Hydrodynamic Delivery

Subjects: Pharmacology & Pharmacy

Contributor: Takeshi Suda , Takeshi Yokoo , Tsutomu Kanefuji , Kenya Kamimura , Guisheng Zhang , Dexi Liu

The principle of hydrodynamic delivery was initially used to develop a method for delivering plasmids into mouse hepatocytes through tail vein injection and has since been expanded for use in delivering various biologically active materials to cells in different organs of several animal species.

hydrodynamic injection systemic regional capillary

1. Introduction

Hydrodynamic delivery was established in 1999 as a simple and efficient non-viral method for delivering plasmids to hepatocytes in mice [1][2]. Because injection of plasmids in saline containing no other components only weakly activates the host's immunity, applications of hydrodynamic delivery in the gene and cell therapy field have been broadly explored. Significant initial efforts have been made to determine the underlying mechanisms of hydrodynamic delivery and to develop a modified procedure that is applicable to large animals. Researchers summarized the progress towards the successful use of hydrodynamic delivery for research and clinical applications.

2. Characteristics of Hydrodynamic Delivery

A single injection of less than 50 μg of plasmid DNA in saline through a mouse tail vein over a period of 5 s in a volume equal to 8 to 10% of the animal's body weight results in transgene expression in up to 40% of hepatocytes [1]. A key determinant of the efficiency of hydrodynamic delivery is the anatomical structure and expansion rate of the target organs after intravascular injection. A rapid influx of a large amount of solution into a capillary quickly extends the cell membrane and creates an invagination through which the solution enters the cell interior [3]. The previous work, employing computed tomography and contrast medium, showed that the optimal expansion rate for the liver is 60%/5 s in mice [4].

Capillaries connect arteries and veins and can be divided into three classes based on differences in two components: the endothelium and the basement membrane [5] (Figure 1). Continuous capillaries consist of tightly connected endothelium and basement membrane without gaps, which prevent the leakage of water-soluble materials of 1 kDa or larger in size. Sinusoid capillaries provide large interendothelial gaps over 1 μm in size, in which there is incomplete shielding by the basement membrane, allowing molecules 100 kDa or larger in size to readily transude. The third type of capillary is the fenestrated capillary; in these capillaries, small fenestrae of 50–

80 nm are present in the endothelium, which has a complete basement membrane. The organs that contain sinusoid capillaries are the most suitable targets for hydrodynamic delivery.

Among the organs that contain sinusoid capillaries, direct connections with the inferior vena cava and a unique system of the portal vein make the liver an ideal target for hydrodynamic delivery from the tail vein. A large volume of solution rapidly injected into the tail vein travels to the heart and induces cardiac congestion, followed by rapid retrograde flow into the hepatic veins, which directly transfers the hydrodynamic impact to the liver [4]. The specific infrastructure of the portal vein provides a natural flow and extra space, which counteracts the hydrodynamic retrograde flow that inhibits spillover of the injected solution into the portal vein and which can accommodate pushed-back preexisting blood and remove nucleases from sinusoids, respectively.

Although the rapid injection of a small volume of fluid can induce a high pressure comparable to that caused by injection of a volume corresponding to 8 to 10% of body weight if the injection speed is high enough, the delivery efficiency achieved is not equivalent to that obtained using authentic hydrodynamic delivery [1]. In a fibrotic liver, injection under the standard hydrodynamic conditions gives rise to much higher pressure and stronger shear stress than those reached using the same injection profile in a normal liver, but transgene expression is markedly lower [6] [7]. Slow injection of a large volume over a longer period can cause the liver to expand to a size similar to that resulting from hydrodynamic delivery; however, gene delivery occurs with much lower efficiency [4].

