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Research Article

Pheochromocytoma PC-12 Cell Line: The Herbicide Picloram Enhances Neurite Growth Induced by Nerve Growth Factor

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Abstract

When cultured rat pheochromocytoma PC12 cell line, of peripheral nervous system origin, were exposed to 0.5 to 3 mM Picloram (4-amino-3,5,6-trichloropicolinic acid), a pyridine derivative herbicide, analogous to the naturally occurring picolinic acid), cell proliferation ceases in a dose- and time-dependent manner. The PC12 cells were growth arrested and remained in a quiescent state and viable for 96 h. 3 mM Picloram induced in most PC12 cells very dense nucleoli, in comparison to control, untreated cells. 3 mM Picloram alone also induced short neurite extensions around the PC12 cell bodies. When PC12 cells were simultaneously treated with 3 mM Picloram and Nerve Growth Factor (NGF, 10 ng/mL or 50 ng/mL; NGF subunit 7S), neurite length was enhanced in a time- and dose-dependent manner. NGF (10 ng/mL) in the presence of 3 mM Picloram, showed enhanced neurite length, in comparison to 10 ng/mL NGF alone (control). The neurite length, induced by 50 ng/mL NGF plus 3 mM Picloram, was greatly enhanced in comparison to 50 ng/mL NGF alone (control). These studies indicate that it is possible to potentiate PC12 neurite growth, in the form of both increase neurite number and length by the combination of Picloram and NGF. Additional experiments with non-neurogenic, virally transformed cells showed that 3 mM Picloram can induced neurite outgrowth in this type of cells. These findings may be useful to understand the neurotoxic effects of Picloram in the peripheral nervous system of animals and humans.

Keywords: PC12 rat pheochromocytoma; Picloram; Herbicides; Nerve growth factor; Nucleolus; Neurite growth; Metallopanstimulin-1 (MPS1/S27)

Abbreviations

NGF-Nerve Growth Factor; MPS1/S27-Metallopanstimulin-1; PC12-Rat Pheochromocytoma Cell Line; NC-Neural Creast; RP-Ribosomal Proteins

Introduction

Pheochromocytoma clonal cell line PC12 has been a useful model system for elucidating the role of growth factors in neuronal differentiation, and to study the potentiation of Nerve Growth Factor (NGF) induced neurite outgrowth in PC12 cells by various drugs, and their molecular mechanisms underlying their actions [1-9]. Although the role of herbicides as neurotoxins is being studied extensively, little is known about the effects of the systemic herbicide Picloram, also known by their names as Gordon and Grazon [10-14]. Picloram is a chlorinated derivative of picolinic acid, a naturally occurring compound in mammals. Thus, Picloram (4-amino-3,5,6-trichloro-2-pyridinecarboxylic acid), belongs to the pyridine carboxylic family of herbicides. It is a systemic herbicide used for a wide range of broad-leaved weeds [11]. Once absorbed by the leaves of weeds or useful or edible plants, Picloram is transported thought the circulatory system of the plant and is deposited in several cell compartments, such as the nucleus [10-14]. Picloram is of moderate toxicity in classical bioassays in rats and mice [10,11]. However, its experimental neurotoxicity, carcinogenicity, and genotoxicity is unclear and has not been studied yet with modern technologies [15-23], briefly described in this paper.

In this study, we present data on NGF-induced neurite outgrowth in PC12 cells by the combination of Picloram and NGF. Both agents act synergistically in the production of enhanced neurite outgrowth. We also found that Picloram induces in culture PC12 cells changes in the nucleolar morphology, manifested by intense condensation of the nucleoli of virtually every cultured cell exposed to Picloram. Furthermore, a disproportionate accumulation of Metallopanstimulin-1 (MPS1-S27) [21] occurs in the nucleoli, and cytoplasm of PC12 cells treated with Picloram, indicating the involvement of Metallpanstimulin-1 (MPS1/S27) [21], in DNA repair by DNA damage [21-23] induced by Picloram.

The studies presented here may be useful to further understand growth, differentiation, and cytotoxic effects of Picloram, and perhaps the toxic actions of Picloram in other cells of the peripheral nervous system of animals and humans. Picloram, as suggested by our studies, affects the nucleoli in PC12 treated cells, and thus, may be acting as a neurotoxin by inhibiting protein synthesis [24-28], at its place of origin: The nucleolus. These studies may have some importance in understanding the damage by herbicides in Eukaryotic cells.

