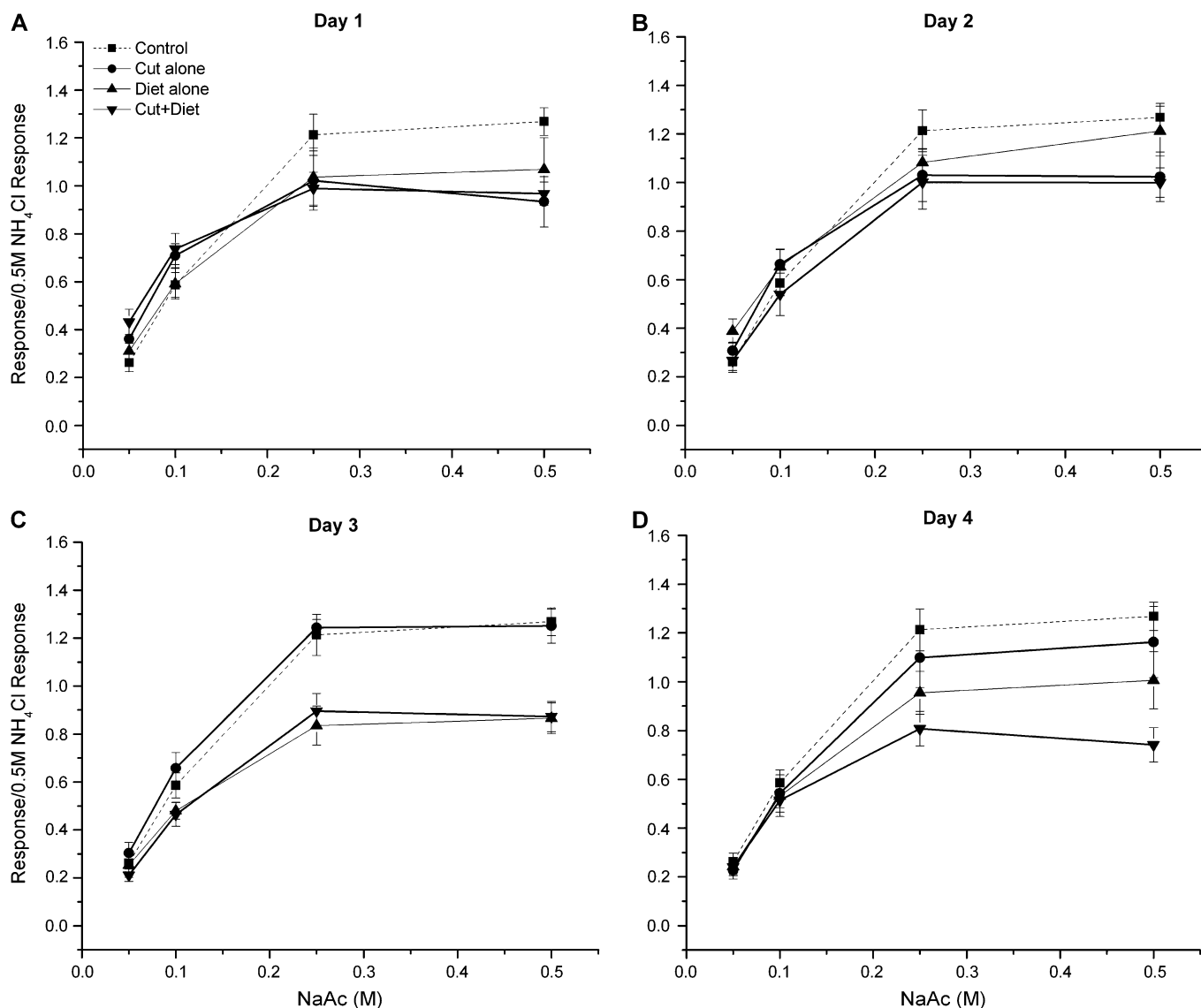
Figure 3 Mean (± standard error of the mean) relative responses to a concentration series of NaAc from the intact CT nerve at day 1 **(A)**, day 2 **(B)**, day 3 **(C)**, and day 4 **(D)** after CT section and/or sodium depletion. Rats receiving both CT section and sodium depletion had reduced responses to 0.50 M NaAc at each day following contralateral injury compared with controls. Nerve section alone significantly decreased responses to 0.50 M NaAc at day 1. Animals treated with sodium depletion alone also displayed diminished responses at day 3 postsection.