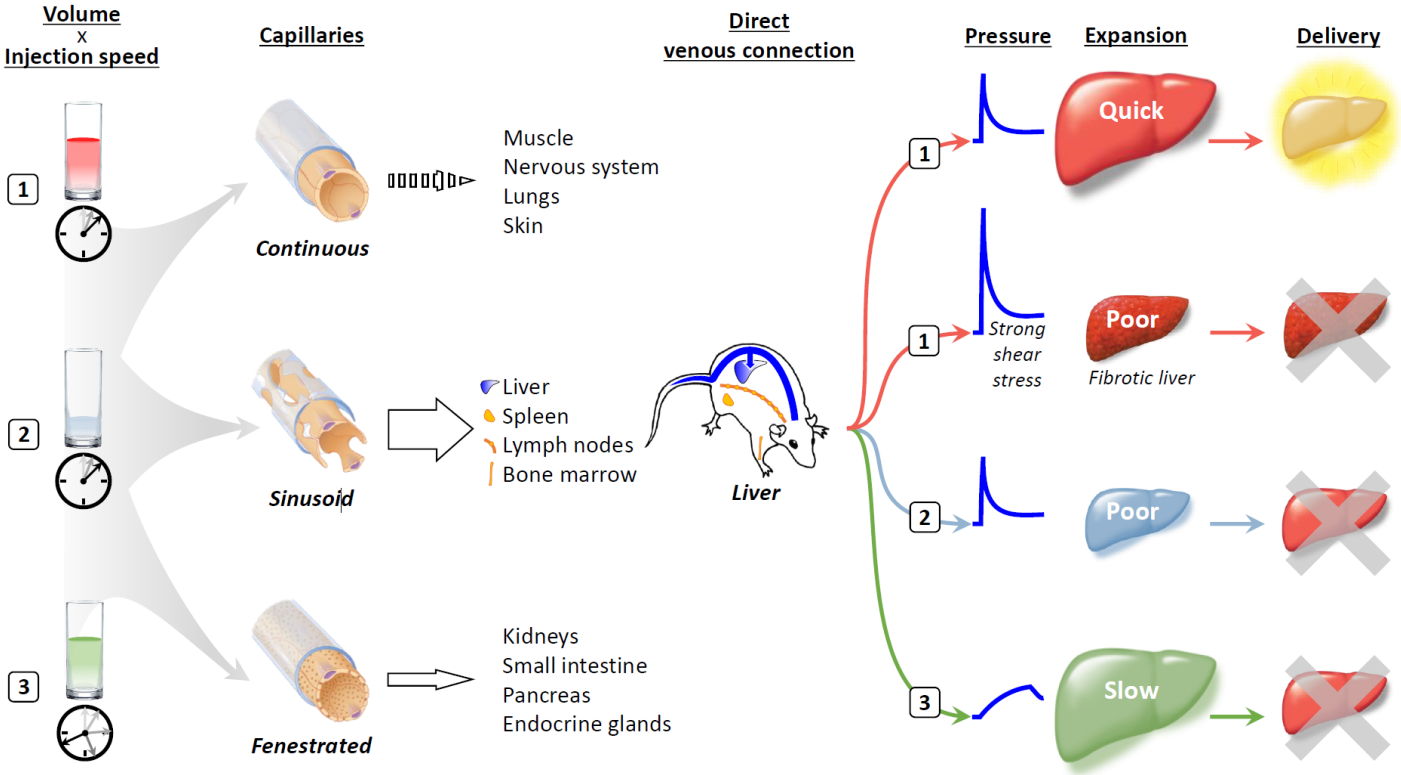

Figure 1. Traverse of hydrodynamic impact from injection to gene transfer sites.

The liver lobes are composed of hexagonal-shaped microscopic units called lobules, where the central structure is a terminal hepatic venule of the central vein. The peripheral vertices are bordered by portal tracts containing the

portal vein, hepatic artery, and bile duct. Since the central vein and portal tracts consist of structures with higher rigidity, such as the basal membrane and vascular smooth muscle, the intervening parenchyma is more susceptible to physical stretch [8]. Rapid flow entering the liver from the central vein passes through the middle zone sinusoids and exits into the portal veins or vice versa. It is expected that a rapid flow exiting from a rigid inlet toward a rigid outlet would accumulate mostly at the front of the rigid outlet. In hydrodynamic delivery via the inferior vena cava or portal vein, transgene expression has been observed mainly at the end of the middle zone opposite the injection site [9].

To achieve effective hydrodynamic delivery, the physical impact of the injection must be transmitted to target cells through the solution's movement. If a physical impact that can quickly traverse the endothelium and basement membrane and cause organs to expand rapidly can be accomplished through local regional injection, hydrodynamic delivery may be a promising strategy not only for the liver but also for other organs.

3. Applications of Hydrodynamic Delivery

Human application is the ultimate goal of gene delivery system development. However, hydrodynamic impacts generated by systemic injection through the tail vein in mice can be temporarily overwhelming for the cardiovascular system. Therefore, when hydrodynamic delivery is applied in humans, hydrodynamic impacts must be limited around the target site. Although the insertion of an injecting device into a corresponding vasculature to target an organ or a part of an organ is an established technique in a clinical setting as interventional radiology, reproducing sufficient hydrodynamic impacts at a target region is challenging.

