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Review:

Induction of thoracic aortic dissection: a mini-review of β-aminopropionitrile-related mouse models*

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Abstract: Thoracic aortic dissection (TAD) is one of the most lethal aortic diseases due to its acute onset, rapid progress, and high rate of aortic rupture. The pathogenesis of TAD is not completely understood. In this mini-review, we introduce three emerging experimental mouse TAD models using β-aminopropionitrile (BAPN) alone, BAPN for a prolonged duration (four weeks) and then with added infusion of angiotensin II (AngII), or co-administration of BAPN and AngII chronically. We aim to provide insights into appropriate application of these three mouse models, thereby enhancing the understanding of the molecular mechanisms of TAD.

Key words: Thoracic aortic dissection (TAD); β-Aminopropionitrile (BAPN); Angiotensin II (AngII); Mouse model; Hypertension

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1 Introduction

Thoracic aortic dissection (TAD) manifests as intramural bleeding in the medial layers of the thoracic aorta, which is initiated by an intimal tear, causing a false lumen and expanding rapidly in the aorta (Elsayed et al., 2017). It is one of the most life-threatening aortic diseases, with a mortality rate of 1%–2% per hour in the first day, 50% after one week, and 90% after one year (Gawinecka et al., 2017; Xu et al., 2018). Hypertension is considered to be one of the major risk factors for TAD, accounting for over 50% of the population-attributable risks for TAD (Landenhed et al., 2015; Gawinecka et al., 2017). The annual incidence of aortic dissection is about 5–6 cases per 100000 people, and the prevalence increases to 21 cases per 100000 people for patients with hypertension (Howard et al., 2013; Landenhed et al., 2015; McClure et al., 2018). The main diagnostic standards for TAD rely on imaging features because it is usually asymptomatic before dissection occurs, which hampers timely diagnosis and treatment (Guo et al., 2006). Most recently, a collagen-IV (Col-IV)-targeted magnetic resonance/fluorescence dual probe was synthesized by Xu et al. (2018) to identify the early stages of TAD. The current therapeutic strategy for Stanford type A dissection (starting in the ascending aorta) is open surgical repair, although endovascular repair is emerging (Nienaber and Clough, 2015). While Stanford

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type B dissection (starting in the descending thoracic aorta) is more benign and control of blood pressure can improve clinical outcomes, its optimal therapeutic strategy is still controversial (Nienaber and Clough, 2015). Effective medical approaches for preventing the progression of aortic dissection are needed urgently. However, the pathogenesis of TAD is not completely understood, with only about 20% of incidences occurring due to underlying genetic mutations, such as fibrillin-1 (*FBN1*), transforming growth factor β receptor 1/transforming growth factor β receptor 2 (*TGFBR1*/*TGFBR2*), and myosin heavy chain 11 (*MYH11*) (van Laer et al., 2014; Sakai et al., 2016; Milewicz et al., 2017). Many TAD mouse models have been reported for studying thoracic aortic aneurysm and TAD. The current models can be divided into two types: genetically modified models (such as genetic manipulations of *FBN1* or *TGFBR1*/*TGFBR2* mutations) and chemical-induced models (such as administration of angiotensin II (AngII), calcium chloride, elastase, or β-aminopropionitrile (BAPN)) (Jones et al., 2010; Johnston et al., 2014; Oller et al., 2017; Xu et al., 2018; MacFarlane et al., 2019; Li et al., 2020). This mini-review will introduce three emerging chemical-induced TAD mouse models, using BAPN alone, BAPN for four weeks and then with added infusion of AngII, or co-administration of BAPN and AngII chronically.

