Pharmacology Biochemistry & Behavior, Vol 21, Suppl , 1, pp 87–92, 1984 © Ankho International Inc. Printed in the U S A 0091-3057/84 $3 00 + 00

Lithium, Rubidium and Cesium: Cerebral Pharmacokinetics and Alcohol Interactions

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MESSIHA, F S *Lithium, rubidium and cesium Cerebral pharmacokinetics and alcohol interaction* PHARMACOL BIOCHEM BEHAV **21**: Suppl 1, 87–92, 1984 —The distribution of exogenously administered Li^+, Rb^+ and Cs^+ in distinct mouse brain regions was studied as a function of time subsequent termination of a short-term daily treatment with these alkali metal salts. The resulting distribution profiles were compared with that obtained from the corresponding endogenous alkali metals. Endogenous Rb^+ and Cs^+ were readily measurable in all 6 brain regions studied compared to traces of measurable Li^+ The Rb^+ concentration was greater than that of Cs^+. Short-term treatment with equal doses of the alkali metals studied showed greater brain accumulation of Rb^+ and Cs^+ than Li^+ with a prolonged brain regions preference for Cs^+ storages as a function of time. Duration of ethanol-mediated narcosis was reduced from saline controls by pretreatment with RbCl or CsCl as contrasted with prolongation by LiCl. The narcotic dosage of ethanol used reduced endogeneous Li^+ and increased Cs^+ levels in the cerebellum. This massive ethanol dosage exerted little effect on the distribution of exogenously administered Cs^+ with exception of the striatum which continued to show a high content of Cs^+. This may have contributed to partial antagonism of ethanol-depressant action and to restoring of motor function, i.e., rapid regaining of righting reflex. The results showed that Cs^+ possessed longer biological life time in the brain than Rb^+ or Li^+ which may be of therapeutic value, i.e., in the use of Cs salts in treatment of brain tumors and in conjunction with psychoactive agents provided the respective chemotherapeutic and antidepressant properties of CsCl have been established.

Brain regions Cerebellum Cesium Ethanol Hippocampus Lithium Pharmacokinetics Striatum

PRECLINICAL evaluation of alkali metals other than lithium, i.e., rubidium, (Rb) and cesium (Cs), have been receiving increasing attention during the last decade. This accounts for their possible therapeutic applications in affective illness [5, 12, 13], in cancer chemotherapy [3, 19, 22, 23], in the management of certain drug-induced movements disorders [14, 17, 21] and in alleviation of certain alcohol-evoked responses [16, 18, 22]. Cesium occupies an important position among alkali metals because of its various industrial usages, i.e., in manufacturing of photo electrical cells, in production of certain vacuum tubes and of x-ray fluorescent screens. In addition, radioactive ^{137}Cs has been an important constituent of radioactive fallout of nuclear bomb testing since 1950. This has resulted in several investigations relevant to the toxicity of Cs, its metabolic disposition and its pharmacokinetics in man [2] and in experimental animals [25,27]. However, little attention has been focused on cerebral uptake and disposition of Rb or Cs particularly when considering their relative long biological half-life time. It is the aim of the present study to investigate the uptake of Li^+, Rb^+ and Cs^+ in discrete mouse brain regions and follow their cerebral disappearance as a function of time. The interaction between Cs and ethanol (ET) was also studied.

METHOD

Male Sprague Dawley mice were purchased from Sprague Dawley Inc., Madison, WI. They were 8 to 10 weeks old and were caged in groups of 6 and had access to Purina pellet food and distilled water ad lib.

In the first set of experiments, the content of endogenous and exogenously administered Li^+, Rb^+ and Cs^+ were tested in discrete brain areas of the mouse. The LiCl, RbCl or CsCl solutions were injected intraperitoneally (IP) 5 mEq/kg, once daily for 7 consecutive days and the controls received saline. The animals were sacrificed by decapitation 4 hr post final injection and the brain was quickly removed, blotted dry with filter paper and dissected over ice into cerebral cortex, striatum, hippocampus, diencephalon, brain-stem and cerebellum. A pool of 3 mouse brain region was used for each individual sample preparation. The tissue was homogenized in ice cold 0.4 M perchloric acid by glass homogenizer and centrifuged at 10,000×g for 30 min at 4°C. The supernatant obtained was decanted and saved. The pellet was then washed twice by suspension in the same acid, homogenized and similarly recentrifuged. Supernatants of pellet wash were pooled with the initial supernatant and their volume measured prior to their quantitative determination by atomic absorption spectroscopy.