Material and Methods

Cell growth

PC-12/CRL-1721 cell line was obtained from the American Type

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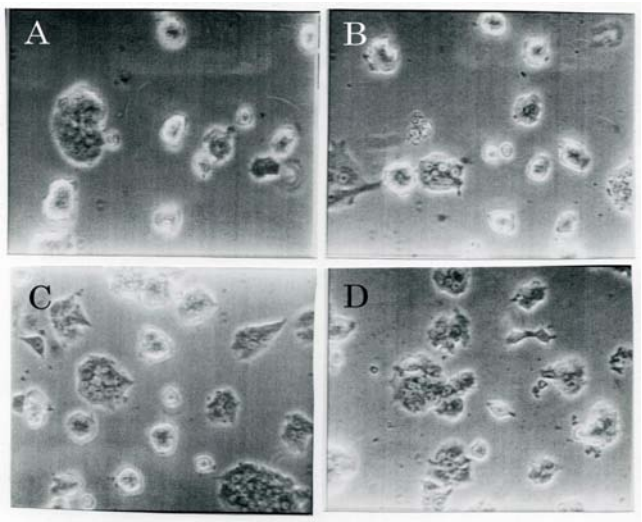

Figure 1: PC12 cells cultured in the presence of increasing concentrations of picloram. PC12 cells were cultured for 48 h. (A) Undifferentiated PC12 cells, no additions, control; (B) PC12 cells cultured in 0.5 mM picloram: The arrows indicate the presence of small dense nucleoli, which are also present in most cells; (C) PC12 exposed to 1 mM picloram; (D) PC12 exposed to 3 mM picloram. Phase contrast microscopy, Mag. X 250.

Culture Collection (Rockville MD, USA). PC12 cells were grown in Dulbecco's modified Eagle's medium plus F12 media (DME/F12), containing 4.5 g/liter glucose supplemented with 10% Fetal Calf Serum (Gibco, Grand Island NY, USA) and 5% horse serum (HS; Gibco).

Growth factors and chemicals

Beta-NGF and Picloram were obtained from Sigma-Aldrich, St. Louis, MO, USA.

Tissue culture growth

PC12 cells were plated at 5 x 105 cells per 60 mm Petri dish in 40 dishes per each experimental condition. After 24 h, the media was changed, and new media containing various concentrations of NGF and/or Picloram were added to the Petri dishes.

Results

Neurite outgrowth requires the continual presence of NGF

PC12 cells cultured in the presence of increasing concentrations of Picloram alone: Figure 1A, shows control, undifferentiated PC12 cells, which did not show neurite outgrowth (no additions control). Figure 1B, shows PC12 cells cultured in 0.5 mM Picloram. The open arrows indicate the presence of small, dense nucleoli, which were present in most cells. Figure 1C, shows PC12 cells exposed to 1 mM Picloram; and Figure 1D, shows PC12 cells exposed to 3 mM Picloram. These results show that at all doses tested Picloram alone did not produced neurite outgrowth, in the absence of NGF.

Picloram potentiates the neurite outgrowth induced by NGF: Figure 2A shows that when PC12 cells were exposed to 10 ng/mL NGF alone a few very short neurites were observed (10 ng/mL NGF, control). Figure 2B shows that, when 0.5 mM Picloram was combined with 10ng/mL NGF, a significant number of short neurites were observed in numerous cells. Figure 2C shows that addition of

