Cytokine 108 (2018) 71–81

Contents lists available at ScienceDirect

Cytokine

journal homepage: www.elsevier.com/locate/cytokine

Role of selective blocking of bradykinin B1 receptor in attenuating immune liver injury in trichloroethylene-sensitized mice

Jiaxiang Zhang[a,b,1], Na Li[b,1], Ling Yang[a,1], Dandan Zang[b], Peng Yang[b], Hui Wang[c], Tong Shen[b,*], Qi-xing Zhu[a,*]

[a] Institute of Dermatology, Anhui Medical University, Hefei, Anhui, China
[b] Department of Occupational Health and Environment Health, School of Public Health, Anhui Medical University, Hefei, Anhui, China
[c] Department of Nutrition, Chaohu Hospital of Anhui Medical University, Hefei, Anhui, China

ARTICLE INFO

Keywords:
Trichloroethylene
Bradykinin B1 receptor
Liver injury
Mitogen-activated protein kinases
Kupffer cell

ABSTRACT

Trichloroethylene (TCE) is able to induce trichloroethylene hypersensitivity syndrome (THS) with multi-system immune injuries. In our previous study, we found kallikrein-kinin system (KKS) activation, including the bradykinin B1 receptor (B1R), which contributed to immune organ injury in TCE sensitized mice. However, the mechanism of B1R mediating immune dysfunction is not clarified. The present study initiates to investigate the potential mechanism of B1R on liver injury. We establish a TCE sensitized BALB/c mouse model to explore the mechanism with or without a B1R inhibitor R715. We found B1R expression was increased in TCE sensitization-positive mice. As expect, hepatocyte intracellular organelles and mitochondria disappeared, glycogen particles reduced significantly as well in TCE sensitization-positive mice via the transmission electron microscopic examination, meanwhile, R715 alleviated the deteriorate above. The blockade of B1R resulted in a significant decreased p-ERK1/2 and increased p-AKT expression. The expression of CD68 kupffer cell and its relative cytokine, including IL-6 and TNF-α, increased in TCE sensitization-positive mice and decreased in R715 pretreatment TCE sensitization-positive mice. Together, the results demonstrate B1R plays a key role in ERK/MAPK and PI3K/AKT signal pathway activation and inflammation cytokine expression in immune liver injury induced by TCE. B1R exerts a pivotal role in the development of TCE induced liver injury.

1. Introduction

1,1,2-Trichloroethylene (TCE), CAS No. 79-01-6, a nonflammable, volatile, chlorinated solvent, has been widely used to degrease metal part and extract chemicals [1,2]. TCE became intensively commercial production in Germany and the United States in the 1920s, then the scale of the production reached hundreds and thousands of tons every year between the 1950s and 1970s [3]. Because of the widespread consumption, TCE came into frequently detected xenobiotics in groundwater [4], even in drinking water and food in certain areas now [5]. The International Agency for Research on Cancer (IARC) reclassified trichloroethylene as group I carcinogen in 2012 [6]. Exposed to TCE was associating with several adverse health in human and animals, such as sever skin lesions, immune-related liver and renal injury [7–9]. The multi system injuries induce by TCE were defined as "occupational dermatitis medicamentosa-like of TCE (ODMLT)" in China, also called TCE hypersensitivity syndrome (THS), which was characterized by fever, generalized rash, liver dysfunction and superficial lymphadenopathy [10]. Takaki encountered a 27-year-old man who died of acute liver failure probably due to trichloroethylene abuse [11]. However the mechanism of the liver failure did not understand yet. Many clinical data suggested type IV allergic reactions or delayed type hypersensitivity reactions playing an important role in THS [12]. However more and more evidences revealed type IV allergic reactions cannot fully explain the multi-organ injuries induced by TCE, especially in immune liver injury [13]. In our previous studies, we reported that complement system and kallikrein-kinin system (KKS) activated in TCE-sensitized animals [13–15]. KKS was an important complex endogenous enzyme system which was implicated in multiple pathological states [16,17]. An enormous amount of data had been published about the KKS which was an important player but still poorly understood and underestimated in many diseases recently [18]. The KKS activation process was able to brief that plasma kallikrein digested high-molecular-weight kininogen (HK) to liberate a biologically active peptide,

