ELSEVIER

European Journal of Pharmacology 285 (1995) 255–260

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Effects of a selective α_2-adrenoceptor antagonist, atipamezole, on hypothalamic histamine and noradrenaline release in vivo

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Received 23 March 1995; revised 28 June 1995; accepted 4 July 1995

Abstract

In vivo microdialysis was used to study the effects of a potent and selective α_2-adrenoceptor antagonist, atipamezole, on histamine and noradrenaline release from the medial hypothalamus in anesthetized rats. Local perfusion with atipamezole via the microdialysis probe increased histamine release significantly and dose-dependently. However, the effect of systemic administration of atipamezole (1 mg/kg) was opposite: it significantly decreased histamine release. Local and systemic administration of atipamezole produced an approx. 2-fold increase in noradrenaline release. To study the modulatory effect of noradrenergic neurons on histamine release, noradrenaline synthesis was inhibited with α-methyl-*p*-tyrosine. In the microdialysis experiment, rats that received α-methyl-*p*-tyrosine exhibited no decrease, but rather a slight increase in histamine release in response to systemic atipamezole administration. These results show clearly that atipamezole enhances noradrenaline release in vivo from rat hypothalamus and its effects on histamine release are dependent on the route of drug administration.

Keywords: Histamine; Noradrenaline; Atipamezole; α_2-Adrenoceptor antagonist; Microdialysis, in vivo; Hypothalamus

1. Introduction

Histamine acts as a neurotransmitter/modulator in the mammalian brain and has been implicated in many physiological functions, including food intake, arousal state, learning and memory, thermoregulation, cardiovascular and neuroendocrine control (for reviews, see Schwartz et al., 1991; Wada et al., 1991; Onodera et al., 1994). In the rat brain, histaminergic cell bodies are located in the tuberomamillary nuclei of the posterior hypothalamus projecting fibers to almost all parts of the brain. The highest density of histaminergic fibers are found in the hypothalamus (Panula et al., 1989).

The release and synthesis of histamine are regulated by histamine H_3 autoreceptors (Arrang et al., 1983; Prast et al., 1994). In addition to autoreceptors, various heteroreceptors appear to participate in the regulation of hypothalamic histamine release in vivo. Glutamate can enhance histamine release through NMDA receptors located on the histaminergic nerve terminals (Okakura et al., 1992). In addition, studies using the push-pull technique showed that noradrenergic, dopaminergic and cholinergic neurons are able to modulate histamine release in the hypothalamus of freely moving rats (Prast et al., 1991, 1993, 1994). Cumming et al. (1991) found that yohimbine, an α_2-adrenoceptor antagonist, increased the extracellular histamine content in the bed nucleus of stria terminalis in conscious rats. Furthermore, experiments with rat brain slice preparations revealed that α_2-adrenoceptors control histamine release also in the cortex (Hill and Straw, 1988; Gulat-Marney et al., 1989).

Atipamezole is a potent and specific α_2-adrenoceptor antagonist (Scheinin et al., 1988). It has a high affinity for α_2-adrenoceptors ($K_i = 1.5$ nM) and it is 200–300 times more selective for α_2-adrenoceptors than yohimbine or idazoxan (Virtanen et al., 1989). Atipamezole is used as an arousal agent after anesthesia with α_2-adrenoceptor agonists in veterinary practice. In behavioral studies, atipamezole has been proposed to have therapeutic potential in cognitive disorders (Sirviö et al., 1993), sexual dysfunction (Linnankoski et al., 1992) as well as inhibiting ethanol-induced behaviors (Durcan et al., 1991; Idänpään-Heikkilä et al.,

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SSDI 0014-2999(95)00410-6

1995), though these hypotheses have still to be tested in clinical situations. α_2-Adrenoceptor antagonists have been shown to increase noradrenaline release in the rat brain in vivo (Itoh et al., 1990; Van Veldhuizen et al., 1993). Atipamezole caused a rapid and dose-dependent increase (ED_{50} values 1–3 mg/kg s.c.) in the central turnover of noradrenaline, as measured from rat brain homogenates (Scheinin et al., 1988). However, no direct effects of atipamezole on noradrenaline release in vivo have been documented. Since it has been postulated that α_2-adrenoceptors have a modulatory influence on histamine release, it was also of interest to study the effect of atipamezole on histamine release in vivo. In the present study an in vivo microdialysis method was used to examine the possible effects of systemic and local administration of atipamezole on histamine release from the hypothalamus of anesthetized rats. The modulatory effect of noradrenergic neurons on histamine release was studied by inhibition of noradrenaline synthesis. In addition, noradrenaline release from medial hypothalamus was determined.

