Antibodies to Nerve Growth Factor Reverse Established Tactile Allodynia in Rodent Models of Neuropathic Pain without Tolerance

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ABSTRACT

A considerable body of evidence implicates endogenous nerve growth factor (NGF) in conditions in which pain is a prominent feature, including neuropathic pain. However, previous studies of NGF antagonism in animal models of neuropathic pain have examined only the prevention of hyperalgesia and allodynia after injury, whereas the more relevant issue is whether treatment can provide relief of established pain, particularly without tolerance. In the current work, we studied the effects of potent, neutralizing anti-NGF antibodies on the reversal of tactile allodynia and thermal hyperalgesia in established models of neuropathic and inflammatory pain in rats and mice. In the complete Freund’s adjuvant-induced hind-paw inflammation, spinal nerve ligation and streptozotocin-induced neuropathic pain models, a single intraperitoneal injection of a polyclonal anti-NGF antibody reversed established tactile allodynia from approximately day 3 to day 7 after treatment. Effects on thermal hyperalgesia were variable with a significant effect observed only in the spinal nerve ligation model. In the mouse chronic constriction injury (CCI) model, a mouse monoclonal anti-NGF antibody reversed tactile allodynia when administered 2 weeks after surgery. Repeated administration of this antibody to CCI mice for 3 weeks produced a sustained reversal (days 4 to 21) of tactile allodynia that returned 5 days after the end of dosing. In conclusion, NGF seems to play a critical role in models of established neuropathic and inflammatory pain in both rats and mice, with no development of tolerance to antagonism. Antagonists of NGF, such as fully human monoclonal anti-NGF antibodies, may have therapeutic utility in analogous human pain conditions.

Nerve growth factor (NGF) was originally discovered as a sarcoma-derived substance that stimulated the outgrowth of dorsal root ganglion (DRG) neurons and is now recognized to be a survival and differentiating factor for neural crest-derived sensory neurons and sympathetic and basal forebrain cholinergic neurons (for review, see Levi-Motachini and Angeletti, 1968; Sofroniew et al., 2001). In primary sensory neurons of the DRG, NGF modulates expression of a multitude of pain-related transmitters, receptors, and ion channels. For example, substance P and calcitonin gene-related peptide precursors are up-regulated by NGF (Lindsay and Harmar, 1989; Gilchrist et al., 1991), as is the vanilloid receptor TRPV1 (Winston et al., 2001) and sodium channels (Friedel et al., 1997; Fang et al., 2005). NGF can also produce morphological changes, such as the sprouting of sympathetic nervous system neurons and formation of sympathetic “baskets” around the cell bodies of sensory neurons in the DRG (Ramer and Bisby, 1999; Zhou et al., 1999).

A considerable body of evidence implicates endogenous NGF in conditions in which pain is a prominent feature. For example, it is up-regulated in DRG Schwann cells for at least 2 months after peripheral nerve injury (Zhou et al., 1999). NGF levels are elevated in synovial fluid from patients with rheumatoid or other types of inflammatory arthritis (Aloe et al., 1992) [similar to arthritic mice (e.g., Aloe et al., 1993)], and NGF is elevated in inflamed or painful bladders (Lowe et al., 1997; Okragly et al., 1999). In addition, NGF is elevated

ABBREVIATIONS: NGF, nerve growth factor; DRG, dorsal root ganglion; PBS, phosphate-buffered saline; mAb, monoclonal antibody; Ab, antibody; CCI, chronic constriction injury model (Bennett model); BDNF, brain-derived neurotrophic factor; trkA, tyrosine receptor kinase A; CFA, complete Freund’s adjuvant; PWT, paw withdrawal threshold; PWL, paw withdrawal latency; STZ, streptozotocin; ANOVA, analysis of variance.
in chronic pancreatitis, in pancreatic cancer, and in some melanomas, especially nerve invasive cancers (Zhu et al., 1999). In patients with diabetes, NGF is either elevated (Azar et al., 1999; Diemel et al., 1999) or decreased (Faradje and Sotelo, 1990; Anand et al., 1999) in serum and skin, leaving the role of NGF in this disease less clear, perhaps because these studies did not specifically examine patients with painful diabetic neuropathy.