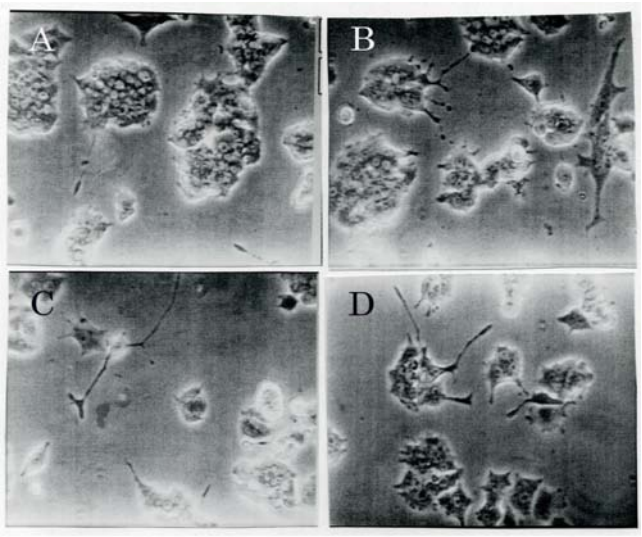

Figure 2: PC12 cells growth in the presence of picloram plus NGF for 48 h. Phase contrast microscopy, Mag. x 250. (A) PC12 cells exposed to 10 ng/mL NGF; (B) 10 ng/mL NGF plus 0.5 mM picloram; (C) 10 ng/mL NGF plus 1 mM picloram; (D) 10 ng/mL NGF plus 3 mM picloram.

1 mM Picloram to 10 ng/mL NGF induced a further increase in the length of neurites, in comparison to control, 10 ng/mL NGF alone (A). Figure 2D further shows, that the increase in neurite length was dose dependent, as 10 ng/mL NGF in combination with 3 mM Picloram produced larger neurites than with 0.5 or 1 mM Picloram (B). Thus, 10 ng/mL NGF-induced outgrowth in PC12 cells, which was potentiated by 3 mM Picloram.

To determine the effects of increasing further the dose of NGF from 10 ng/mL to 50 ng/mL, on neurite outgrowth extension, we performed additional experiments. Figure 3A shows that PC12 cells exposed to 50 ng/mL NGF alone (control) show in numerous cells, very long neurites. Figure 3B shows that, when 0.5 mM Picloram

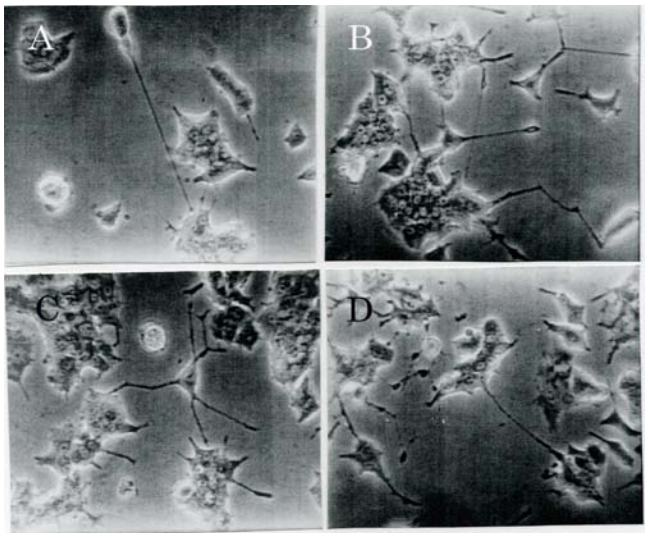

Figure 3: PC12 cells growth in the presence of picloram plus NGF for 48 h. Phase contrast microscopy, Mag. x 250. (A) PC12 exposed to 50 ng/mL NGF; (B) 50 ng/mL NGF plus 0.5 mM picloram; (C) 50 ng/mL NGF plus 1 mM picloram; (D) 50 ng/mL NGF plus 3 mM picloram.