2. Materials and methods

2.1. Brain microdialysis

Male Wistar rats (300–400 g) were anesthetized with chloral hydrate (400 mg/kg i.p.), with supplementary doses administered as necessary to maintain anesthesia. The body temperature was monitored by a rectal thermometer and was maintained constant throughout the experiment with a heating lamp. A microdialysis probe (membrane length 2 mm, CMA/12, Carnegie, Sweden) was stereotaxically implanted into the medial hypothalamus. The coordinates were AP: −2.3, L: 0.8, V: 10.2 relative to bregma and skull surface, according to Paxinos and Watson (1986). The probe was perfused at a rate of 2 μl/min with artificial cerebrospinal fluid (aCSF), composed of 138 mM NaCl, 5 mM KCl, 1 mM $MgCl_2$, 1.1 mM $CaCl_2$, pH 7.4 adjusted with 5% CO_2/95% O_2. In vitro recovery for histamine was 19 ± 1% (mean ± S.E.M., $n = 10$). Brain perfusate was collected every 30 min using a refrigerated fraction collector (CMA/170, Carnegie, Sweden). Basal samples were collected for 90–120 min before drug treatment. Atipamezole (25 or 50 μM) was either infused via the microdialysis probe for 60 min or given subcutaneously (1 or 10 mg/kg). Control rats received saline s.c. The effects of atipamezole (1 or 10 mg/kg s.c.) on histamine release were studied also after extensive inhibition of noradrenaline synthesis. At the end of each experiment, the brain was removed for histological verification of the probe location.

2.2. Noradrenaline depletion with α-methyl-p-tyrosine

α-Methyl-*p*-tyrosine (250 mg/kg i.p.) was administered to the rats 16 h prior to microdialysis experiments. To assess the extent of noradrenaline depletion in brain, a separate experiment was performed. A group of rats received α-methyl-*p*-tyrosine at the same dose and time schedule as the rats in the microdialysis experiments; control rats receiving saline. These rats were decapitated 16 h later and brains were removed for high performance liquid chromatographic (HPLC) analysis of noradrenaline.

2.3. Drugs

Atipamezole hydrochloride (Orion-Farmos Group, Turku, Finland) was dissolved in 0.9% NaCl when administered s.c. (1 ml/kg) and in the aCSF prior to infusion through the microdialysis probe.

α-Methyl-DL-*p*-tyrosine methyl ester hydrochloride (Sigma, St. Louis, USA) was dissolved in 0.9% NaCl prior to i.p. injection (0.5 ml/kg). All reagents used in the chemical assays were of HPLC analytical grade.

2.4. Histamine and noradrenaline analysis

For histamine analysis, perfusate was collected in microtubes containing 10 μl of 20% $HClO_4$. Samples were analyzed immediately by HPLC using cation exchange column, postcolumn derivatization and fluorescent detection, as described by Yamatodani et al. (1985) with slight modifications (Yamatodani, 1991). The detection limit for histamine was approx. 10 fmol/injection.

The noradrenaline content of the microdialysis samples was determined using HPLC with electrochemical detection by the method of Itoh et al. (1990), with slight modifications. In brief, the perfusate was collected into microtubes containing 20 μl of 0.1 M $HClO_4$ and stored at −80°C until analysis. Samples were transferred into new tubes containing 10 mg of activated alumina. Tris buffer (200 μl, 0.5 M, pH 8.0) and internal standard, 3,4-dihydroxybenzylamine, were added and the mixture was shaken for 1 min to allow noradrenaline absorption into the alumina. The alumina was washed twice with 1 ml of distilled water, finally 100 μl of acetic acid (2%) was added and the tubes were vortexed for 1 min. After centrifugation, 70 μl of supernatant was injected into the HPLC. The mobile phase (0.1 M acetic acid, 0.1 M citric acid, 150 mg/l octyl sodium sulphate and 10% methanol) was delivered at a flow rate of 0.9 ml/min by an LKB 2150 pump (Bromma, Sweden) onto an RP-18 column (250 × 4.6 mm, 5 μm, Ultrasphere, Beckman). Detection was carried out with a coulometric detector (ESA Coulochem, model 5100 A) with dual electrode analyti-

cal cell. The conditioning cell was set at +0.17 V and electrode 1 at +0.35 V.

