The Toxic Effect of Ytterbium on Planaria May Involve a Variety of Ion Channels

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Citation

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Abstract

The effect of toxic concentrations of Yb3+ on the Ca, K, Na, Mg, and Cl channels of planaria was investigated through the use of various agonists and antagonists to those channels. Results reveal that Yb toxicity is mediated through L-type Ca channels, but not T-type. Toxicity is also mediated by way of some sub-type of K channel, Na channels, and Cl. The mechanisms of Yb toxicity have some overlap with, but are not identical, to that seen for La. More detailed studies of this metal needs to be conducted.

1. INTRODUCTION

Ytterbium and other metals of the lanthanide series are used in a variety of applications in both industry and medicine. The technology industry makes wide use of the lanthanides for substances ranging from semiconductors, lasers, alloys, optics, to magnets. The medical field is also making use of these trivalent metals for contrast agents, especially gadolinium. Experimental therapeutics such as terbium-doped gadolinium nanoparticles are being tested [1] as well as ytterbium microspheres for radio-embolization [2]. Because of their greater use there is greater environmental release of these metals and increased human exposure. Yet, our understanding of the pharmacology and toxicology of these metals is limited.

One little studied metal is Ytterbium (Yb). Yb lies on the opposite end of the lanthanide series of metals from its comparatively well studied cousin lanthanum. Studies that have examined the pharmacology of ytterbium are few, but, do give clues to Yb's biological activity. Yb appears to have activity at the aquaporins (in plants; Vorob'ev et al, 2019) and at voltage activated Ca channels [4, 5, 6], and some K channels [7]. Yb disturbs the accumulation of trace elements in the developing brain [8]. Hongyan et al [9] demonstrated both inhibition and stimulation of a variety of liver enzymes, depending on both the dose and time course of Yb exposure. Yb has anticoagulant activity [10] and has also been demonstrated to bind to transferrin [11]. Yb accumulates largely in the bone, liver and spleen [12] and has been associated with hypertension [13].

This study seeks to further explore the activity of ytterbium using planaria as the experimental system. Planaria are simple organisms that are hardy and use a very simple culture media. We used systematic pharmacologic challenges to Yb activity to further elucidate the mechanism of Yb toxicity. This study uses the same approach and format as one published earlier by this laboratory investigating the toxicology of La [14}.

2. MATERIALS AND METHODS

2.1. Husbandry

Planaria (*Girardia dorotocephala*) were initially purchased from Carolina Biological and have since been raised at room temperature in 2-L plastic containers containing dechlorinated tap water and fed frozen beef liver weekly. Worms were fasted for at least 5 days prior to testing.

2.2. Test Cultures and Conditions

Unless otherwise specified, all tests were conducted in plastic petri dishes containing 10 mL of culture media. Culture media consisted of a slight modification of Montjuic salts (1.6 mM NaCl, 1 mM CaCl2, 1.1 mM MgSO4, 0.1 mM KCl, 1.2 mM NaHCO3), unless otherwise indicated. Five worms were used in each dish. A minimum of 15 dishes were used for each test condition.

2.3. Test Procedure

Five worms were placed in the plastic culture dish containing 10 mL of culture media and test substances added to the desired concentration. Animal responses to each test condition were evaluated every 24 h using the Planaria Stress Scale (PSS; see Table 1) the suitability of using this scale was demonstrated in an earlier study done by this laboratory [14]. The average PSS score for each culture dish was used as the unit of measure for analysis.

The test solution consisted of the drug and metal under consideration dissolved in culture media. All chemicals were reagent grade or better. In some instances the chemicals were insoluble in water and DMSO was used as the vehicle. Probe trials were conducted to ensure that the vehicle had no effect, as does the use of control groups. Concentrations of test drugs were the maximum concentration tolerable by planaria, as determined by probe trials. Concentrations are expressed in mM, unless indicated otherwise. Media pH was checked after the addition of test agents to ensure no change in pH had occurred.

2.4. Statistics

Statistical analysis was conducted with one-way ANOVA using SPSS, with $p < 0.05$ indicating statistical significance. An ANOVA was conducted for each of the challenge conditions (calcium, potassium, sodium, chloride, magnesium) with each treatment condition acting as a separate group. A minimum of 15 dishes were used for each test condition. A separate ANOVA was conducted for each day. Follow-up statistics were conducted using Tukey's test with the control condition and Yb 0.5 mM condition acting as the comparison points for the other treatments. Data is expressed as mean (standard deviation). The effect of a manipulation was considered to be reliable only if a statistically significant effect was seen for at least 3 days.