In the second set of experiments, the effect of a single narcotic dose of ET on endogenous and exogenously administered alkali metals was studied. A 25% (w/v) ET solution, prepared by diluting a 95% ET by saline to required concentration, was administered to experimentally untreated

TABLE 1

COMPARISON BETWEEN DISTRIBUTION OF ENDOGENOUS AND EXOGENOUSLY ADMINISTERED ALKALI METALS IN DISTINCT MOUSE BRAIN REGIONS

Brain Region	Source of Alkali Metal	Alkali Metal Concentration (mEq/kg/g Wet Weight) Li^+	Rb^+	Cs^+
Cortex	Endogenous	NM	1 3 ± 0 1	0 04 ± 0 01
	Exogenous	1 4 ± 0 3	9 4 ± 2 5	3 3 ± 0 5
Striatum	Endogenous	NM	1 7 ± 0 6	0 10 ± 0 04
	Exogenous	1 6 ± 0 1	7 6 ± 0 8	3 6 ± 1 5
Hippocampus	Endogenous	NM	2 5 ± 0 4	0 28 ± 0 09
	Exogenous	1 8 ± 0 2	9 6 ± 0 2	5 4 ± 1 5
Diencephalon	Endogenous	NM	1 3 ± 0 5	0 18 ± 0 05
	Exogenous	1 7 ± 0 16	9 7 ± 1 1	4 3 ± 0 9
Brain Stem	Endogenous	NM	1 3 ± 0 02	0 12 ± 0 04
	Exogenous	1 8 ± 0 4	10 4 ± 1 3	3 9 ± 1 1
Cerebellum	Endogenous	NM	1 6 ± 0 1	0 13 ± 0 01
	Exogenous	1 8 ± 0 4	10 2 ± 1 1	4 5 ± 0 5

Values are means ± SE of the mean of alkali metal Li^+, Rb^+ and Cs^+ concentration derived from endogenous, experimentally naive mice, or from exogenously administered LiCl, RbCl or CsCl solutions Alkali metals were injected, 5 0 mEq/kg, IP, once daily for 7 days and the animals were sacrificed 4 hr post terminal treatment Non-measurable (NM) endogneous Li^+ is indicated Each value represents a mean for 4 to 7 independent determinations A pool of 3 mouse brain regions was used for each individual assay accounting for a total of 96 mice

mice (control for endogenous alkali metals group) or to mice pretreated with alkali metals. The latter group received the ET injection 4 hr after termination of a 7 day treatment period with a daily IP injection of CsCl, RbCl or CsCl, 5 mEq/kg. The controls of this treatment group received daily saline injections for 7 days and ET was similarly given 4 hr post the terminal treatment. Animals were sacrificed 3 min after the ET injection, during which time all animals showed loss of their righting reflex, and their brains were removed and were similarly dissected and processed as mentioned above for alkali metal determinations.

In the third set of experiments, the effect of short-term pretreatment with alkali metals on the central depressant action of ET was studied by the evaluation of duration of ET-produced narcosis in the mouse The daily IP injection of LiCl, RbCl or CsCl was instituted at 5 mEq/kg for 7 consecutive days and the controls received saline for the same duration of time. In a separate experiment, related to ET-narcosis, LiCl was injected once at 1, 3, 4, 10, or 12 mEq/kg, IP, 20 min prior to ET testing. Narcosis was produced by a narcotic dose of ET, 5 g/kg, IP Experimental variables which may alter duration of ET-narcosis as measured by duration of loss of righting reflex, were taken into account [15]. In addition, the time expired between ET injection and the loss of the righting reflex was recorded as "onset-time" for ET-narcosis The results were expressed as percent change from control designated as 100%

In the fourth set of experiments, the retention of exogenously administered alkali metals in distinct mouse brain regions was studied as a function of time. Daily IP injections of LiCl, RbCl or CsCl, 5 mEq/kg were made for 7 days and the controls received saline. These solutions were injected into 4 groups of 60 mice each. Each treatment group was divided into 4 subgroups of 15 mice and the animals were sacrificed by decapitation 1, 2, 6, or 12 days after discontinued drug administration. The brains were similarly dissected and processed for alkali metal determinations as mentioned earlier. A pool of 3 mouse brain region served for each individual determination. Likewise, whole blood samples derived from a pool of 3 mice were collected in heparinized tubes. Ice cold trichloroacetic acid was added to the blood specimens, mixed vigorously and centrifuged for 15 min at 10,000×g to obtain the supernatant fluid for the alkali metal determinations

Statistical significance of the results was evaluated by the Students *t*-test for independent means.