The noradrenaline and dopamine content of the rat brains were determined by the method of Mefford (1981), by homogenizing the brains in 4 vols. 0.1 N $HClO_4$. The homogenate was centrifuged and 200 μl extracted through alumina, eluted with 200 μl 0.1 N $HClO_4$ and approximately 15 μl injected into the HPLC as described above. The noradrenaline metabolite, 3-methoxy-4-hydroxyphenyl-glycol sulphate (MHPG-SO_4) was determined fluorometrically from the brain homogenates by the method of Kohno et al. (1979).

2.5. Statistics

The data are expressed as percentages of the averaged basal release of two consecutive samples prior to drug treatment. The effects of the drugs were assessed by one-way analysis of variance (ANOVA) followed by Dunnett's *t*-test.

3. Results

The mean basal release of histamine from the medial hypothalamus was 90 ± 5 fmol/30 min (mean ± S.E.M., $n = 15$). Following probe implantation, histamine release in individual rats remained constant throughout the experiment.

Local perfusion (1 h) with atipamezole (25 or 50 μM) increased histamine release up to 120 and 157%, respectively, of the basal release. At a concentration of 50 μM, histamine release increased significantly, reaching maximal output 60 min after the start of drug perfusion ($P < 0.05$) (Fig. 1). When atipamezole was injected systemically (1 or 10 mg/kg s.c.), the effect of the drug was opposite: histamine release clearly decreased compared to the saline-treated control rats. The decrease (40%) was significant at a dose of 1 mg/kg at 60 min after injection of atipamezole ($P < 0.05$) (Fig. 2).

The noradrenaline release from the medial hypothalamus was fairly stable 90–120 min after the probe implantation. The mean basal release of noradrenaline was 53 ± 7 fmol/30 min (mean ± S.E.M., $n = 10$). Systemic administration of atipamezole (1 mg/kg s.c.) produced a rapid and long-lasting increase in the noradrenaline release compared to the control rats ($P < 0.05$) (Fig. 3A). Local perfusion (1 h) with atipamezole (50 μM) increased noradrenaline release from the medial hypothalamus to a similar extent as systemic injection. However, the increase was not significant compared to the basal values due to the large variation in the individual responses between the animals. In addition, the elevation of the extracellular noradrenaline took place 30 min later as compared to the systemic administration (Fig. 3B).

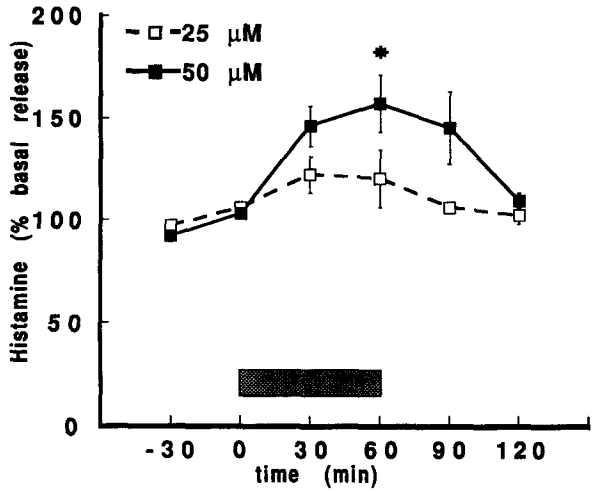

Fig. 1. The effect of local perfusion (60 min) with atipamezole (25 and 50 μM) on histamine release from the medial hypothalamus. The results are expressed as percentages of the basal release, means ± S.E.M., $n = 4–6$, * $P < 0.05$ vs. pretreatment value.