Not only does local or systemic administration of NGF elicit both hyperalgesia and allodynia in rats (Lewin et al., 1994), but also intravenous infusion of NGF in humans produces a whole body myalgia, whereas local administration additionally evokes injection site hyperalgesia and allodynia (Petty et al., 1994). Concordant with the hypothesis that NGF produces pain in physiological events, it has been demonstrated repeatedly that antagonism of NGF function prevents pain behavior. In models of neuropathic pain, such as nerve trunk or spinal nerve ligation, systemic injection of neutralizing antibodies to NGF prevents both allodynia and hyperalgesia (Ramer and Bisby, 1999; Ro et al., 1999). Likewise, an antinociceptive effect has been demonstrated to a short-term noxious stimulus (McMahon et al., 1995) in an incision model of inflammatory pain (Banik et al., 2005) and in subacute inflammatory pain (Woolf et al., 1994; McMahon et al., 1995) with no inhibition of the inflammatory process (e.g., edema). Perhaps as predicted by clinical findings (Lowe et al., 1997; Zhu et al., 1999; Oktaraly et al., 1999), anti-NGF treatment has been shown to prevent pain from developing in response to sarcoma growth in the bone (Halvorson et al., 2005; Sevick et al., 2005), and Watson et al. (2006) reported an antinociceptive effect of an NGF-neutralizing molecule (trkAd5) in a bladder model of visceral pain.

Taken together, these articles suggest a clear physiological role for NGF in pain, independent of injury or inflammatory processes. Given that NGF is elevated in human and animal painful conditions and that anti-NGF treatment can prevent the development of hyperalgesia in a variety of models, it is reasonable to predict that anti-NGF treatment would successfully reverse hyperalgesia. Indeed, Woolf (1996) demonstrated that anti-NGF could reverse hyperalgesia 5 days after CFA injection to the paw and, more recently, Shelton et al. (2005) demonstrated that anti-NGF treatment can reverse established ankle flexion-induced vocalization in a rat model of CFA-induced arthritis without affecting disease progression. In addition, Delafey et al. (2003) demonstrated reversal of inflammatory colitis with anti-NGF 7 days after TNBS administration.

In contrast to inflammatory pain, previously published studies of NGF antagonism in animal models of neuropathic pain have examined only the prevention of hyperalgesia and allodynia after injury. From a clinical perspective, the more relevant issue is whether treatment can provide relief of established pain. In this study, we showed that acute administration of anti-NGF antibodies reversed established pain behavior in models of neuropathic pain in rats and mice as well as in a rat model of inflammatory pain. Finally, the effects of repeated treatment with an anti-NGF antibody were also examined in a mouse model of neuropathic pain, with the results showing no loss of efficacy after 3 weeks of dosing.

Materials and Methods

**Subjects.** Male Sprague-Dawley rats (Charles River Laboratories, Wilmington, MA) weighing between 200 and 400 g were used. Male C57BL/6 mice (Charles River Laboratories) weighing between 21 and 27 g (approximately 9 weeks of age) were also used. Food and water were available ad libitum, and lights were on for 12 h per day. All testing was performed in accordance with the Guide for the Care and Use of Laboratory Animals as adopted and promulgated by the U.S. National Institutes of Health and the approval of the Institutional Animal Care and Use Committee (IACUC) at Amgen Inc.

**Test Materials.** A goat polyclonal anti-NGF antibody (AF556-NA) was purchased from R&D Systems (Minneapolis, MN) and reconstituted in phosphate-buffered saline (PBS) to a concentration of 2 mg/ml. Intraportal doses were varied by adjusting the injection volume. The control was a nonspecific IgG (Amgen Inc.), also in PBS.

A commercially available mouse monoclonal Ab (a3s-18) was purchased from Exalpa Biologicals, Inc. (Maynard, MA) as a reagent for multiple dose in vivo studies in mice. Because the antibody is a mouse anti-mouse mAb, it was expected that any in vivo effects would not suffer interference from antibodies forming against the mAb. This is a likely problem when administering a goat polyclonal anti-NGF Ab to rats or mice. The Ab was dissolved in PBS for subcutaneous dosing to mice, and PBS also served as the control.