* Corresponding authors at: Institute of Dermatology, Anhui Medical University, Hefei, Anhui, China (Q. Zhu). Department of Occupational Health and Environment Health, School of Public Health, Anhui Medical University, Hefei, Anhui, China (T. Shen).
E-mail addresses: shentong@ahmu.edu.cn (T. Shen), zqxing@yeah.net (Q.-x. Zhu).
[1] Co-first author: These authors contributed equally to this article.

https://doi.org/10.1016/j.cyto.2018.03.024
Received 27 October 2017; Received in revised form 2 March 2018; Accepted 19 March 2018
Available online 27 March 2018
1043-4666/

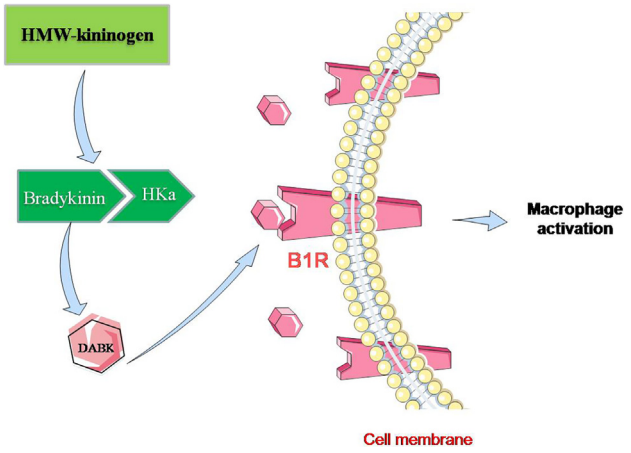

Fig. 1. Schematic representation of signaling pathways activated by B1R (des-Arg^9-BK). HMW-kininogen, high-molecular-weight kininogen; DABK, des-Arg^9-BK; B1R, Bradykinin B1 Receptor.

called bradykinin (BK). Then BK removed the C-terminal arginine residue, produced desArg^9-bradykinin (DABK) which showed proinflammatory activity [19,20]. DABK and BK acted their activity by two G-protein-coupled receptors, the bradykinin B1 receptor (B1R) and bradykinin B2 receptor (B2R) [19]. B2R was found in healthy tissues commonly in contrast to B1R which was not constitutively expressed at significant levels in normal tissues [21]. B1R was selectively expressed during the host inflammatory response. Activation of B1R by its endogenous ligand (DABK in rodents and Lys-DABK in humans) produced a proinflammatory profile similar to B2R activation, and characterized by a stimulation of inflammatory cell accumulation [22] (Fig. 1). In our previous studies, we found B1R expression was increased and took part in an important role in immune injury induced by TCE, but the potential mechanism was not revealed yet [15,23].

It has been suggested that B1R induced many signaling pathways activation including the mitogen-activated protein kinases (MAPK) and phosphoinositide 3-kinase (PI3K)/Akt pathways [24–26]. MAPK takes part in a number of signaling events which play an important role in inflammatory response. MAPK pathway includes three major subfamilies: the extracellular signal-regulated kinase (ERK), p38 and Jun N-terminal kinase (JNK) subfamilies [27]. It has been shown that Toll like receptor (TLR)-induced MAPK activation and cytokine production (TNF-α, IL-6 and IL-10) is independent of both TAB2 and TAB3 in macrophages [27,28]. In present study, activation of the RAS/MEK/ERK signaling cascade was observed in mice which exposed by TCE [29]. In addition, PI3K/AKT/mTOR signal pathway regulates inflammatory response in the liver [30]. Akt is an important member of the PI3K signal transduction enzyme family, which regulates cell

Table 1
qRT-PCR primer pairs used.

Primer	Sequences
GAPDH forward	5′-ACCCCAGCAAGGACACTGAGCAAG-3′
GAPDH reverse	5′-GGCCCCTCCTGTTATTATGGGGGT-3′
TNF-α forward	5′-CCCTCCTGGCCAACGGCATG-3′
TNF-α reverse	5′-TCGGGGCAGCCTTGTCCCTT-3′
IL-6 forward	5′-CCACTTCACAAGTCGGAGGCTTA-3′
IL-6 reverse	5′-GCAAGTGCATCATCGTTGTTCATAC-3′

Table 2
Sensitization rates and scores.