Following α-methyl-*p*-tyrosine treatment, the brain noradrenaline content was significantly reduced by 94% ($P < 0.001$), brain dopamine by 92% ($P < 0.001$) and MHPG-SO_4 concentrations by 79% ($P < 0.001$). In the microdialysis experiment, rats which had received α-methyl-*p*-tyrosine did not exhibit any decrease, but rather a slight increase in histamine release in response to systemic atipamezole administration (Fig. 4). No differences were found in the basal histamine release from medial hypothalamus between normal and α-methyl-*p*-tyrosine-treated rats (90 ± 5 vs. 88 ± 6 fmol/30 min, respectively).

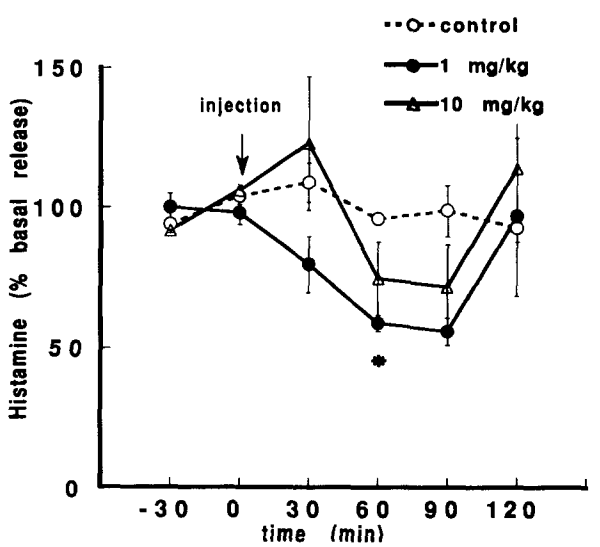

Fig. 2. The effect of systemic injection of atipamezole (1 and 10 mg/kg s.c.) or saline on histamine release from the medial hypothalamus. The results are expressed as percentages of the basal release, means ± S.E.M., $n = 4–5$, * $P < 0.05$.

4. Discussion

The present study demonstrates that atipamezole, a potent and selective α_2-adrenoceptor antagonist, increased noradrenaline release from the medial hypothalamus in vivo and also modulated histamine release from the same brain region. Furthermore, the modulatory effect of this α_2-adrenoceptor antagonist on histamine release was dependent on the route of drug administration: atipamezole administered via the microdialysis probe increased histamine release whereas systemic injection decreased it.

The average output of noradrenaline in our study was 9 pg/30 min. This result is in the range of other studies, for example the average baseline level of noradrenaline from the paraventricular hypothalamus was 13.3 pg/sample (Stanley et al., 1989) or 3.8 pg/30 min from the medial hypothalamus (Itoh et al., 1990). The values reported for basal noradrenaline output vary markedly between laboratories depending on the experimental conditions, including anesthesia and brain region. α_2-Adrenoceptors control noradrenaline release via presynaptic α_2-autoreceptor activation: noradrenaline inhibits its own release and α_2-adrenoceptor agonists mimic the effects of endogenous noradrenaline, whereas α_2-adrenoceptor antagonists increase the release of noradrenaline by blocking these autoreceptors. Previous reports have shown that the selective α_2-adrenoceptor antagonist, idazoxan, elicited a marked increase in noradrenaline release from the hypothalamus, cortex and hippocampus (Routledge and Marsden, 1987; Dennis et al., 1987; Thomas and Holman, 1991). Atipamezole is a more specific α_2-adrenoceptor antagonist than idazoxan. It does not bind to 5-HT_{1A} receptors, unlike idazoxan and yohimbine which both have affinities for this receptor in the nanomolar range (Winter and Rabin, 1992). In the present study, atipamezole (1 mg/kg s.c.) rapidly and significantly increased noradrenaline release from the medial hypothalamus, demonstrating that atipamezole is a potent antagonist at the central α_2-adrenoceptors also in vivo. Moreover, local perfusion of atipamezole (50 μM) enhanced noradrenaline release indicating that atipamezole directly blocked the presynaptic and/or postsynaptic α_2-adrenoceptors located on the noradrenergic nerve terminals of the medial hypothalamus. However, the release was not so rapid and variation between the responses was bigger than that observed after systemic administration. This result resembles the effects of idazoxan on hippocampus: locally administered idazoxan was able to increase noradrena-