**Determination of In Vitro Potency and Selectivity of Antibodies.** DRG were dissected from embryonic day 19 rats and dissociated into single cells using papain (Worthington Biochemical Corp., Freehold, NJ). The dissociated cells were plated into 96-well plates coated with poly-or-thine (Sigma, St. Louis, MO) and laminin (In-vitrogen, Carlsbad, CA) at a density of 10 × 10⁵ cells/well in complete medium. Treatments of human NGF (R&D Systems), rat NGF (R&D Systems), mouse NGF (Calbiochem, San Diego, CA), and anti-NGF (R&D or Exalpa Biologicals, Inc., Maynard, MA) were applied 2 h after plating. Based on their concentration-effect curves, the concentration of NGF used for IC₅₀ studies was 0.38 nM for human, rat, and mouse NGF, a submaximal concentration. The treated cells were cultured for 48 h. At the end of the culture, the cells were fixed, and neuronal survival was measured by trpV1 expression using trpV1 time-resolved fluorescence. TrpV1 is a specific marker for small diameter sensory neurons in DRG. The fixed cells were incubated with anti-trpV1 antibody (Amgen Inc.) and followed by a Europium-labeled secondary antibody (PerkinElmer Life Sciences and Analytical Sciences–Wallac Oy, Turku, Finland). The fluorescence signal was measured using a Victor Multilabel Counter (PerkinElmer Life and Analytical Sciences, Boston, MA).

To assess potential inhibition of BDNF, mesencephalic dopaminergic neurons from ventral midbrain were dissected from embryonic day 19 rats and dissociated with papain (Worthington Biochemical Corp.). The dissociated cells were plated into 96-well plates coated with poly-or-thine and laminin at a density of 100,000/cm² as described previously (Louis et al., 1992). BDNF (Amgen Inc.) at a submaximal concentration of 1 nM was added to the cells 2 h after plating, followed by serial concentrations of anti-NGF samples (R&D or Exalpa Biologicals). Anti-BDNF antibody (Amgen Inc.) was used as a positive control. After 6 days, high-affinity dopamine uptake capacity of the mesencephalic neurons was assessed as described previously (Friedman and Mytilineou, 1997).

**Rat CFA Model of Inflammatory Pain.** Rats (200 g) were lightly anesthetized with iso-urane inhalant anesthesia, and the left hind paw was injected with complete Freund’s adjuvant (CFA) emulsion (Sigma), 0.15 ml. This procedure results in tactile allodynia in the left hind paw. Rats were included in the study only if they did not exhibit motor dysfunction (e.g., paw dragging or dropping) or broken skin and their paw withdrawal threshold (PWT) was below 39.2 mN (equivalent to 4.0 g). CFA injection also leads to the development of thermal hyperalgesia in the injected hind paw. At least 15 days after CFA injection, rats were treated with the polyclonal anti-NGF antibody (0.3, 1, or 3 mg/kg) or control IgG (3 mg/kg) once by i.p.
injection, and PWT and thermal paw withdrawal latency (PWL) were determined each day thereafter without purposeful blinding.

Rat Chung Model of Spinal Nerve Ligation. Rats (200 g) were anesthetized with isoflurane inhalant anesthesia, and the left lumbar spinal nerves at the level of L5 and L6 were tightly ligated (4-0 silk suture) distal to the DRG and before entrance into the sciatic nerve, as first described by Kim and Chung (1992). The incisions were closed, and the rats were allowed to recover. This procedure results in tactile allodynia in the left hind paw. Rats were included in the study only if they did not exhibit motor dysfunction (e.g., paw dragging or dropping) and their PWT was below 39.2 mN (equivalent to 4.0 g). Spinal nerve ligation also leads to the development of thermal hyperalgesia in the injected hind paw. At least 7 days after surgery, rats were treated with polyclonal anti-NGF antibody (3 or 10 mg/kg) or control IgG (3 mg/kg) once by i.p. injection, and PWT and PWL were determined each day thereafter without purposeful blinding.