3. RESULTS

3.1. Ytterbium Concentration Response Ranging

The PSS is used to measure the stress responses of planaria to toxic substances (see Table 1). It is used as an Excel spreadsheet on a portable device. The number of worms exhibiting the behavior is entered "under number of animals" and multiplied by the value generating a total for the row and a grand total for all the rows, then divided by the number of animals in the dish. Animals may exhibit more than one characteristic. Tactile stimulation is performed by gently touching the worm with a blunt needle tip. Dead animals have no scores for other behaviors. For example, for a dish with five animals, three animals exhibiting irregular outlines, two of which exhibited no spontaneous behavior, produces a mean score of 1.6 for the dish. Each dish is reevaluated every 24 h. This instrument may be freely used and modified, so long as proper citation is given.

Table 1

Planaria Stress Scale (PSS).

Planaria Stress Scale	Value	# Animals	Total for Row
Dead	15		
Free floating, no contact with container or surface tension	3		
Curled	3		
No response to tactile stimulation	3		
Irregular body outline or head degeneration	2		
Center of dish, not near wall	1		
Lack of spontaneous movement	1		
No signs of stress	0		
Total		Grand Total →	
		Mean→	

Test exposures with concentrations of YbCl3 ranging from 0.06 to 1 mM were conducted with the resulting PSS scores shown in Table 2, which indicates that predictable toxicity begins at a concentration of 0.25 mM. We elected to conduct further experimentation at YbCl3 (simply abbreviated as Yb for the rest of the paper, for the sake of simplicity) concentration of 0.5 mM, the concentration which resulted in a toxic response that was robust, but, could still be pharmacologically antagonized or enhanced. Data from control animals (culture media only) are shown for reference in each table and do not represent multiple control trials. Similarly, the Yb 0.5 mM group acted as a positive control and is used as a reference for all tables, and does not represent multiple Yb 0.5 mM trials.

Table 2

Ytterbium concentration response data. Planaria response to varying concentrations of Yb using the PSS; mean (SD). Concentrations are in mM. A Yb concentration of 0.5 mM gives a robust response, yet, it can still be antagonized. This concentration was used for the remainder of the study.

Yb	Day 1	2	3	4
0.06	0.34 (028)	0.09 (0.15)	0.34 (0.23)	0.46 (0.28)
0.12	0.50 (0.37)	0.35 (0.26)	0.53 (0.42)	0.48 (0.28)
0.25	2.05 (0.63)	1.73 (0.65)	2.43 (0.59)	1.90 (0.82)
0.5	3.43 (0.59)	4.50 (1.52)	5.70 (2.36)	8.25 (2.87)
1	10.00 (1.80)	15.00 (0.0)	15.00 (0.0)	15.00 (0.0)

3.2. Calcium Challenges

To explore the effect of ytterbium on calcium channels, planaria were exposed to the following test conditions: YbCl3 0.5 mM; nifedipine 0.01 mM; 1-octanol 0.1 mM; CaCl2 6 mM added to the media; YbCl3 0.5 mM and nifedipine 0.01 mM; YbCl3 0.5 mM and 1-octanol 0.1 mM; YbCl3 0.5 mM and CaCl2 6 mM added to the media; calcium-free media; YbCl3 0.5 mM and calcium-free media. Calcium-free media is a modification of the culture media and consisted of: 2.7 mM NaCl; 1.1 mM MgSO4; 0.1 mM KCl; 1.2 mM NaHCO3.

The results of four days of exposure to each condition are shown in Table 3, with increased calcium levels partially blocking the effect of Yb and the voltage-activated L-type calcium channel antagonist nifedipine magnifying the toxic effects of Yb. We consider the effect of Ca-free media on Yb activity at days two and three to be spurious, and similarly for 1-ocatanol on days one and four; the effect of a manipulation was considered reliable only if there was an effect for at least three days.

Table 3

Calcium challenges to Yb activity. Data are mean (SD) for scores on the Planaria Stress Scale, minimum 15 dishes/cell.