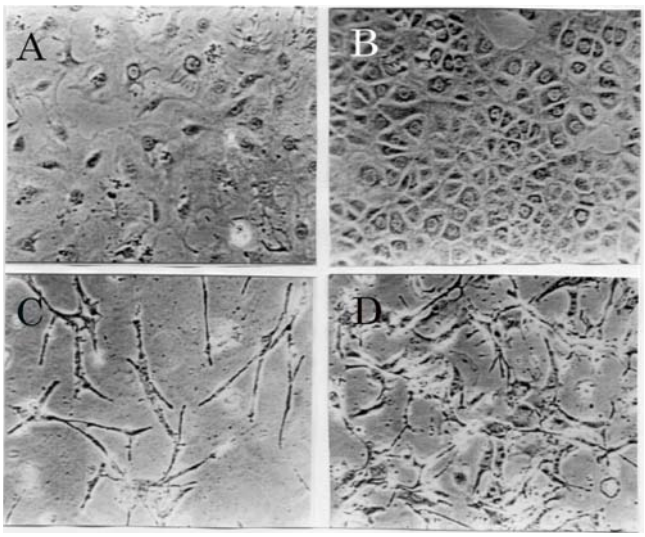

Figure 4: Normal NRK cells, and virally transformed SV-NRK and K-NRK cells grown in the presence of 3 mM picloram for 72 h. Phase contrast microscopy, Mag. x 250. (A) NRK cells exposed to 3 mM picloram for 72 h; the cell show cytotoxicity and no Neurite growth is observed; (B) NRK cells untreated, at 72 h; the cells show contact inhibition of growth, with no signs of cytotoxicity; (C) SV-NRK exposed to 3 mM picloram for 72 h show pronounced cytotoxicity and elongation of Neurites; (D) K-NRK exposed to 3 mM picloram for 72 h show pronounced cytotoxicity, fragmentation of nucleoli, and elongation of Neurites.

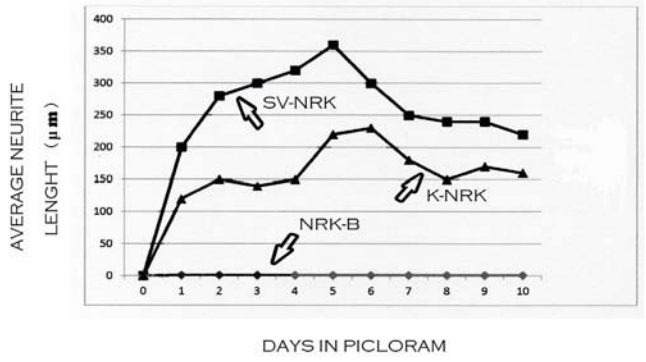

Figure 5: Quantitative analysis of Neurite length in NRK, SV-NRK, and K-NRK cells Neurite extension in function of time. The quantitative analysis of Neurite length during 10 days in 3 mM picloram is shown. No Neurite growth was observed in normal NRK cells. The longest average Neurite length was observed in SV-NRK with an average length of approximately 150 um. K-NRK cells reached an average Neurite length of about 150 um. Thus, the results indicate that 3 mM picloram induced a time-dependent and quantitative increased in Neurite length in virally-transformed cells, while normal NRK cells were unable to show any Neurite increase in length when exposed to 3 mM picloram.

was combined with 50 ng/mL NGF, a large number of neurites were observed in most cells. Figure 3C, shows that addition of 1 mM Picloram to 50 ng/mL NGF induced further increase in the length of neurites, in comparison to control, 50 ng/mL NGF alone (A). Figure 3D, shows, that the increase in neurite length was dose-dependent, as 50 ng/mL NGF in combination with 3 mM Picloram produced larger and thicker neurites than with 0.5 or 1 mM Picloram (B, C). Thus, 50 ng/mL NGF induced a pronounce outgrowth in most PC12 cells which was potentiated by the presence of 3 mM Picloram.

Picloram induced cytotoxicity and elongation of neurites in virally transformed SV-NRK and K-NRK cells: Formation and elongation of neurites is not exclusive for PC12 cells in the presence of Picloram as neurite elongation were also observed in virally transformed Normal Rat Kidney (NRK) cells in the presence of Picloram. Figure 4 show NRK and virally transformed Simian Virus 40 (SV-NRK) and Kirsten Sarcoma virus (K-NRK) cells grown in the presence of 3 mM Picloram for 72 h. Figure 4A shows NRK cells exposed to 3 mM Picloram for 72 h; the cells show growth inhibition at low density, and very short neurite outgrowth is observed in a few cells. Figure 4B shows NRK cells untreated, at 72 h (control); the cells show contact inhibition of growth and look healthy with no signs of cytotoxicity. Figure 4C shows SV-NRK cells exposed to 3 mM Picloram for 72 h; growth inhibition at low density, pronounced cytotoxicity, and elongation of neurites is observed. Figure 4D shows K-NRK cells exposed to 3 mM Picloram for 72 h; growth inhibition at low density, pronounced cytotoxicity, fragmentation of the nucleoli, and elongation of neurites is observed.