Rat STZ-Induced Neuropathic Pain Model. Streptozotocin (STZ) is a pancreatic β cell toxin, often used to produce a diabetic state by depleting the supply of insulin, and also produces tactile allodynia. The dose of STZ used here to produce tactile allodynia in male Sprague-Dawley rats of approximately 350 g b.wt. was 50 mg/kg i.p. Body weight was monitored after injection as an indication of diabetes production (failure to gain at control rate) and to ensure that no rat lost excessive body weight during the course of the study. Other signs of diabetes were noted, particularly increased urinary output; however, blood glucose levels were not assessed. In general, tactile allodynia developed and reached a stable level 4 weeks after STZ administration and then lasted for another 4 weeks. The success rate for producing rats with neuropathic pain symptoms was 50 to 90%. Rats were included in the study only if their PWT was below 39.2 mN (equivalent to 4.0 g). At least 4 weeks after STZ administration, rats were treated with polyclonal anti-NGF antibody (10 mg/kg) or control IgG (10 mg/kg) once by i.p. injection, and PWT was determined each day thereafter without purposeful blinding.

Mouse Chronic Constriction Injury Model. To test the in vivo activity of the mouse monoclonal anti-NGF antibody (Exalpha Biologicals, Inc.), the mouse chronic constriction injury (CCI) model of neuropathic pain was used. In brief, the animals were anesthetized using isoflurane inhalant anesthetic, and the sciatic nerve was loosely ligated (6-0 silk suture) in the mid-thigh as described for rats by Bennett and Xie (1988). The incisions were closed, and the mice were allowed to recover for a minimum of 2 weeks before dosing. This model produces symptoms of tactile allodynia similar to the rat Chung model of neuropathic pain although presurgery PWT is much lower than that in rat. Mice were treated with anti-NGF antibody (100 mg/kg) or vehicle by i.p. injection by an investigator blinded to the treatment, and PWT was determined each day thereafter by an observer also blinded to the treatment.

Tactile Allodynia Assessment. Tactile allodynia was assessed by recording the pressure at which the affected paw was withdrawn from graded stimuli (von Frey filaments ranging from 4.0 to 148.1 mN, or 0.4 to 15 g of force) applied perpendicularly to the plantar surface of the paw through wire-mesh observation cages. PWT was determined by sequentially increasing and decreasing the stimulus strength and analyzing withdrawal data using a Dixon nonparametric test, as described by Chaplan et al. (1994).

Thermal Hyperalgesia Assessment. Thermal hyperalgesia was assessed using a Hargreaves “hot-box” apparatus. Rats were placed in a Plexiglas enclosure resting on a glass surface, and a halogen light was maneuvered beneath the plantar surface of the paw. Activation of the light started a timer and began to heat the glass directly under the rat’s hind paw. PWL was the time it took for the rat to remove its paw from the thermal stimulus.

Statistical Analysis. Data were analyzed for significant differences by ANOVA and, if warranted, followed by t-tests with Bonferroni’s correction of p values for multiple comparisons using the computer program Prism (GraphPad, San Diego, CA). The p value for significance was set at 0.05. Graphs were drawn with the same program.

Results

In Vitro Activity of Antibodies. The IC<sub>50</sub> of the goat polyclonal antibody from R&amp;D Systems was determined to be 129 nM against human NGF (0.38 nM) and 0.5 nM against rat NGF (0.38 nM). The IC<sub>50</sub> of the mouse monoclonal antibody from Exalpha Biologicals was determined to be 0.48 nM against mouse NGF (0.38 nM). Neither antibody was capable of inhibiting the activity of BDNF (1 nM) when tested at concentrations up to 10 μM.

Rat CFA Model of Inflammatory Pain. Behavior indicative of inflammatory pain was induced by the injection of CFA into the hind paw of rats. One week after CFA injection, a single i.p. injection of anti-NGF antibody (R&amp;D Systems) or control IgG was administered, and tactile allodynia and thermal hyperalgesia were assessed daily. For tactile allodynia, ANOVA revealed a significant main effect of treatment (F = 11.4, p < 0.0001) and of time (F = 37.6, p < 0.0001) with a significant interaction (F = 17.4, p < 0.0001). Subsequent Bonferroni corrected t-tests determined that allodynia was significantly reversed by 1 and 3 mg/kg beginning on day 3 after treatment and that this effect persisted through day 7 after treatment. At a dose of 0.3 mg/kg, allodynia was significantly reversed on days 4 and 5 (Fig. 1A). For thermal hyperalgesia, ANOVA revealed a significant main effect of time (F = 8.4, p < 0.016) but not of treatment (F = 2.5, P =
injected with a single dose of the pancreatic NGF. For tactile allodynia, ANOVA revealed a significant main effect of treatment (F = 18.6, p < 0.0001) and of time (F = 17.7, p < 0.0001) with a significant interaction (F = 15.6, p < 0.0001). Subsequent Bonferroni-corrected t tests determined that allodynia was significantly reversed by 10 mg/kg beginning on day 2 after treatment and that this effect persisted through day 7 after treatment. At a dose of 3 mg/kg, allodynia was significantly reversed from day 5 to day 7 (Fig. 2A). For thermal hyperalgesia, ANOVA revealed a significant main effect of treatment (F = 9.3, p = 0.0003), but the interaction term did not reach statistical significance (F = 7.2, p = 0.107). Therefore, further post hoc analysis was not performed, although the main effect of treatment seems to be across day 4 to day 7 for both doses of anti-NGF (Fig. 2B).