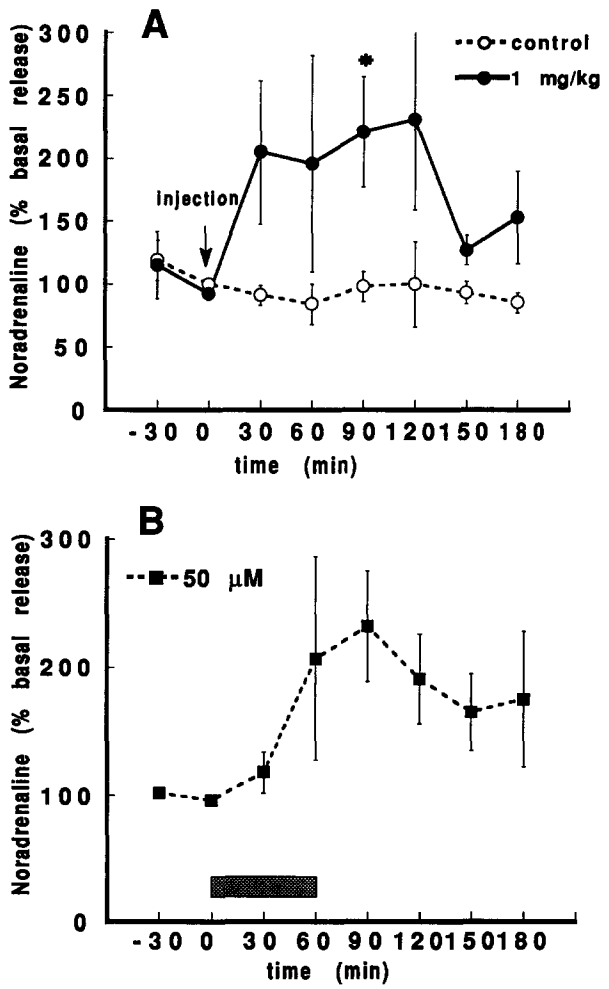

Fig. 3. (A) The effect of systemic injection of atipamezole (1 mg/kg s.c.) or saline on noradrenaline release from the medial hypothalamus. The results are expressed as percentages of the basal release, means ± S.E.M., $n = 4$, * $P < 0.05$. (B) Effect of local perfusion (60 min) with atipamezole (50 μM) on noradrenaline release, means ± S.E.M., $n = 7$.

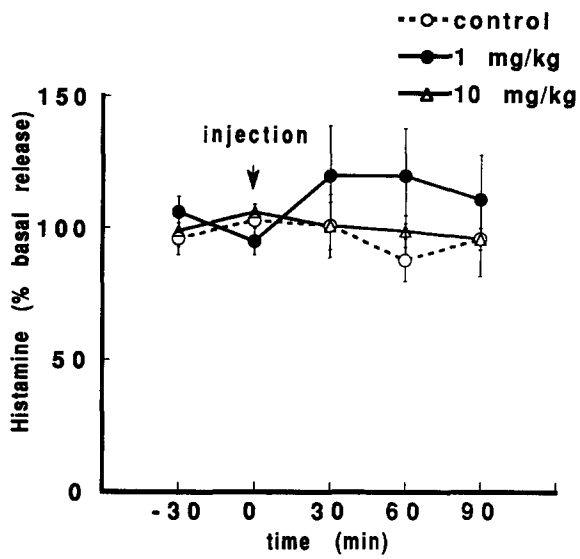

Fig. 4. The effect of systemic injection of atipamezole (1 and 10 mg/kg s.c.) or saline on histamine release from the medial hypothalamus after α-methyl-p-tyrosine treatment. The results are expressed as percentages of the basal release, means ± S.E.M., $n = 4$–5.

line release but less than via the systemic route (Thomas and Holman, 1991). The doses of atipamezole that were used to study its effects on noradrenaline release were based on its modulatory action on histamine output.

In the present study, basal histamine levels in the medial hypothalamus were similar to those reported by other groups using anesthetized rats (Itoh et al., 1991; Okakura et al., 1992). Previous in vivo microdialysis studies have clearly demonstrated the neuronal origin of histamine release in the rat hypothalamus (Mochizuki et al., 1991; Itoh et al., 1991). In the rat brain, histamine exists also in the non-neuronal pool of mast cells. However, mast cells are found almost exclusively within the thalamus and are virtually absent from the hypothalamus (Hough et al., 1984).