Quantitative analysis of neurite length during neurite extension in normal (NRK) and virally transformed (SV-NRK and K-NRK) cells exposed to Picloram

Figure 5 shows the quantitative analysis of neurite length during 10 days in 3 mM Picloram on NRK, SV-NRK and K-NRK cells. As shown by the line indicated by rhomboidal symbols, no neurite growth was observed in normal NRK-B cells. The cells that showed the largest average neurite length were SV-NRK with a maximum length of about 150 um. K-NRK cells reached a neurite length of about 150 um. Thus, 3 mM Picloram induced a quantitative neurite length increase only in virally-transformed cells SV-NRK and K-NRK cells, while normal NRK-B cells were unable to show any neurite increase in length when exposed to 3 mM Picloram.

Discussion

Like neuroblastoma, Pheochromocytoma (PC) is a neural crest-derived tumor of the neuroendocrine system [15,17,18]. PC is rare, mostly occurring in the adult medullary adrenal gland chromaffin cells which produce epinephrine and nor-epinephrine [15,17]. PC also occur external to the adrenal gland [17]. PCs can metastasize, and there is no effective therapy [17]. Mouse models of PCs have shown misregulation and mutagenesis of numerous genes involved in neural crest development [15,17,18]. PCs can also be chemically induced [15,17]. PCs are thus, heterogeneous in nature [18]. The emergence of Genome Context Analysis [22], Nucleoli studies [24-26], and Biogenesis of ribosomal [22] and their ex-traribosomal protein functions [21,23,27] may help to define the metastatic and migrating nature of the PCs.

Introduction of DNA or RNA viruses in the PC12 genome induce an alteration in the extension of neurite-like processes [15]. When NGF is added to virally transformed cells, changes in the signaling pathways responding to NGF also occur [15,17]. The PC12 cells can respond to NGF by proliferation or differentiation, depending on the type of virus and culture conditions [15,17].

PC12 cell line is a cloned obtained from a pheochromocytoma of the rat adrenal medulla [3]. PC12 cells originate from the neural crest that has two types of cells: neuroblasts and eosinophilic cells [15,17,18]. PC-12 cell lines were developed by Goodman et al [4]

as models of neuronal differentiation as they are easy to culture, and can be manipulated pharmacologically such as with NGF and numerous other agents [6,8,9]. PC12 cell division is arrested and terminal differentiates when treated with NGF or dexametazone [15]. Treatment of PC12 cells with NGF induces long processes denoted neurites [5,17]. The use of other pharmacological agents suggests that PC12 cell line can be a good model for toxicological studies and diseases of the peripheral nervous system [6-9]. However, PC12 cells have not been used to test the effects of herbicides such as Picloram in growth, differentiation or neurite formation.

The studies presented here, show previously unrecognized actions of Picloram alone or in combination with NGF in PC-12 cells in culture. Picloram affects cell growth, differentiation, and induces MPS1/S27 [27] expression in PC12 cells, in the presence of Picloram and/or NGF. These findings suggest neurotoxic actions of Picloram in PC12 cells, a cell line derived from the peripheral nervous system of animals and humans. NGF is required for both the development and maintenance of the sympathetic nervous system [17,18]. If beta-NGF is chemically or immunologically suppressed in neonatal mice, the sympathetic nervous system is essentially repressed (95% of the cell population of both the paravertebral and prevertebral ganglia are destroyed) [17]. Chemical agents that inhibit protein synthesis, also have similar effects on the sympathetic nervous systems [17,18].

However, little is known, on the chronic toxic effects of herbicides in the peripheral nervous system. In the case of Picloram, as suggested by the present studies, the nucleoli observations in essentially all PC12 cells treated with Picloram may be showing signs of neurotoxicity as a result of inhibitor of protein synthesis in PC12 cells by Picloram [23-27]. Numerous drugs and viruses alter nucleolar morphology as a sign of toxicity [23-28]. In this case, it is worth noting that MPS1/S27, a ribosomal protein with multiple functions such as DNA repair and biogenesis of ribosome's, is increased by Picloram, and thus, this increase in MPS1/S27 may be an indication of inhibition of protein synthesis, cytotoxicity and enhanced carcinogenicity produced by Picloram [24-28]. Our studies with PC12 cells, may be important in understanding damage by Picloram to Eukarya (plant and animals), and also molecular mechanisms involve in the regeneration of the peripheral nervous system, when damaged by toxic agents [16].