**Rat STZ-Induced Neuropathic Pain Model.** Rats were injected with a single dose of the pancreatic β cell toxin STZ, and typical features of neuropathic pain (tactile allodynia) developed in the hind paws within 2 to 3 weeks. After 4 weeks, a single i.p. injection of anti-NGF antibody (10 mg/kg) or control IgG was administered and tactile allodynia was assessed daily. ANOVA revealed a significant main effect of treatment (F = 61.46, p < 0.0001) and of time (F = 4.7, p = 0.0001), with a significant interaction (F = 2.65, p = 0.014). Subsequent Bonferroni-corrected t tests determined that a statistically significant reversal of allodynia was observed beginning on day 2 and that this effect persisted through day 6 after treatment (Fig. 3). Thermal hyperalgesia was not assessed.

**Mouse Chronic Constriction Injury Model.** The mouse mAb from Exalpha Biologicals produces single-dose, repeated-dose, and sustained reversal of allodynia in the CCI model as shown in Figs. 4 and 5. Approximately 2 weeks after CCI surgery, an i.p. dose of anti-NGF Ab (100 mg/kg i.p.) or vehicle was administered twice, with each administration separated by 2 weeks. Tactile allodynia data were analyzed by ANOVA, and significant main effects of treatment (F = 8.01, p = 0.02) and time (F = 4.18, p < 0.0001) were observed, as well as a significant interaction (F = 3.95, p < 0.0001) (Fig. 4). In additional single-dose studies (data not shown), a dose of 50 mg/kg also was effective, but 10 mg/kg was not.

An extended repeated dose study was conducted to assess possible tolerance to the long-term depletion of NGF. Anti-NGF Ab (100 mg/kg i.p.) or vehicle (i.p.) was administered thrice weekly for 3 weeks, and tactile allodynia was assessed at regular intervals for 28 days. ANOVA revealed a significant main effect of treatment (F = 84.34, p < 0.0001) and time (F = 4.27, p < 0.0001), as well as a significant interaction (F = 4.06, p < 0.0001). Subsequent Bonferroni corrected t tests determined that a statistically significant reversal of allodynia was observed from days 4 to 21 (Fig. 5). No behavioral consequences were observed other than this continued reversal of tactile allodynia throughout the dosing period.

**Discussion**

Although inflammatory pain can be both prevented (Woolf et al., 1994) and reversed (Woolf, 1996; Shelton et al., 2005) with anti-NGF treatment, previous studies of neuropathic
pain have demonstrated the prevention of pain behavior only when the anti-NGF treatment was applied before, or concurrent with, the pain-inducing stimulus (Ramer and Bisby, 1999; Ro et al., 1999). Here, we demonstrate for the first time that anti-NGF treatment reversed established pain behaviors in rat and mouse models of neuropathic pain when the treatment was applied well after the pain-inducing stimulus. Furthermore, there was no development of tolerance to the antiallodynic effects of anti-NGF treatment over 3 weeks in the mouse CCI model of neuropathic pain.

Although the closely related growth factors BDNF and NT-3 have a possible role in pain, the effects observed here are likely to be due to the selective sequestration of NGF. The two antibodies used here were tested in vitro against NGF and BDNF and found to be potent (subnanomolar) inhibitors of NGF but not of BDNF at concentrations up to 10 μM. Actual plasma levels were not determined here, but a 10 mg/kg i.v. dose of another antibody to rat resulted in a maximum plasma concentration of only 1.6 μM (L. Nguyen, unpublished observations). The activity against NT-3 was not tested here, but given that the antibodies can discriminate NGF from BDNF, the epitopes are likely to be on regions of NGF not well conserved in this family of growth factors (see Wiesmann et al., 1999).