2 Brief introduction of mouse TAD models

Due to increased endovascular approaches, surgical TAD specimens have become rare. In addition, those that are available are mostly from advanced disease stages with no comparable normal controls. Therefore, animal models have become the most valuable tools to study TAD pathophysiology (Nienaber and Clough, 2015). The current experimental TAD mouse models involve genetic modification or chemical application. The genetic factors associated with TAD involve mutations in *FBN1*, *TGFBR1*/*TGFBR2*, lysyl oxidase (*LOX*), and some other genes (Lee et al., 2016; Sakai et al., 2016; MacFarlane et al., 2019). Genetically modified models are optimal for studying genetically mediated human TAD. Classically, long-term AngII infusion via an implanted subcutaneous pump can induce aortic dissection (Saraff et al., 2003; Tieu et al., 2009). This mini-review will focus on introducing BAPN-related TAD mouse models.

3 BAPN-induced TAD mouse models

3.1 Brief history of BAPN

Ponseti and Baird (1952) first reported that rats fed seeds of the sweet pea, *Lathyrus odoratus*, exhibited disruptions of the aorta, bone, and other mesodermal structures. A crystalline substance, BAPN, was isolated from sweet pea seeds by Schilling and Strong (1954). They demonstrated that BAPN was one of the toxic factors in sweet pea seeds that affect vascular and skeletal systems (Wawzonek et al., 1955). Later, BAPN was identified as an irreversible inhibitor of LOX, the enzyme that plays a crucial role in the process of elastin and collagen maturation, particularly the crosslinking of elastin and collagen (Levene, 1962; O'Dell et al., 1966; Pinnell and Martin, 1968; Narayanan et al., 1972). Elastin is an essential component of the aorta, responsible for its structural integrity and reversible extensibility and deformability. In the thoracic aorta, elastin comprises about 60% of the extracellular matrix (Zhang et al., 2012). Elastin is produced mainly from midgestation to postnatal childhood, followed by variation and degradation with aging (Fhayli et al., 2020; Yanagisawa and Wagenseil, 2020). Thus, administration of BAPN into immature and fast-growing animals was suggested, which greatly inhibits elastic fiber formation and is more frequent in TAD induction (Behmoaras et al., 2008).

Several features were identified in BAPN-administered mammals. Aortic aneurysms were observed, with swollen and disorganized smooth muscle cells (SMCs), fragmented and depleted elastic fibers, and disrupted and accumulated collagen fibers. The disturbance of the aortic architecture induces decreased tensile strength and vulnerability to spontaneous tears (Péterszegi et al., 2008; Gao et al., 2019). The lathyritic animals presented with curvature of long bones, kyphoscoliosis, and cleft palate (Péterszegi et al., 2008). Recently, several studies reported that these BAPN-administered animals had decreased body weight gains and lower serum lipid levels.

BAPN has been widely applied to establish turkey and rat aortic dissection models, but it was not until 2010 that BAPN was used in mouse TAD models

in which it was co-administered simultaneously with AngII to mature mice (Wawzonek et al., 1955; Waibel et al., 1964; Kanematsu et al., 2010).

3.2 Mouse model 1: TAD induced by BAPN alone

Three-week-old male C57BL/6 mice were administered BAPN at 1 g/(kg·d) (in drinking water) for four weeks. Mice began to die during the second week, and at the endpoint the rates of TAD (59%–90%) and related death (20%–70%) were high (Table 1).

The typical pathological changes of the aorta seen in BAPN-induced models included medial disruption characterized by elastic fiber fragmentation and SMC loss, which mimicked TAD in humans (Jia et al., 2017; Milewicz et al., 2017). The elastic fiber fragmentation occurred in the second week, and worsened with the progression of TAD, as shown by macroscopic observation and image examination (Xu et al., 2018). Detection of endothelial cell loss by Col-IV-targeted magnetic resonance/fluorescence dual probe can identify early-stage TAD, because the endothelial injury precedes elastic fiber fragmentation and aortic dilation (Xu et al., 2018). BAPN-induced TAD was associated with inflammation, endoplasmic reticulum stress, and endothelial dysfunction (Jia et al., 2015, 2017; Zhao et al., 2019).