RESULTS

The cerebral contents of measurable endogenous alkali metal Li^+, Rb^+ and Cs^+ are summarized in Table 1 and are compared with that obtained from exogenously IP administered LiCl, RbCl or CsCl, 5 mEq/kg/day for 7 days Measurable endogenous Li^+ levels in brain regions studied could not be obtained by the procedure used. Endogenous Rb^+ was readily demonstrable and was found equally distributed throughout the brain with exception of the high levels assayed in the hippocampus, which was not statistically significant. Endogenous Rb^+ concentration assayed was at least 10 fold greater than Cs^+ in all corresponding brain regions. Likewise, endogenous Cs^+ was equally distributed in brain regions studied with a major difference between the hippocampus and the cortex

Table 1 also lists the distribution of exogenously injected alkali metal in identical discrete brain areas of the mouse

The levels assayed were in the following order: $Rb^+ > Cs^+ > Li^+$. Regional brain Rb^+ accumulation was at least 2 and 5 fold greater than Cs^+ and Li^+, respectively. The distribution of regional brain Rb^+ content was in the same order and magnitude with slight decreased uptake by the striatal tissue. Similarly, little variation in distribution of Cs^+ was found and the high hippocampus concentration was not statistically significant. The data in Table 1 also show differences in the capacity of brain regions to accumulate exogenously administered Li^+, Rb^+ and Cs^+ relative to their endogenous content. For example, cerebral cortex, diencephalon, brain-stem and cerebellum accumulated exogenous Rb^+ between 6 to 8 folds over endogenous content compared to a concentration range between 3.8 and 4 5 fold for the striatum and the hippocampus, respectively. The same comparison for Cs^+ indicates an exogenous Cs^+ build-up between 20 to 35 folds over endogenous levels in all brain regions studied with a much greater enrichment occurring in the cortex

Figure 1, upper panel, shows the effect of short-term pretreatment with equal concentration of Li^+, Rb^+ or Cs^+, 5 mEq/kg/day for 7 consecutive days, on the onset of and the duration of ET-produced narcosis in the mouse. The results are expressed as percent change in measured response from saline control. There was a moderate potentiation ($p<0.05$) in time required for the onset of ET-narcosis in Li-pretreated mice compared to marked enhancement by the Rb ($p<0.001$) and the Cs treatment ($p<0.005$). The duration of ET-narcosis was prolonged by LiCl ($p<0$ 05) as contrasted with a reduction of the same by RbCl ($p<0.001$) and by CsCl ($p<0.001$).

Figure 1, lower panel also shows that a single dose of LiCl as high as 10 or 12 mEq/kg, IP, profoundly enhanced ET-narcosis from saline control by 2 and 2.4 fold ($p<0.01$), respectively.

Table 2 summarizes the effect of a narcotic IP dosage of ET, 5 g/kg, on mouse brain regional content of endogenous and of exogenously administered alkali metals. The ET injection was given 4 hr after terminal treatment with LiCl, RbCl or CsCl, 5 mEq/kg/day for 7 days, and the animals, including saline controls, were sacrificed 3 min thereafter. This coincided with approximate onset time of ET-narcosis Ethanol exerted a decrease in Li^+ concentration in brain stem and cerebellum of animals pretreated with LiCl while endogenous Li^+ levels were not measurable to evaluate the ET effect. Ethanol reduced both endogenous and exogenous ($p<0.02$) Rb^+ concentration in the hippocampus. There was a moderate, but not statistically significant, rise in endogenous striatal Rb^+. Little changes were noted in Rb^+ levels in the remainder of the brain regions studied. Conversely, the ET-treatment gave rise to endogenous Cs^+ in all brain regions which was not demonstrable in Cs-pretreated mice with exception of that measured in the striatum.