It is noteworthy that our studies seem to show that lower doses of the same anti-NGF antibody were effective in the CFA model of inflammatory pain (Fig. 1) compared with the Chung or STZ models of neuropathic pain (Figs. 2 and 3) in rats. Although this could be a result of the different stimulus intensity of these models, it could also be due to a higher level of NGF produced in nerve injury compared with inflammatory conditions or a larger role of NGF in inflammatory pain. Unfortunately, the literature does not resolve this issue; no other studies have compared the same antibody in these different models. The nearest comparison is a study of anti-NGF in both the CCI and Chung models of neuropathic pain, reported by Ramer and Bisby (1999), in which tactile allodynia was prevented more effectively in the CCI model than in the Chung model. Further studies will be required to determine differential sensitivity of different types of pain.

It is also noteworthy that thermal hyperalgesia was not robustly reversed in the CFA and Chung models where it was assessed. However, the observed variability in the thermal hyperalgesia data was higher than in the tactile allodynia data, limiting the statistical power. A main effect of treatment was observed for thermal hyperalgesia in the Chung model as well as a trend in the CFA model. Furthermore, reversal of thermal hyperalgesia has been reported in the literature (Woollf, 1996). Viewed from a mechanistic perspective, it may be more surprising that tactile allodynia was significantly reversed by anti-NGF treatment. Alldynia is believed to be mediated by large Aβ fibers, which are not normally regarded as NGF-sensitive. Perhaps reversal of tactile allodynia is mediated through interruption of a C-fiber-mediated central sensitization process or of an intermediate signaling process from trkA-positive C fibers to Aβ fibers, such as BDNF (Woolf, 1996). However, it should also be noted that some Aβ fibers do express the high-affinity NGF receptor trkA, resulting in apparent control of Nav 1.8 expression and function (Fang et al., 2005), a sodium channel believed to be important in neuropathic pain.

The time course and duration of anti-NGF efficacy is of interest with regard to possible mechanisms of action. The biological effect of anti-NGF Ab in these rat studies is consistent with the 11 day half-life reported in the literature for an IgG1 Ab (Davis et al., 1995). In our mouse studies using a mouse monoclonal anti-NGF Ab, the duration of action was shorter than observed in rat (Fig. 4), but a study of the normal duration of IgG in mouse plasma found the half-life to be 4 days (Faherty and Robinson, 1963), which can be shortened to 2 days by increasing the plasma concentration of IgG beyond normal, such as with large exogenous doses. Because mice would not be expected to generate a neutralizing immune response to a mouse monoclonal Ab, the observed time courses are probably due to normal pharmacokinetic behavior. Still, sustained sequestration of NGF could lead to up-regulation of NGF, overcoming and terminating the antibody effect. This possibility was addressed in the mouse CCI model, where a second administration of anti-NGF was effective shortly after the effect of the first administration had ended (Fig. 4). Furthermore, repeated dosing of the antibody in mice led to a sustained reversal of pain behavior for more than 3 weeks (Fig. 5). Thus, it seems unlikely that increased production of NGF in response to the Ab explains the termi-
nation of effect in either rat or mouse; i.e., there is no apparent tolerance to sustained depletion of NGF. It is noteworthy that tactile allodynia returned after 3 weeks of suppression with anti-NGF treatment, indicating that anti-NGF treatment does not lead to a permanent reversal of pain in this time period, perhaps because the underlying nerve injury is still present.

In conclusion, NGF seems to be a critical mediator of all types of pain, including short-term pain (McMahon et al., 1995), surgical pain (Banik et al., 2005), inflammatory pain (Woolf et al., 1994), visceral pain (Watson et al., 2006), and, as we report here, neuropathic pain. It is noteworthy that a lack of tolerance to NGF sequestration was demonstrated over a 3-week period. Thus, NGF may be an excellent therapeutic target for these short- and long-term indications. Either a polyclonal or a monoclonal Ab was shown here to reverse pain behavior, improving the likelihood of producing and developing an effective therapeutic agent, such as a fully human monoclonal anti-NGF antibody.

References

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