It has been reported that BAPN can reduce high blood pressure in rats, but has little or no effect on normal blood pressure (Iwatsuki et al., 1977). Later studies showed that the diastolic, but not systolic blood pressure of normotensive mice was also reduced after BAPN administration, possibly due to increased aortic stiffness (Ren et al., 2016; Jia et al., 2017). Moreover, BAPN showed no hemodynamic effect in the period of administration or at the time of aortic rupture (English et al., 2015). In BAPN-administered mice that had developed TAD, more than half experienced spontaneous aortic rupture without systolic blood pressure elevation (Ren et al., 2016). Therefore, the relationship between TAD (including thoracic aortic rupture (TAR)) and blood pressure should be further explored.

3.3 Mouse model 2: TAD induced by sequential administration of BAPN and then AngII

In this model, three-week-old male C57BL/6 mice were first administered BAPN (1 g/(kg·d), in drinking water, for four weeks), and then 24–72 h before termination, they were also administered AngII (1000 ng/(kg·min), by pump). This led to profound TAD and a high death rate (Anzai et al., 2015; Ren et al., 2016; Wang et al., 2016). However, in three-week-old mice with a Friend leukemia virus B (FVB) background, BAPN alone caused much less TAD (10%–25%) and fatal TAR (15%) than in C57BL/6 mice. Of note, 24 h of AngII infusion led to drastically increased TAD (53%–100%) and TAR (20%–37%) rates in FVB mice (Kurihara et al., 2012; Ren et al., 2016; Zhao et al., 2019). BAPN leads to a pre-dissection status and exhibits heterogeneity in different mouse strains. Subcutaneous infusion of AngII promotes TAD onset in BAPN-administered mice (Table 2).

The major risk factors for aortic dissection include specific gene mutations, hypertension, and smoking, which destroy the aortic structure and deteriorate its mechanical properties over time (Gawinecka et al., 2017). Then heavy athletic activity as well as severe emotional upset produces aortic dissection in these susceptible individuals, possibly correlated with elevated blood pressure, exceeding the tensile limit of the aortic wall (Elefteriades and Farkas, 2010). Therefore, BAPN, administered first in this sequential-administration TAD mouse model, induces a precondition of TAD

Table 1 Details of BAPN-only mouse TAD model

Mouse age and strain	BAPN administration (dose; route; duration)	Occurrence of first death	TAD rate at the BAPN treatment end point	Reference
Three weeks old; C57BL/6	1 g/(kg·d); in drinking water; four weeks	NG	88.9% TAD; 55.6% TAR	Jia et al., 2015
		NG	77.8% TAD; 33.3% TAR	Jia et al., 2017
		Week 2	70.0% TAR	Xu et al., 2018
		NG	87.5% TAD; 37.5% TAR	Ren et al., 2018
		Week 2	59.3% TAD	Han et al., 2018
		Week 3	81.8% TAD; 42.4% TAR	Wang et al., 2018
		NG	80.0% TAD; 46.7% TAR	Zhou et al., 2019
		Week 2	90.0% TAD; 70.0% TAR	Gao et al., 2019

BAPN: β-aminopropionitrile; NG: not given; TAD: thoracic aortic dissection; TAR: thoracic aortic rupture

Table 2 Details of sequential BAPN and AngII mouse TAD model

Mouse age	Administration (dose; route; duration)	Mouse strain	Occurrence of first death	TAD rates at the BAPN treatment end point	Effects of AngII on TAD rate	Reference
Three weeks old	BAPN: 1 g/(kg·d); in drinking water; four weeks +Ang II: 1000 ng/(kg·min); by pump; 24–72 h	FVB	NG	10% AD	Increase	Kurihara et al., 2012
		C57BL/6	NG	25% TAD	Increase	Ren et al., 2016
			Week 2	15% TAR	Increase	Zhao et al., 2019
			NG	NG	73.2% AD/AR	Anzai et al., 2015
			NG	87% TAD; 20% AR	Remain	Ren et al., 2016
			Week 3	80% AD; 20% AR	Remain	Wang et al., 2016

AD: aortic dissection; AngII: angiotensin II; AR: aortic rupture; BAPN: β-aminopropionitrile; FVB: Friend leukemia virus B; NG: not given; TAD: thoracic aortic dissection; TAR: thoracic aortic rupture

with disruption of the thoracic aorta, and then short-term AngII administration causes blood pressure elevation in the later stages, which may mimic the exertional or emotional change in some patients when TAD onset. This makes it possible to explore the preconditions and triggers of TAD, and provides us some valuable insights into the natural pathophysiological progression of human aortic dissection.