Although neutrophil numbers quickly return to baseline level in animals on the normal diet, the response appears to be enhanced and prolonged by sodium depletion (Wall and McCluskey 2007). Conversely, an activated macrophage response to CT sectioning is coupled with normal taste function. In control-fed rats, macrophage levels are increased on the intact side of the tongue at day 2 postsectioning when taste function returns to normal. In sodium-depleted rats, macrophage levels remain low as do neural responses to sodium (McCluskey 2004; Cavallin and McCluskey 2005). Macrophages responding to injury may release diffusible factors that ultimately benefit taste receptor cell function, whereas neutrophils likely have a detrimental effect.

Previous studies demonstrated normal CT responses at 4–85 days after furosemide injection and dietary sodium restriction in unoperated rats (Hill and Phillips 1994; McCluskey and Hill 2002). Here, normal CT responses were observed at day 4 after furosemide injection and sodium restriction, which is consistent with those reports. However, neural sensitivity to sodium was reduced at days 2–3. We suggest that furosemide transiently reduces CT responses to sodium, whether through its action as a diuretic or via side effects. Others have shown acute decreases in CT responses to 0.5 M NaCl at 24 h after injection using a similar treatment (Bernstein and Taylor 1992). The recovery of normal sodium sensitivity at day 4 in unoperated rats may relate to
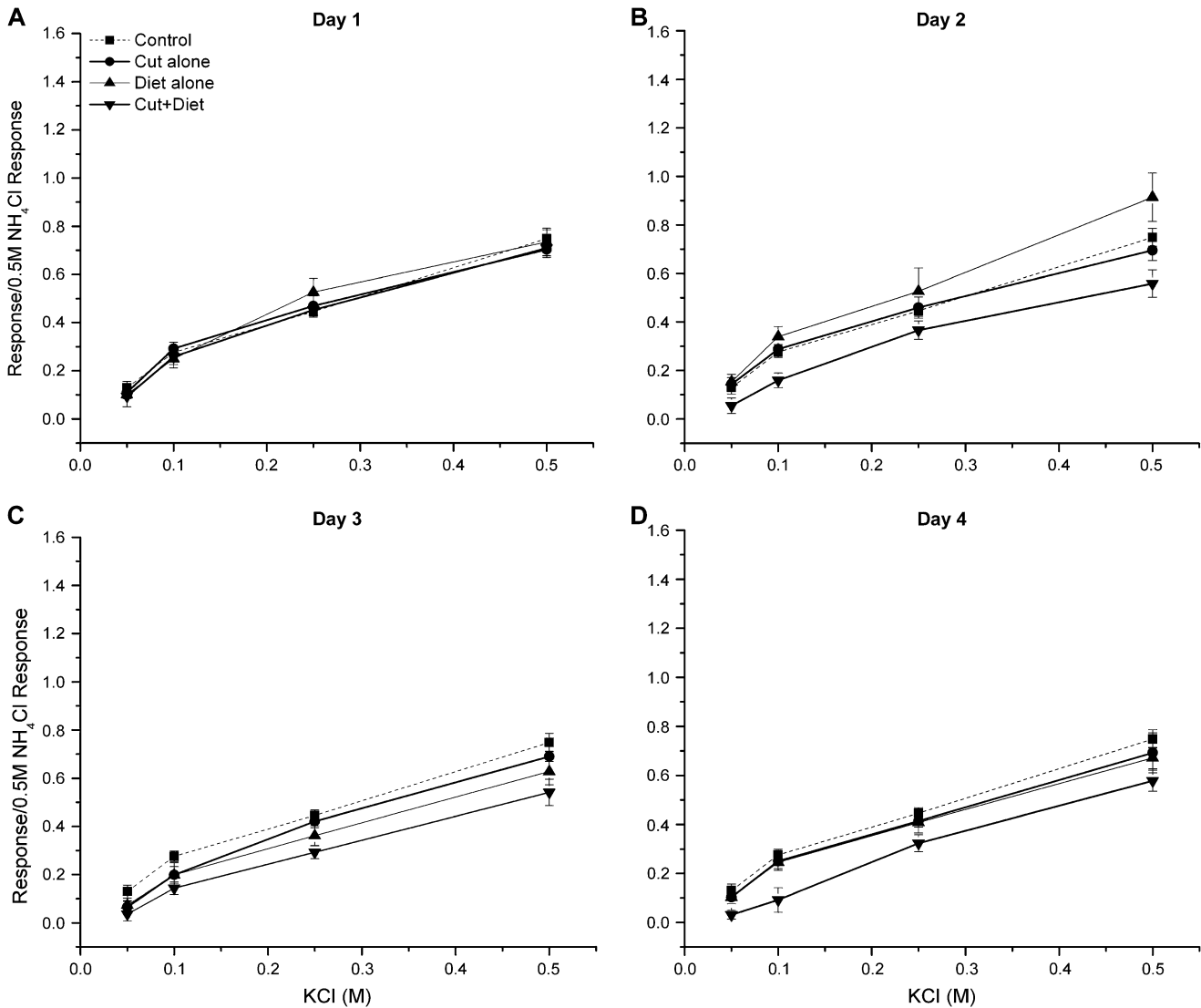
Figure 4 Mean (± standard error of the mean) relative responses to a concentration series of KCl from the intact CT nerve at day 1 **(A)**, day 2 **(B)**, day 3 **(C)**, and day 4 **(D)** after nerve section and/or initiation of sodium depletion. Rats treated with both CT sectioning and sodium depletion displayed reduced responses to several concentrations of KCl at days 3 and 4 compared with controls. Dietary and/or surgical treatments did not affect the neural responses from other groups.