Table 3 shows the whole blood and cerebral disposition of exogenously administered alkali metal after discontinued administration of equal daily dosage of LiCl, RbCl or CsCl, 5 mEq/kg, IP for 7 consecutive days, as a function of time. The results are expressed as percent of alkali metals concentration relative to that assayed for the 24 hr period post drug treatment No measurable Li^+ could be determined in brain regions examined at 2, 6, or 12 days after drug withdrawal except for that found in the cortex 2 days post drug cessation. Both Rb^+ and Cs^+ were measurable throughout the 12 day testing period. All brain regions studied showed similar retention of exogenously given Rb^+ and Cs^+ which declined progressively as a function of time. However, the disappearances of Rb^+ from the brain was faster than that of Cs^+ This

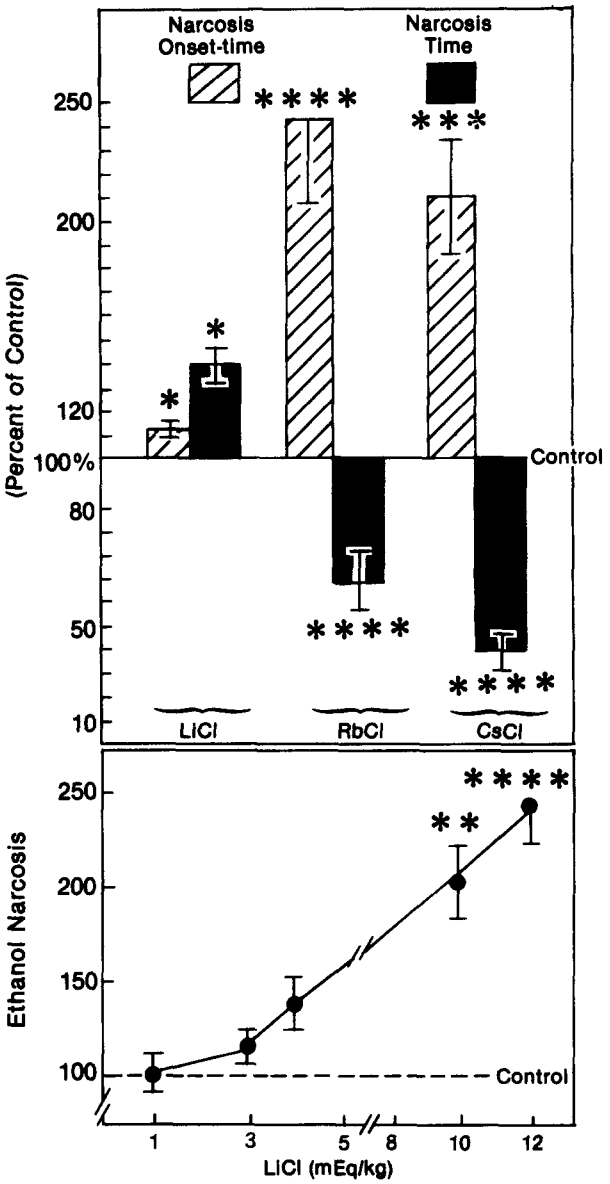

FIG 1 The effect of selected alkali metal salts on ethanol-mediated CNS-depression in the male mouse Animals were injected LiCl, RbCl or CsCl, 5 0 mEq/kg, IP, once daily for 7 days and the controls received saline. Ethanol (ET) narcosis was produced by IP injection of a single narcotic dosage of 25% ET given 20 min post terminal alkali metal dosage Time elapsed from ET injection to loss of righting reflex and its regaining by the animal are expressed as "narcosis onset time" and duration of narcosis time, respectively The lower panel shows the effect of single dosage of LiCl on duration of ET-narcosis time The LiCl was injected once 20 min preceding the ET dosage, 5 g/kg IP ****$p<0.001$, ***$p<0$ 005, **$p<0$ 01; *$p<0$ 05

was shown by at least 50% decrease of Rb^+ content compared to little to moderate increase in regional brain Cs^+ levels, occurring 6 days post drug termination. Likewise, an average range between 7% to 14% and between 36% to 58% of initial mean 24 hr value were determined for Rb^+ and Cs^+ 12 days post drug discontinuation, respectively. The whole blood levels of Rb^+ tended to reflect that of brain regions more than that of Cs^+.