Drug 1	Drug 2	Day 1	Day 2	Day 3	Day 4
Yb 0.5 ♯-all days		4.36 (1.33)	5.09 (1.66)	6.45 (1.90)	8.77 (2.58)
Yb 0.5 ♯-all days	Nifedipine 0.01	6.40 (1.72)*	9.80 (2.48)*	11.80 (1.82)*	13.07 (1.62)*
Yb 0.5 ♯-all days	Ca-Free	4.73 (1.16)	6.53 (0.92)*	7.87 (2.36)*	8.73 (3.33)
Yb 0.5 ♯-all days	1-Octanol 0.1	5.47 (1.88)*	5.00 (1.56)	6.00 (2.00)	6.73 (1.83)*
Yb 0.5 ♯-all days	Ca 6	2.00 (1.07)*	2.33 (0.82)*	2.80 (0.77)*	2.93 (0.80)*
Control *-all days		0.52 (0.53)	0.37 (0.43)	0.30 (0.38)	0.30 (0.35)
1-Octanol 0.1 *-all days		0.79 (0.53)	0.80 (0.68)	0.56 (0.49)	0.61 (0.47)
Ca-Free *-all days		0.41 (0.37)	0.25 (0.24)	0.39 (0.33)	0.66 (0.46)
Ca 6 *-all days		0.48 (0.39)	0.25 (0.37)	0.44 (0.35)	0.39 (0.41)
Nifedipine 0.01 *-all days		0.94 (0.65)	0.91 (0.36)	0.94 (0.42)	0.91 (0.29)

* indicates significantly different from Yb 0.5; ♯ indicates significantly different from control.

3.3. Potassium Challenges

To explore the activity of Yb on potassium channels, planaria were exposed to the following test conditions: YbCl3 0.5 mM; K-free media; KCl 0.1 mM added to the media; minoxidil 2 mM; tetraethylammonium (TEA) 16 mM; quinine HCl 0.02 mM; 4-aminopyridine (4-AP) 0.03 mM; YbCl3 0.5 mM and TEA 16 mM; YbCl3 0.5 mM and 4-AP 0.03 mM; YbCl3 0.5 mM and quinine HCl 0.02 mM; YbCl3 0.5 mM and KCl 0.1 mM added to the media; YbCl3 0.5 and minoxidil 2 mM; YbCl3 0.5 mM and K-free media. K-free media consisted of: 1.7 mM NaCl, 1mM CaCl2, 1.1 mM MgSO4, 1.2 mM NaHCO3.

The results of four days exposure to each condition are shown in Table 4. Potassium-free media completely attenuated the toxicity of Yb. The K-channel antagonist TEA, but not 4-AP, accentuated the activity of Yb. The K-ATP agonist minoxidil modestly enhanced Yb toxicity. Quinine had no effect. The effect of 4-AP on day 4 was considered spurious; the effect of a manipulation was considered reliable only if there was an effect for at least three days.

Table 4

Potassium challenges to Yb activity. Data are mean (SD) for scores on the Planaria Stress Scale, minimum 15 dishes/cell.

Drug 1	Drug 2	Day 1	Day 2	Day 3	Day 4
Yb 0.5 ♯-all days		4.36 (1.33)	5.09 (1.66)	6.45 (1.90)	8.77 (2.58)
Yb 0.5 ♯-all days	TEA 16	7.00 (1.96)*	8.47 (1.73)*	9.93 (2.49)*	11.40 (2.95)*
Yb 0.5 ♯-all days	4-AP 0.03	4.67 (0.98)	5.07 (1.16)	5.33 (1.35)	6.87 (1.89)*
Yb 0.5 ♯-all days	Quinine 0.02	4.6 (0.99)	5.73 (0.88)	6.87 (1.73)	8.13 (2.00)
Yb 0.5 ♯-all days	K 0.1	4.60 (0.91)	5.80 (0.86)	6.20 (1.15)	7.60 (1.50)
Yb 0.5 ♯-all days	Minoxidil 2	6.73 (1.49)*	7.00 (2.95)*	8.40 (3.07)*	9.87 (2.90)
Yb 0.5	K-Free	0.81 (0.75)*	0.75 (.58)*	0.56 (0.63)*	0.44 (0.51)*
Control *-all days		0.52 (0.53)	0.37 (0.43)	0.30 (0.38)	0.30 (0.35)
Minoxidil 2 *-all days		1.24 (0.41)	1.18 (0.29)	1.41 (0.43)	1.59 (0.43)
TEA 16 *-all days		1.21 (0.38)	0.81 (0.37)	0.97 (0.23)	0.89 (0.46)
Quinine 0.02 *-all days		0.87 (0.83)	0.93 (0.70)	1.07 (0.96)	1.13 (0.52)
4-AP 0.03 *-all days		0.66 (0.54)	0.73 (0.40)	0.84 (0.45)	0.93 (0.41)
K-Free *-all days		0.39 (0.35)	0.47 (0.39)	0.34 (0.31)	0.35 (0.35)
K 0.1 *-all days		0.51 (0.42)	0.31 (0.34)	0.32 (0.38)	0.40 (0.37)