In hydrodynamic delivery of material injected into the tail vein, the injected solution never flows out of the body, making it a closed system (Figure 2). Under closed circulation, the hydrodynamic impact of the injection is reproducibly generated as a function of injection volume and speed. However, in regional hydrodynamic delivery, the solution is injected into an open system and can readily flow out of the target area through latent vascular connections [10]. Therefore, the hydrodynamic impact of regional hydrodynamic delivery cannot be reproducibly generated using fixed parameters of injection volume and speed. To achieve safety and reproducibility in the open system, a computer-controlled hydrodynamic delivery system called HydroJector has been developed, in which the injected solution is propelled by carbon dioxide gas [11] or by an electric motor [12]. By compensating for leakage from the target area, the system controls the injection in a way that creates a reproducible intravascular pressure–time curve at the injection site.

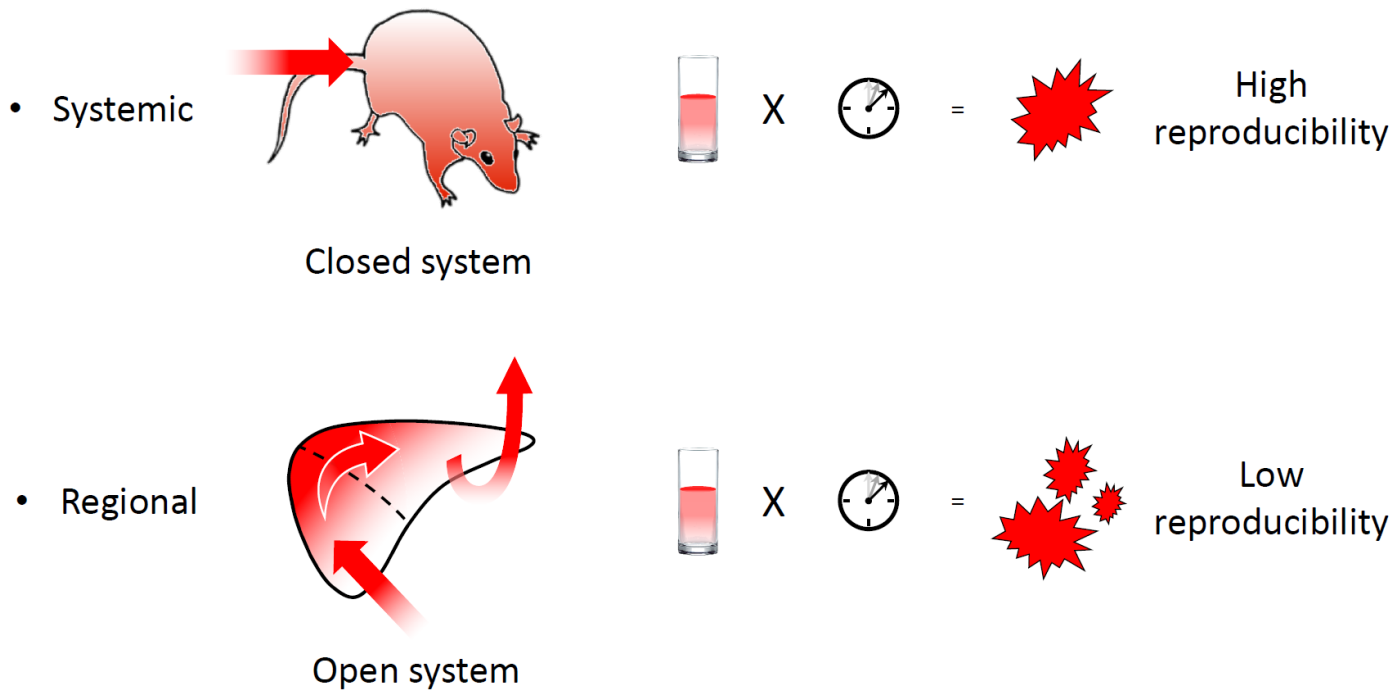

Figure 2. Establishment of hydrodynamic impacts in systemic and regional injections.

Recent studies on hydrodynamic delivery are reviewed from multiple perspectives, including the targeted animal species and routes of administration (Table 1), the types of diseases being treated (Table 2), and the delivery materials and strategies used (Table 3), particularly within the last five years.

Table 1. Animals, target organs, and routes for which hydrodynamic delivery has been applied.