NGF induces neurite outgrowth in PC12 cells in a process that involves the coordinate induction of microtubule assembly and certain promoting factors [5]. The neurite extension in PC12 cells, a clonal cell line derived from a rat pheochromocytoma is very useful for neurite studies, as PC12 cells in response to NGF, regulates the development and maintenance of sympathetic and sensory neurons [15]. PC12 cells are ideal to test neurite outgrowth as these projections are readily induced by NGF and extend long distances [5,17]. The mechanism by which neurite growth occurs is not yet well understood [17]. Potentiation of NGF induced neurite outgrowth in PC12 cells have been shown to be induced by various pharmacological agents. For example, if enprodil significantly potentiated NGF-induced neurite outgrowth, in a concentration dependent manner [6].

The nucleolus of PC12 cells was affected by treatment with Picloram alone. The nucleous become dark, small, and fragmented, in a large number of cells, after 24 h of treatment with 3 mM Picloram, indicating toxic effects of this agent in the nucleoli. Within the nucleoli, ribosome biogenesis, such as ribosomal RNA synthesis, processing, and ribosome subunit assembly, takes place [23-28]. Several lines of evidence show that the nucleolus has numerous non-ribosomal functions, such as the case of the extra-ribosomal functions of MPS1/S27A/E/L [23, 27]. We have previously shown that UV light irradiation induces DNA damage in the nucleus and the nucleolus [21]; indicating genotoxic effects of UV light [24-26]. Several DNA repair systems are involved and one of them includes MPS1/S27 in Eukarya [22, 27]. It is conceivable that the changes in nucleolar density observed in PC12 cells after exposure to Picloram is due to genotoxic stress [24] induced by this herbicide. Karlas A, et al [23] found that Ribosomal Protein MPS1/S27A and other genes of the 'small ribosomal subunit' are important for the cellular damage induced by the influenza virus and its replication as well as genotoxic stress. Moreover, they found that the expression of Ribosomal Protein S27A mRNA in multiple human tissues and cancer cell lines [23]. Previously Fernandez-Pol et al, characterized MPS1/S27A/L/E, and mutants of MPS1, in multiple cancer cell lines and more than one-hundred different human cancers [27], were the levels of these MPS1 ribosomal proteins are increased in comparison to normal tissues.

Specific Ribosomal Proteins are critical for maintenance of cell integrity. Reactome (www.reactome.org) analysis of a data base of biological pathways in human cells done by Karlas A et al [23], confirmed that Metallopanstimulin-1 (MPS1 and its analogues) [21,27], are involved in the following functions: Translation(RPS27A), gene expression (RP27A), cell cycle (RP27A), HIV infection (RP27A), DNA repair (RP27A), and signaling in immune system (RP27A). Moreover, they found that RPS27A and other genes of the 'small ribosomal subunit' are important for infection of influenza viruses [23]. These analysis are in agreement with the data of Berthon et al [22] using Genome Context analysis, and with previously published data of Fernandez-Pol, et al on the increased of MPS1/S27E, L and A and MPS1 mutated analogues during infection with numerous viruses [27].

Conclusion

The findings presented here may be useful to further understand neurite growth, nucleolar changes, and neurotoxic effects of Picloram in PC12 cells in the presence and absence of NGF. As suggested by the changes in the density of the nucleoli in PC12 treated with Picloram, these observations may be an important sign of genotoxicity and inhibition of protein synthesis in PC12 cells induced by Picloram. These studies may have some importance in understanding damage by herbicides and pesticides in Eukarya (plant and animal cells). Furthermore, the greatly increased expression of MPS1/S27 mRNA and MPS-1-like proteins in human serum [27], have been demonstrated in multiple human carcinogenesis processes [27]. Genomic-wide screening revealed one important finding [23]: That Influenza infection requires expression of RPS27A in human cells, and these results are in precise accordance with previous results in all types of DNA and RNA viruses as previously discovered by Fernandez-Pol [19,21,27], including genotoxicity by numerous if not all pathogenic viruses and chemotherapeutic agents which involved complex functions of MPS1/S27L and MPS1-like proteins involved in carcinogenesis [27].

Acknowledgement

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