* indicates significantly different from Yb 0.5; ♯ indicates significantly different from control. Note that Yb 0.5 mM and K-free media condition was not significantly different from control.

3.4. Sodium Challenges

To explore the effects of Yb on sodium channels, planaria were exposed to the following conditions: YbCl3 0.5 mM; Na-free media; carbamazepine 0.2 mM; NaCl 1.6 mM added; lidocaine HCl 0.25 mM; YbCl3 0.5 mM and Na-free media; YbCl3 0.5 mM and carbamazepine 0.2 mM; YbCl3 0.5 mM and NaCl 1.6 mM added; YbCl3 0.5 mM and lidocaine HCl 0.25 mM. Na-free media consisted of: 3.9 mM CaCl2, 1.1 mM MgSO4, 0.1 mM KCl.

The results for the conditions relevant to sodium are shown in Table 5. Blocking Na activity with lidocaine, or carbamazepine, or removing Na from the media, enhanced the toxicity of Yb.

Table 5

Sodium challenges to Yb activity. Data are mean (SD) for scores on the Planaria Stress Scale, minimum 10 dishes/cell.

Drug 1	Drug 2	Day 1	Day 2	Day 3	Day 4
Yb 0.5 ᶠ-all days		4.36 (1.33)	5.09 (1.66)	6.45 (1.90)	8.77 (2.58)
Yb 0.5 ᶠ-all days	Na-Free	7.81 (4.17)*	12.00 (2.58)*	13.94 (1.39)*	14.56 (0.81)*
Yb 0.5 ᶠ-all days	Carbamazepine 0.2	9.00 (1.00)*	10.87 (1.92)*	14.87 (0.35)*	15.00 (0.00)*
Yb 0.5 ᶠ-all days	Na 1.6	4.06 (0.93)	4.88 (0.96)	6.69 (1.85)	8.44 (1.89)
Yb 0.5 ᶠ-all days	Lidocaine 0.25	4.73 (1.49)	8.67 (2.38)*	11.20 (2.81)*	11.13 (2.42)*
Control *-all days		0.52 (0.53)	0.37 (0.43)	0.30 (0.38)	0.30(0.35)
Carbamazepine 0.2 *-all days		1.40 (0.51)	1.36 (0.68)	1.21 (0.79)	1.50 (0.71)
Lidocaine 0.25 *-all days		1.13 (0.46)	1.31 (0.85)	1.29 (0.48)	1.58 (1.63)
Na 1.6 *-all days		0.40 (0.33)	0.39 (0.38)	0.45 (0.42)	0.64 (0.45)
Na-Free *-all days		0.51 (0.36)	0.43 (0.38	0.43 (0.35)	0.43 (0.46)

* indicates significantly different from Yb 0.5; ᶠ indicates significantly different from control.

3.5. Chloride Challenges

The role of Cl channel activity was explored in part by examining the GABAa channel receptor complex. This was accomplished by exposing planaria to the following conditions: YbCl3 0.5 mM; picrotoxin 0.25 mM; GABA 5 mM; Cl-free media; Yb 0.5 mM and picrotoxin 0.25 mM; YbCl3 0.5 mM and GABA 5 mM; YbCl3 0.5 mM and Cl-free media. Cl-free media consisted of; 1.7 mM NaSO4, 1.1 mM MgSO4, 1.2 mM NaHCO3.

The results of the Cl challenges are presented in Table 6. Removal of Cl from the media consistently attenuated the toxic effect of Yb. Picrotoxin also enhanced the toxicity of Yb, presumably by blocking the Cl channel. GABA consistently attenuated the effect of Yb.