Target\Animal		Mouse	Rat	Treeshrew	Chicken	Rabbit	Pig	Dog	Monkey	Baboon	Human
Systemic	LVR	TV [1][2]	TV [13]	ROS [14]	JV [15]						
	KDNY				JV [15]						
	BCEC	TV [16]									
	FTS	TV [17]									
	IST HCC	TV [18] [19] [20]									
Regional	LVR	IVC, PV	IVC, PV, BD,			IVC, HV [24]	IVC, HV, PV,	HV [36] [37]		HV under prep.	ex vivo [38]

Target\Animal	Mouse	Rat	Treeshrew	Chicken	Rabbit	Pig	Dog	Monkey	Baboon	Human
	[2][9] [11]	ex vivo [11][21] [22][23]				BD [11][25] [26][27] [28][29] [30][31] [32][33] [34][35]				
KDNY	RV, RP [39]	RV [11][40] [41][42]				RV [11]				
MSL	TA, LV, TV [43] [44] [45] [46] [47]	LV, LA * [11][48] [49][50] [51][52] [53]			LV [54]	LV, LA [53][55]		LV, LA [56][57]		
PCAS		SMV [58]								
GND		LA, GV, GA [56]								
HCC		HA [59]								
BT		CA [16][60]								
MCD		ex vivo [61][62]								
SV										ex vivo [61]

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developed, which could serve as a foundation for the development of next-generation hydrodynamic delivery devices. Regional hydrodynamic delivery could provide a platform for sophisticated gene therapy, allowing for site-directed editing, repopulation, and activation control of genes with minimal auxiliary effects.

Table 2. Diseases for which hydrodynamic delivery has been utilized to explore the pathogenesis and/or therapeutic potential.

Infectious	Cancer	Hereditary	Liver
Hepatitis B virus (HBV)	Hepatocellular carcinoma	Hemophilia A and B [71][72][73][74][75][76]	Liver fibrosis [77][78][79][80][81][82]

Infectious	Cancer	Hereditary	Liver
[63][64][65][66]	[59][67][68][69][70]		
Hepatitis C virus [83][84][85][86][87][88][89] [90]	Hepatoblastoma [91][92][93]	Pseudoxanthoma elasticum [94]	Nonalcoholic fatty liver diseases [78][95][96][97][98]
Hepatitis D virus [99]	Cholangiocellular carcinoma [100][101][102][103]	von Willebrand disease [104][105][106][107]	Alcoholic liver injury [108][109]
Influenza virus [110][111]	Colorectal cancer [18][19][112][113][114]	Thrombotic thrombocytopenic purpura [115][116][117][118]	Portal hypertension [119]
Enterovirus 71 [120]	Lung cancer [121]	Mucopolysaccharidosis I and VII [122][123]	Fulminant hepatitis & regeneration [124][125][126]
Vaccination (HBV, Malaria, Influenza) [65][66][110][127][128] [129]	Brain tumor [60]	Phenylketonuria [130]	Acute liver injury [131][132]
Malaria parasite [127][128]	Lymphoma [133]	Tyrosinemia [134][135][136]	**Others**
Streptococcus [137]	Melanoma [19][138][139]	Leber congenital amaurosis [140]	Atopic skin & cutaneous diseases [141][142][143][144]
Sepsis [145]	Metastasis (melanoma, breast cancer, RCC * (lungs, liver, kidneys)) [113][146][147]	Sickle cell disease [148]	Cardiovascular & ischemic diseases [149][150][151][152][153] [154][155]
Trypanosome [156]	*, renal cell carcinoma	Cystathionine β-synthase deficiency [157]	Kidney diseases & hyperparathyroidism [158][159][160][161]
		Fabry disease [162]	Diabetes mellitus & obesity [163][164][165][166]
		α-1 antitrypsin deficiency [167]	Hypertriglyceridemia [168]
		Growth hormone deficiency [169]	Inflammatory diseases [170][171][172][173][174]
		Metachromatic leukodystrophy	Osteoporosis [176]

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Infectious	Cancer	Hereditary	Liver
		[175]	
Delivery Materials	**Technological Developments**		**Gene Editing**
Minicircle DNA [30][107][123][130][133][141][155][157]	US-targeted microbubble destruction [165]		PhiC31 Integrase [182]
microRNA [44][81][97][183][184][185][186]	Computer-assisted hydrodynamic delivery [11][12]		Sleeping Beauty [27][91][116][148][186][187][188][189][190]
Circular RNA [139]	Bioluminescence imaging [44][191][192][193][194]		piggyBac [139][195]
shRNA [69][196][197]	Tissue clearing [194]		Cre-loxP [198][199][200]
siRNA [86][201][202][203]	Repopulation [184][204]		CreER [189][205]
Cell [146]	Reprogramming [165][190][206][207][208][209]		Optogenetic genome engineering [199]
Polyplex [22][47][210]			CRISPR-Cas9 [17][70][191][211][212]
Cationic liposome [122]			Prime editor [140]
Adeno-associated virus [78][129][213][214][215][216]			Split prime editor [136]
Lentivirus [37][217][218]			adenosine deaminase acting on RNA [219]
Foamy virus vector [31]			Adenine base editor [135]

4. Conclusions

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