TABLE 2

EFFECT OF A SINGLE NARCOTIC DOSAGE OF ETHANOL ON ENDOGENOUS AND EXOGENOUSLY ADMINISTERED ALKALI METALS IN DISTINCT MOUSE BRAIN REGIONS

Brain Region	Source of Alkali Metal	Perecent Change of Alkali Metal Ions Concentration of Controls		
		Li^+	Rb^+	Cs^+
Cortex	Endogenous	NM	92	225
	Exogenous	91	95	103
Striatum	Endogenous	NM	175	230
	Exogenous	82	99	198
Hippocampus	Endogenous	NM	71	179
	Exogenous	104	77*	103
Diencephalon	Endogenous	NM	128	150
	Exogenous	108	84	97
Brainstem	Endogenous	NM	113	125
	Exogenous	64	91	89
Cerebellum	Endogenous	NM	109	239†
	Exogenous	70	85	105

Values represent percent change in mouse brain region contents of endogenous and of exogenously administered LiCl, RbCl or CsCl, 5 mEq/kg, IP, once daily for 7 days, from corresponding mean control value, designated as 100% A 25% (w/v) ethanol dosage, 5 g/kg, was administered IP 4 hr post terminal treatment and animals were sacrificed 3 min after ethanol injection Values derive from 5 to 7 independent determinations using a pool of 3 mouse brain regions for each individual assay A total of 144 mice, including controls, were used

*$p<0.025$, †$p<0.02$

TABLE 3

THE RETENTION OF EXOGENOUSLY ADMINISTERED ALKALI METALS AS A FUNCTION OF TIME IN BRAIN REGIONS AND WHOLE BLOOD OF THE MOUSE

Brain		Percent of Alkali Metals Concentration Relative to Initial 24 hr						
		Li^+	Rb^+			Cs^+		
	Days	2	2	6	12	2	6	12
Cortex		12 ± 2	97 ± 5	39 ± 7	7 ± 0 4	116 ± 21	117 ± 14	51 ± 13
Striatum		NM	86 ± 6	41 ± 7	11 ± 0 9	114 ± 22	103 ± 18	36 ± 10
Hippocampus		NM	81 ± 6	46 ± 7	13 ± 1 0	129 ± 19	175 ± 35	62 ± 16
Diencephalon		NM	82 ± 15	44 ± 6	11 ± 0 7	115 ± 23	149 ± 29	47 ± 14
Brain-Stem		NM	96 ± 8	38 ± 8	9 ± 0 5	115 ± 22	160 ± 32	56 ± 18
Cerebellum		NM	94 ± 4	49 ± 7	14 ± 0 8	124 ± 25	180 ± 31	58 ± 16
Whole Blood		31 ± 11	99 ± 4	55 ± 7	8 ± 0 2	149 ± 31	105 ± 28	31 ± 9 6

Animals were injected LiCl, RbCl or CsCl, 5 mEq/kg/day, for 7 days and were sacrificed 1, 2, 6 or 12 days post terminal treatment Endogenous Rb^+ and Cs^+ concentration of controls were subtracted from the corresponding values of treated mice Values are means ± SE of mean percent of alkali metal levels relative to corresponding initial mean determined 24 hr after drug cessation Nonmeasurable (NM) Li^+ is also indicated Values derive from 5 independent determinations A pool of 3 brain regions served for each individual assay A total of 240 mice were used

DISCUSSION

The present study shows the presence of measurable endogenous concentration of Rb^+ and Cs^+ in specific brain regions compared to traces of Li^+. The cerebral Rb^+ levels assayed exceeded that of Cs^+ by several folds and the hippocampus contained the largest amounts of both. This suggests a possible role for these ions in cerebral activity in general and that of the hippocampus in particular, which is involved in a variety of emotional and motivational aspects of behavior and also in learning and memory. Interestingly, Rb salts were used in clinical trials for management of the depressive illness [4–6, 12, 24] and likewise CsCl has been shown to possess antidepressant property [2, 20, 21]. Therefore, it appears likely that the hippocampus may play a role in the cerebral action of Rb^+ and Cs^+. Short-term administration of equal mEq concentration of alkali metals resulted in greater brain accumulation of Rb^+ than Cs^+ with minimal Li^+ level. This indicates that Rb^+ penetrated the blood brain barrier at greater rate than Cs^+ and/or is faster absorbed from the GI-tract. However, evaluation of the capacity of distinct brain regions to store exogenously administered alkali-metals studied relative to their endogenous content showed greater affinity for Cs^+ build-up over Rb^+ particularly in the cortex.