Table 6

Chloride challenges to Yb activity. Data are mean (SD) for scores on the Planaria Stress Scale, minimum 15 dishes/cell.

Drug 1	Drug 2	Day 1	Day 2	Day 3	Day 4
Yb 0.5 ᶠ-all days		4.36 (1.33)	5.09 (1.66)	6.45 (1.90)	8.77 (2.58)
Yb 0.5 ᶠ-all days	Picrotoxin 0.25	7.20 (1.37)*	8.87 (1.30)*	10.20(1.93)*	12.60 (1.40)*
Yb 0.5 ᶠ-all days	GABA 5	3.67 (0.62)	3.80 (0.86)*	4.33 (1.29)*	5.20 (1.52)*
Yb 0.5	Cl-Free	0.94 (1.06)*	1.06 (1.06)*	0.75 (0.93)*	0.81 (1.11)*
Control *-all days		0.52 (0.53)	0.37 (0.43)	0.29 (0.38)	0.30 (0.35)
Cl-Free *-all days		0.37 (0.36)	0.35 (0.32)	0.31 (0.33)	0.24 (0.31)
Picrotoxin 0.25 *-all days		0.37 (0.39)	0.28 (0.30)	0.32 (0.31)	0.25 (0.31)
GABA 5 *-all days		0.43 (0.41)	0.52 (0.39)	0.76 (0.45)	0.55 (0.51)

* indicates significantly different from Yb 0.5; ᶠ indicates significantly different from control.

3.6. Magnesium Challenges

The role of magnesium in Yb activity was explored by exposing planaria to the following conditions: YbCl3 0.5 mM; Mg-free media; MgCl2 1.1 mM added; YbCl3 0.5 mM and Mg-free media; YbCl3 0.5 mM and MgCl2 1.1 mM added. Mg-free media consisted of: 1.6 mM NaCl, 1.0 mM CaCl2, 1.1 mM NaSO4, 0.1 mM KCl, 1.2 mM NaHCO3. The results of manipulating the Mg environment are presented in Table 7. Adding Mg to the media reduced Yb toxicity by a modest degree.

Table 7

Magnesium challenges to Yb activity. Data are mean (SD) for scores on the Planaria Stress Scale, minimum 15 dishes/cell.

Drug 1	Drug 2	Day 1	Day 2	Day 3	Day 4
Yb 0.5 ᶠ-all days		4.36 (1.33)	5.09 (1.66)	6.45 (1.90)	8.77 (2.58)
Yb 0.5 ᶠ-all days	Mg-Free	4.44 (0.81)	4.81 (2.14)	5.81 (3.08)	7.38 (3.63)
Yb 0.5 ᶠ-all days	Mg 1.1	3.40 (0.51)*	4.07 (0.70)	4.33 (1.45)*	5.13 (1.73)*
Control *-all days		0.52 (0.53)	0.37 (0.43)	0.30 (0.38)	0.30 (0.35)
Mg 1.1 *-all days		0.81 (0.52)	0.41 (0.38)	0.46 (0.44)	0.39 (0.36)
Mg-Free *-all days		0.52 (0.40)	0.33 (0.32)	0.20 (0.27)	0.27 (0.26)

* indicates significantly different from Yb 0.5; ᶠ indicates significantly different from control.

4. DISCUSSION

That Yb is active at L-type voltage-activated Ca channels is demonstrated by the synergistic effect of nifedipine to enhance Yb toxicity. The lack of a synergist effect of Yb and 1-octanol, a T-type calcium channel antagonist [15], indicates that the T-type calcium channel is not meaningfully involved in Yb toxicity; although T-type channels are blocked by lanthanide metals, including Yb [6, 16]. It is interesting to note that 1-octanol is a well-known gap-

junction blocker [17], whatever the toxic mechanisms of Yb, it does not seem to involve gap junctions.

That a CaCl2 concentration over 6 mM does not completely antagonize the toxicity of Yb, nor did exposure to Ca-free media. This argues that Yb exhibits its activity through additional mechanisms other than the L-type calcium channel. With other lanthanides, in particular La, toxic concentrations produce oxidative stress [18, 19] which alters Ca signaling, as well as the behavior of a variety of Ca channels [20]. This is not well studied for Yb, with only one study demonstrating this oxidative stress associated with Yb exposure [21].