Group	Animals (n)	Score				Sensitization-positive animals (n)	Sensitization rate (%)
		0	1	2	3		
Blank control	5	5	0	0	0	0	0
Vehicle control	5	5	0	0	0	0	0
TCE	22	11	7	3	1	11	50.00
TCE + R715	37	25	9	3	0	12	32.43

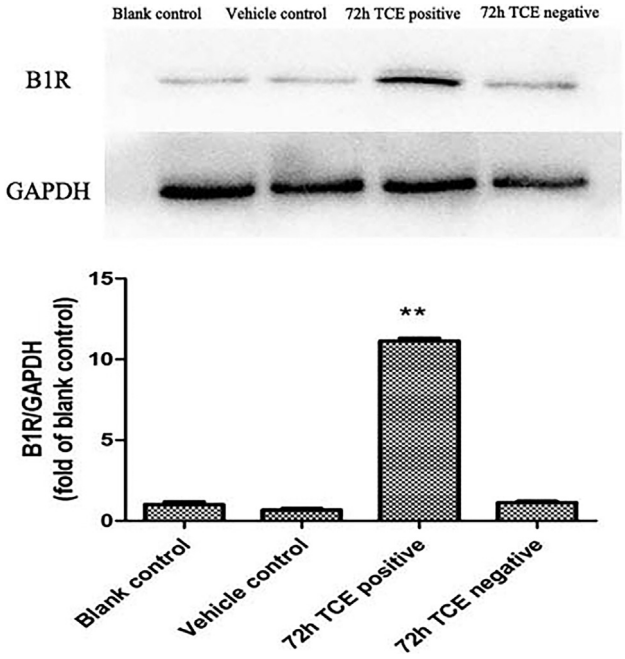

Fig. 3. B1R expressed in liver tissue in TCE mouse model. B1R protein expression in liver tissue was analyzed by Western-blot. $^{**}P < 0.01$, vs. the blank control group.

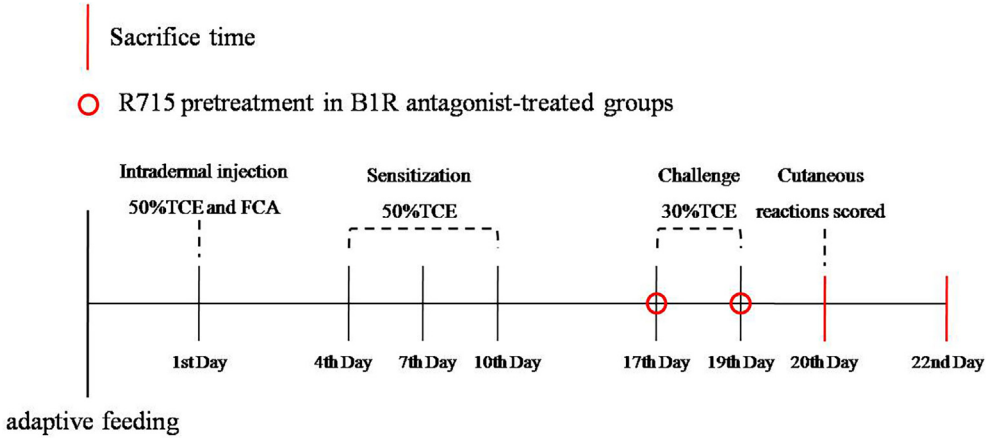

Fig. 2. Expriment schedule for trichloroethylene (TCE) induction of sensitization. After 7 days of adaptive feeding, TCE was applied to the abdomen by intradermal injection. On the 4th, 7th and 10th day, TCE was spread on the back of the mice for sensitization. The animals were challenged again with TCE on 17th day and 19th day. The R715 was applied to the TCE + R715 groups 1 h before challenge Executing animals and taking materials at 20th day and 22nd day.