The results of ET-narcosis study is consistant with that previously reported [16] indicating augmentation of the depressant action of ET by Li^+ as contrasted with that of Rb [1] and Cs-evoked [16] antagonism which persisted for as long as 5 days subsequent discontinued administration of similar dose regimens of alkali metals. It appears that both Rb and Cs salts may be beneficial for certain alcoholic patients especially these suffering from underlying affective components, which can prevail as high as 12% to 20% [11]. In addition, both these elements are potential modifier of depressive behavior [12,13] and cause aversion to ET preference in the rat [18,20]. This suggests certain potential for these salts in the management of such a "disease" with diversified and incomplete defined ethiology as alcoholism.

In this study, a massive narcotic dose of ET exerted different effects on the levels of endogenous and exogenously given alkali metals depending on the element and the brain region studied. For example, ET-reduced Li^+ concentration in the cerebellum which is involved in maintaining equilibrium and in modulating performance of voluntary movement. Moreover, the hippocampal high content of endogenous Rb^+ was markedly reduced by ET as was exogenous Rb^+ levels. This suggests a role for this brain region content of Rb^+ for the ET effect monitored. It remains to be determined, however, if this ET-effect is a biological concomitant to ET narcosis or is a causative factor for the elicited action observed. The present experiments, also show a rise in endogenous brain Cs^+ occurring shortly after a massive dose of ET particularly in the cerebellum. However, exogenously administered Cs^+ was less affected by ET with exception of the striatal region of the brain which continued to show high levels of Cs^+. Accordingly, it appears that ET may alter membrane permeability to allow for rapid entry of Cs^+ in the striatal tissue and this may conceivably contribute to CNS reactivity of motor function resulting in shorter duration of ET-narcosis and of rapid regaining of righting reflex observed.

The disappearance rate of exogenously injected alkali metals from distinct mouse brain regions differed according to the element and to the time of measurement subsequent drug-withdrawal. This was demonstrated by the presence of small amounts of Li^+ which was only measurable in cerebral cortex 48 hr of the LiCl treatment compared to little changes in Rb^+ and Cs^+ content in all brain regions for the same time period. The subsequent disappearance of exogenously administered Rb^+ and Cs^+ from the mouse brain followed different patterns showing the presence of approximately 50% of Rb^+ and of Cs^+, from initial 24 hr levels at 6 and 12 days post drug cessation. This is consistent with reports obtained for ^{137}Cs in man showing greater $T^1/_2$ for Cs^+ than Rb^+ obtained from body fluids data, i.e., mainly urine [3, 9, 10]. Accordingly, the pharmacokinetics of the present study demonstrate both rapid absorption and penetration of alkali metal tested into the mouse brain and indicates a prolonged cerebral retention time for Cs^+ over Rb^+ or Li^+. The whole blood content of Rb^+ measured between 2 and 12 days of drug termination showed a trend similar to that determined for brain regions studied which may be a better reflection of cerebral Rb^+ content.

The results presented on cerebral pharmacokinetics of endogenous and exogenously administered selected alkali metals may have some paradoxical implications For example, the exposure of industrial workers to Cs salts may result in toxic manifestation due to rapid absorption of Cs in GI-tract [7,8], its distribution in soft tissue, bone and muscle [7,8] and in the brain as demonstrated by this study. Considering the long $T^1/_2$ of Cs^+ then this may give rise to wide adverse reactions until its disposition from the body is attained. Conversely, the presence of Cs in the muscle and in the brain may be of therapeutic value in management of certain diseases of motor function and affect as has been earlier suggested [17,21]. Analogenously, the use of Cs salts as adjuvant to certain drugs acting on motor function and the psyche may be beneficial provided a safe application method for Cs salts can be established. The long $T^1/_2$ of cerebral Cs^+, if occurred in man, may be useful in brain cancer chemotherapy, where Cs salts may exert a yet undefined antitumor activity

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