the excretion of furosemide and the termination of its effects, even as the sodium-restricted diet is maintained.

Contralateral nerve injury and/or dietary sodium depletion alter neural responses to sodium quite selectively, as described here and in previous work (Hill and Phillips 1994; Phillips and Hill 1996; McCluskey and Hill 2002). Responses to nonsodium stimuli are generally unaffected by these treatments. Because the portion of the sodium response that varies with treatment is amiloride sensitive, it is likely that ENaCs expressed by taste receptor cells are the primary sites of functional changes. Many factors that regulate ENaC in other systems are associated with nerve injury, including cytokines (Dickie et al. 2000; Husted et al. 2000;

Fukuda et al. 2001; Barmeyer et al. 2004; Dagenais et al. 2004; Roux et al. 2005; Tuyen et al. 2005), growth factors (Zhou et al. 1996; Tong and Stockand 2005), and neutrophil-derived elastase (Caldwell et al. 2005; Harris et al. 2007). Dietary sodium also upregulates aldosterone, which modulates ENaC function in the taste system (Herness 1992; Lin et al. 1999). Thus, dietary sodium depletion may upregulate hormones that affect ENaC, whereas neural injury and degeneration stimulate another (or overlapping) set of modulatory factors.

Most studies of the effects of nerve injury focus on the damaged nerve and denervated target cells. However, the spinal ligation model of hyperalgesia is a well-defined
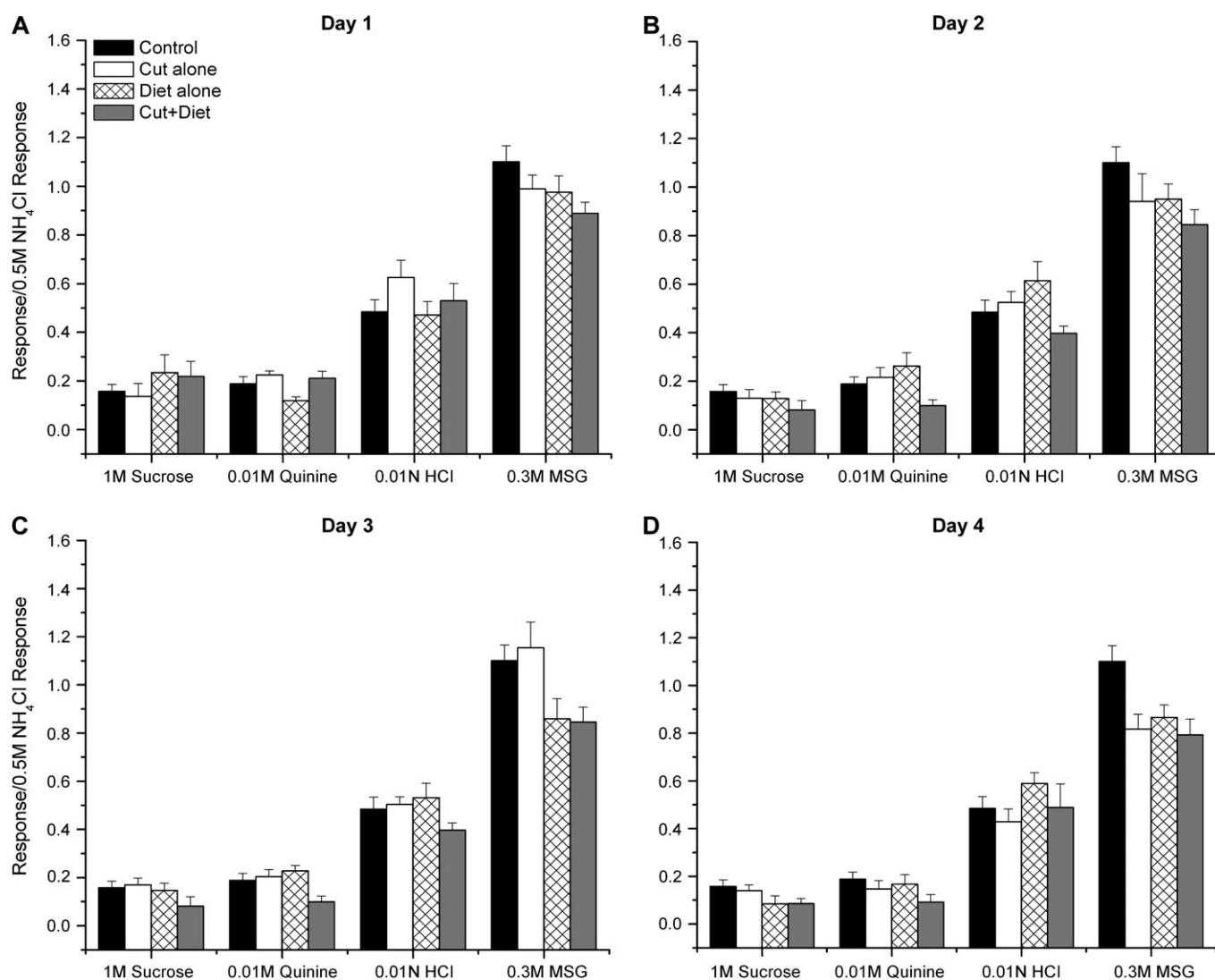