However, the apparent hemodynamic effects of AngII may disguise its non-hemodynamic effects, which overemphasize the effect of increased blood pressure in the initiation of TAD. AngII increases blood pressure, and norepinephrine infusion in BAPN-administered mice elevates blood pressure in the same way. However, norepinephrine does not augment the BAPN-induced TAD rate (Kurihara et al., 2012). Thus, the increased blood pressure caused by AngII may not be a driving factor augmenting TAD. Therefore, a trigger, which is independent of hemodynamic force, may provide insights into the formation and propagation of TAD.

3.4 Mouse model 3: TAD induced by BAPN and AngII co-administration

A constant infusion of AngII (1000 ng/(kg·min)) and BAPN (different doses) has been administered to male C57BL/6 mice aged 5–15 weeks, through a subcutaneously implanted osmotic pump. Some articles also reported the administration of BAPN to mice in drinking water (1 mg/mL), at a concentration comparable to 20 mg/(kg·d) administered by pump (Table 3).

TAD and catastrophic rupture occurred in 0%–40% and 0%–50% of mice co-infused by pump with BAPN (150 mg/(kg·d)) and AngII, respectively (Kanematsu et al., 2010; Imanishi et al., 2016, 2018; Kawai et al., 2017; Tomida et al., 2019). Note that the rate of TAD reached 40% in 5- to 6-week-old mice after BAPN administration, but no TAD was found in 13- to 15-week-old mice, indicating that mouse age plays a critical role in BAPN- and AngII-induced TAD (Tomida et al., 2019) (Table 3).

In 7-week-old mice infused with BAPN at 37.5 or 32.5 mg/(kg·d) (by pump) and AngII, the TAD rate was low, and the survival rate was increased at the experiment endpoint (four weeks) compared with mice infused with BAPN 150 mg/(kg·d) (by pump) and AngII (Kurobe et al., 2013a, 2013b) (Table 3). Later studies showed that mice given low doses of BAPN developed spontaneous TAD with a high mortality rate, but only dilated aortas were observed when mice were given high doses of BAPN (Li et al., 2013). As mouse body weight gains decreased as the BAPN dose increased, BAPN may stunt the growth of immature animals, suggesting that the proper dose of BAPN was required for aortic dissection onset (Zhang et al., 2012; Li et al., 2013; Ren et al., 2016).

In 8-week-old mice administered BAPN at 1 mg/mL (in drinking water, about 20 mg/(kg·d) by pump) and AngII, aortic rupture rates differed sharply, perhaps resulting from variation in the water intake of each mouse. Unexpectedly, the mortality was higher than the rate of mice infused with BAPN at 37.5 or 32.5 mg/(kg·d) (by pump) and AngII, which possibly indicates that the mice were more TAD-prone by drinking water containing BAPN (Obama et al., 2015; Kawai et al., 2017; Suehiro et al., 2019) (Table 3). Moreover, administering BAPN by injection increased the thickness of the thoracic aortic media, but the aortic diameter or TAD occurrence was not changed (Li et al., 2013).