Previous in vitro studies using cortical slices have shown that histamine release was regulated by α_2-adrenoceptors. Hill and Straw (1988) showed that noradrenaline and clonidine, an α_2-adrenoceptor agonist, inhibited the K^+-evoked release of [^{3}H]histamine, this effect being antagonized by the α_2-adrenoceptor antagonists, idazoxan and yohimbine. Since yohimbine failed to increase [^{3}H]histamine release in vitro and [^{3}H]histamine formation in vivo, it was concluded that adrenoceptors are not activated by endogenous noradrenaline released under basal conditions (Gulat-Marney et al., 1989). However, in an in vivo study using the push-pull method, superfusion with yohimbine or idazoxan enhanced histamine release from the posterior hypothalamus of conscious rats whereas noradrenaline and clonidine suppressed it (Prast et al., 1991). In addition, we found that atipamezole increased histamine release, when perfused into the hypothalamus. Collectively these data suggest that locally administered α_2-adrenoceptor antagonists stimulate histamine release from the rat hypothalamus.

In the microdialysis study of Cumming et al. (1991), systemic injection of yohimbine increased extracellular histamine in the bed nucleus of the stria terminalis in freely moving rats. Interestingly, systemic injection of a selective α_2-adrenoceptor antagonist caused a significant decrease in hypothalamic histamine release in the present study. These opposite results may reflect differences in the brain region studied, selectivity of the antagonists and/or in the distribution of α_2-adrenoceptors.

The decrease in histamine release after systemic administration of atipamezole could be explained by simultaneous increase in the noradrenaline output, as described above. The released noradrenaline would act in turn as an α_2-adrenoceptor agonist activating the α_2-heteroreceptors located on histaminergic cell bodies. Systemic injection of the α_2-adrenoceptor antagonist inhibits the α_2-autoreceptors located on the noradrenergic cell bodies of brain stem enhancing the noradrenaline release in the terminal fields, including the hypothalamus. Anatomical evidence suggested that the histaminergic cell clusters received noradrenergic input from the brain stem (Ericson et al., 1989). Using quantitative ex vivo autoradiography, it was found that [^{3}H]atipamezole accumulated rapidly in the brain, and its distribution paralleled that of α_2-adrenoceptors. High amounts of [^{3}H]atipamezole were found in several hypothalamic nuclei (Biegon et al., 1992). Administration of an α_2-adrenoceptor antagonist will lead to competition between endogenously released noradrenaline and the antagonist molecules for the occupancy of the α_2-adrenergic heteroreceptors. In the present study, both local and systemic administration of atipamezole enhanced noradrenaline release with similar magnitude. Therefore the ultimate effect on histamine release may depend on the local concentration of the antagonist. The atipamezole concentration would expected to be lower after systemic than local administration thus allowing noradrenergic dominance and inhibition of the histamine release.

To test the modulatory action of endogenous noradrenaline, we inhibited noradrenaline biosynthesis with α-methyl-*p*-tyrosine. This treatment reduced brain noradrenaline content by 94% and its main metabolite by 79%, indicating a marked reduction in the noradrenaline synthesis and release. In vivo microdialysis experiments following noradrenaline depletion revealed, indeed, that systemic injection of atipamezole was no longer able to reduce histamine release, instead it caused a slight increase. These results further confirm that endogenous noradrenaline inhibits the histamine release via α_2-adrenoceptors.

Systemic injection of atipamezole, will affect not only the nerve terminals but also the cell bodies. On the other hand, the effects of locally applied drug are restricted to the region of the nerve terminals of the medial hypothalamus, without having effects on the noradrenergic or histaminergic cell bodies.

In conclusion, atipamezole is a potent releaser of noradrenaline in vivo and modulates also histamine release from the rat hypothalamus. Furthermore, the effects of atipamezole on histamine release seems to be dependent on the route of drug administration. Such interactions between these two neurotransmitter systems may have important implications in the therapeutic evaluation of novel selective α_2-adrenoceptor antagonists.

Acknowledgements

This study was supported by the Elli Turunen fund of the Finnish Cultural Foundation and the Academy of Finland, Medical Research Council.

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