In contrast to the calcium challenges are the findings connected to the potassium challenges. Particularly striking is the finding that K-free media completely and reliably antagonizes the effects of Yb exposure. Yet, tetraethylammonium (TEA), an antagonist to voltage-activated K channels, significantly enhanced Yb toxicity, indicating some linkage to calcium-activated K channels. TEA is a blocker of some calcium-activated potassium channels at submillimolar concentrations [22], but our concentrations were much greater, resulting in a less selective blockade. 4-AP (4-aminopyridine) did not have any effect on Yb toxicity, despite it also being a blocker of voltage activated K-channels, especially Kv1, suggesting there are some differences in the activity of Yb at that location. Our previous study using La demonstrated an enhancement of toxicity of that metal for both TEA and 4-AP [14]. This fits with the studies by Nachshen [23] who demonstrated considerable differences amongst the various lanthanides in their ability to inhibit K stimulated Ca influx.

The exact role of the various Ca-activated K channels (BK, SK, IK, and others) in Yb toxicity will require additional study. Minoxidil, a K-channel opener for inwardly rectifying ATP-sensitive K channels mildly enhanced the effects of Yb, suggesting that this family of channels may play a role in the toxicity of Yb. As mentioned previously, La, the exemplar metal of this group, produces significant oxidative stress [18, 19], which may play a role in its toxicity, but, this has not been well studied for YB, leaving the question open. La is also transported into cells [24], another unknown for Yb.

Preventing the entry of Na into cells by way of blocking with carbamazepine, blocking with lidocaine, or removal from the media enhanced Yb toxicity. There are no studies on the effect of Yb on Na channels. However, La has been shown to enter the cell by way of the Na/Ca exchanger, substituting for Ca [24]. If Yb behaves in a manner similar to La then, once accumulated in the planarial cell, removal of Yb by the Na-dependent plasma membrane calcium pump (PMCA) may be inhibited by removal of Na from the media, or by the blockage of Na channels with lidocaine or carbamazepine. These are all suppositions that Yb and La behave similarly in this instance, which may well not be the case as carbamazepine did not enhance La toxicity in our previous work [14]. This and the role the potential role of oxidative stress does need to be explored as well.

The addition of Mg, the last cation we investigated, diminished Yb toxicity. However, removal of Mg from the culture media had no effect on the toxicity of Yb. One explanation for this may be the general view that the overall activity of Ca is antagonized by the presence of Mg. However, Mg is also active at the Na/Mg antiporter, the Mg/Ca-activated K channels, and Mg- and voltage-activated Ca channels [22]. The role of Mg at Ca-activated K channels appears to be especially complex [16, 25, 26]. The blockade of Ca at any of these channels by Yb could alter a wide variety of cellular functions. Yet, how the addition of Mg would reduce Yb toxicity is puzzling and needs to be investigated at the cellular, rather than the organismic level.

The removal of chloride from the media fully antagonized the effects of Yb toxicity. However, manipulating the activity of the GABAa chloride channel decreased Yb toxicity, with Cl channel blockade with picrotoxin leading to enhanced Yb toxicity. It should also be noted that increasing the Cl concentration by adding KCl, NaCl, and MgCl2 to the media (see above) had no effect on Yb toxicity. This leads to the reasonable postulation that Yb has activity at one or more of the Ca-activated Cl channels (CaCCs), although other anion channels may be involved [27 28].

This approach does suffer from some shortcomings. This is an examination of mechanisms at an organismic level and not at the cell membrane. Metals in this type of media may form a variety of complexes with other media constituents. Immediate and delayed effects cannot be separated out, and effects on the activity of other molecules, such as enzymes, were not explored. The simultaneous activity of Yb on several mechanisms at once is also a difficulty. However, we clearly demonstrate that the activity of Yb can be both accentuated and antagonized at the organismic level giving clues to its mechanism of action in a complex environment.

5. CONCLUSIONS

In conclusion, Yb has considerable action at the L-type Ca channel, as well as other major ion channels. Yet, much of the exact nature of this metal's activity is not well understood due to a dearth of data. More work needs to be done on this, and other lanthanides, a matter of considerable importance due to the expanding role of these substances in human endeavors.

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