Figure 5 Mean (± standard error of the mean) relative responses to 1 M sucrose, 0.01 M quinine, 0.01 N HCl, and 0.3 M MSG from the intact CT nerve at day 1 **(A)**, day 2 **(B)**, day 3 **(C)**, and day 4 **(D)** following contralateral CT section and/or institution of the low-sodium diet. Responses to MSG from animals receiving both nerve section and sodium depletion were decreased at days 2–4 compared with controls. At day 4, responses to MSG from groups treated with CT sectioning alone were also significantly reduced. Responses to sucrose, quinine, and HCl to examine sweet, bitter, and acid pathways, respectively, were unaffected by dietary or surgical treatment.

exception. As in the gustatory system, neural injury induces functional plasticity in neighboring, intact neurons in spinal nerves. The timing of functional changes is remarkably similar to what we report, as spontaneous activity is enhanced in uninjured neurons by day 1 postinjury (Wu et al. 2002). In that model, neural injury and inflammation induce several factors that alter activity in intact fibers, including nerve growth factor (Obata et al. 2006) and tumor necrosis factor-α (Sorkin et al. 1997). Multiple receptors and channels on uninjured neurons provoke the ectopic activity, including the transient receptor potential vanilloid type 1 channel (Obata et al. 2004). The amiloride sensitivity and sodium specificity of the effects in the current work suggest that

ENaC ultimately mediates functional changes in the taste system.