Table 3 Details of combined BAPN and AngII mouse TAD model

Mouse age (week)	Details of AngII infusion			Details of BAPN administration			TAD rates at the BAPN and AngII treatment end point	Reference
	Dose (ng/(kg·min))	Route	Duration (week)	Dose (mg/(kg·d))	Route	Duration (week)		
5–6	1000	By pump	2	150.0	By pump	2	40.0% TAD; 50.0% TAR	Tomida et al., 2019
8	1000	By pump	4	150.0	By pump	2	25.0% TAR	Takayanagi et al., 2014
8	1000	By pump	4	150.0	By pump	2	52.4% AR	Kawai et al., 2017
8	1000	By pump	6	150.0	By pump	2	20.0% TAD/TAR	Hu et al., 2019
9	1000	By pump	6	150.0	By pump	2	2.2% TAD; 20.0% TAR	Kanematsu et al., 2010
10	1000	By pump	6	150.0	By pump	2	14.6% AR	Imanishi et al., 2018
10–12	1000	By pump	6	150.0	By pump	2	7.8% AD; 15.7% AR	Izawa-Ishizawa et al., 2019
13–15	1000	By pump	6	150.0	By pump	2	No death	Imanishi et al., 2016
7	1000	By pump	4	37.5	By pump	4	7.7% AD	Kurobe et al., 2013a
7	1000	By pump	4	32.5	By pump	4	5.6% AD	Kurobe et al., 2013b
8	1000	By pump	4	1 mg/mL*	In drinking water	2	16.7% TAR	Obama et al., 2015
8	1000	By pump	4	1 mg/mL	In drinking water	2	45.0% AR	Kawai et al., 2017
8	1000	By pump	4	1 mg/mL	In drinking water	2	15.0% AR	Suehiro et al., 2019

AD: aortic dissection; AngII: angiotensin II; AR: aortic rupture; BAPN: β-aminopropionitrile; TAD: thoracic aortic dissection; TAR: thoracic aortic rupture. * 1 mg/mL≈20 mg/(kg·d)

As to the mechanism of TAD onset in the BAPN and AngII co-infusion model, Izawa-Ishizawa et al. (2019) reported that TAD was triggered by endothelial dysfunction in a pre-TAD status, leading to a degenerated aorta characterized by medial elastic fiber disruption. Further experiments are needed to explore the relevant mechanisms involved in this combined BAPN and AngII mouse TAD model.

AngII induced hypertension in this co-infusion mouse model, which mimicked TAD in patients who have suffered from long-term hypertension (Landenhed et al., 2015). However, the induction of TAD in this model was low and differed widely as BAPN application methods changed, indicating heterogeneity in mechanisms.

4 Summary and perspectives

BAPN induces TAD in the absence or presence of AngII. The occurrence of TAD is affected by mouse age, mouse strains, and the methods of application of the chemicals. BAPN induces pre-TAD status, and subsequent AngII infusion acts as a trigger for TAD occurrence. This sequential-administration TAD mouse model has high induction of TAD, and mimics the natural history of human TAD. Mouse models with administration of BAPN are becoming popular for studying TAD because of their many benefits.

Contributors

Jian-an WANG and Hong S. LU provided the theme and design, and edited the manuscript. Hai-qiong ZHENG participated in searching and summarizing the relevant literature as well as designing and writing the manuscript. Jia-bing RONG, Fei-ming YE, and Yin-chuan XU provided comments and edited the manuscript. All authors have read and approved the final manuscript.

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Compliance with ethics guidelines

Hai-qiong ZHENG, Jia-bing RONG, Fei-ming YE, Yin-chuan XU, Hong S. LU, and Jian-an WANG declare that they have no conflicts of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

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中文概要

题　目：β-氨基丙腈相关的小鼠胸主动脉夹层模型的综述

概　要：胸主动脉夹层具有发病急、发展迅速、主动脉破裂率高的特点，是最致命的大动脉疾病之一。但是胸主动脉夹层的发病机制目前还没有被完全了解。本综述介绍了三种新兴的β-氨基丙腈相关的小鼠胸主动脉夹层模型，分别是：单用β-氨基丙腈；先用β-氨基丙腈处理（四周）再用血管紧张素 2（AngII）处理；β-氨基丙腈和 AngII 同时进行处理。希望通过更好地运用这三种β-氨基丙腈相关的小鼠胸主动脉夹层模型，从而对胸主动脉夹层的分子机制有更深入的了解。

关键词：胸主动脉夹层；β-氨基丙腈；血管紧张素 2；小鼠模型；高血压