This work defines a 24-h period when functional deficits occur in the uninjured nerve after contralateral trauma, which is critical for identifying underlying mechanisms. Although function is quickly restored under normal postinjury conditions, dietary sodium depletion prolongs the aberrant neural responses for at least 85 days (Hill and Phillips 1994). The peripheral taste system is an excellent model to explore the effects of injury on the remaining intact nerve and receptor cells. In fact, uninjured nerves and target cells in other systems may be equally susceptible to distant injury, with functional alterations occurring faster than widely
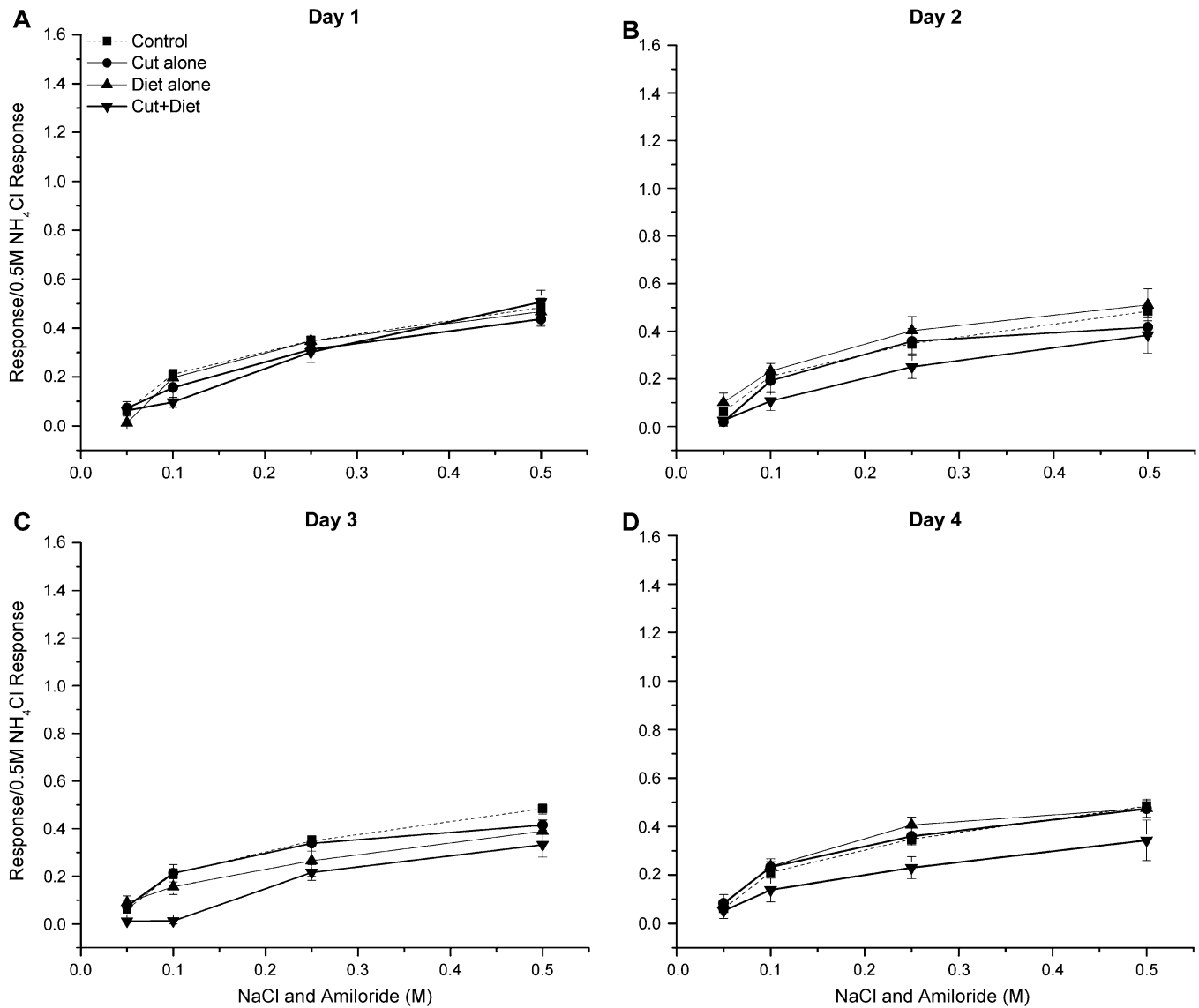
Figure 6   Mean (± standard error of the mean) relative responses to a concentration series of NaCl and 50 μM amiloride from the intact CT nerve at day 1 **(A)**, day 2 **(B)**, day 3 **(C)**, and day 4 **(D)** after contralateral nerve section and/or initiation of a low-sodium diet. The ENaC antagonist, amiloride, eliminated differences between groups at each time point.

appreciated. Determining the factors that promote normal taste responses during a specific window may suggest general strategies for promoting neural recovery from injury.

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