Influence of the adenosine A₁ receptor on blood pressure regulation and renin release

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Submitted 3 May 2005; accepted in final form 9 December 2005

Brown, Russell D., Peter Thorén, Andreas Steege, Ralf Mrowka, Johan Sällström, Ole Skott, Bertil B. Fredholm, and A. Erik G. Persson. Influence of the adenosine A₁ receptor on blood pressure regulation and renin release. Am J Physiol Regul Integr Comp Physiol 290: R1324–R1329, 2006. First published December 15, 2005; doi:10.1152/ajpregu.00313.2005.—The present study was performed to investigate the role of adenosine A₁ receptors in regulating blood pressure in conscious mice. Adenosine A₁-receptor knockout (A₁R−/−) mice and their wild-type (A₁R+/+) littermates were placed on standardized normal-salt (NS), high-salt (HS), or salt-deficient (SD) diets for a minimum of 10 days before telemetric blood pressure and urinary excretion measurements in metabolic cages. On the NS diet, daytime and nighttime mean arterial blood pressure (MAP) was 7–10 mmHg higher in A₁R−/− than in A₁R+/+ mice. HS diet did not affect the MAP in A₁R−/− mice, but the daytime and nighttime MAP of the A₁R+/+ mice increased by ~10 mmHg, to the same level as that in the A₁R−/−. On the SD diet, day- and nighttime MAP decreased by ~6 mmHg in both A₁R−/− and A₁R+/+ mice, although the MAP remained higher in A₁R−/− than in A₁R+/+ mice. Although plasma renin levels decreased with increased salt intake in both genotypes, the A₁R−/− mice had an approximately twofold higher plasma renin concentration on all diets compared with A₁R+/+ mice. Sodium excretion was elevated in the A₁R−/− compared with the A₁R+/+ mice on the NS diet. There was no difference in sodium excretion between the two genotypes on the HS diet. Even on the SD diet, A₁R−/− mice had an increased sodium excretion compared with A₁R+/+ mice. An abolished tubuloglomerular feedback response and reduced tubular reabsorption can account for the elevated salt excretion found in A₁R−/− animals. The elevated plasma renin concentrations found in the A₁R−/− mice could also result in increased blood pressure. Our results confirm that adenosine, acting through the adenosine A₁ receptor, plays an important role in regulating blood pressure, renin release, and sodium excretion.

In addition to its hemodynamic effects, the A₁R has been shown to be involved in regulating the release of renin from the granular cells in the afferent arteriole (26). The inhibitory effect of the A₁R on renin release has been demonstrated both in vivo and in vitro, using A₁R antagonists, as well as A₁R agonists (8, 13). A₁Rs have also been found to be distributed throughout the nephron and in the glomerulus, the proximal tubule, and the collecting ducts and are involved in the tubular reabsorption of sodium chloride (18). There is evidence that A₁Rs also take part in the regulation of blood pressure. In rats, long-term treatment with an adenosine receptor agonist can cause hypertension, with the systolic blood pressure increasing as much as 40 mmHg (8). In an earlier study by our group (2), it was found that A₁R knockout (A₁R−/−) mice, under anesthesia, had an increased blood pressure compared with their wild-type (A₁R+/+) littermates (2). In contrast, Schermann and his group (29), using another A₁R knockout mouse of a slightly different background, observed no significant differences in blood pressure between the genotypes (29). The present study was therefore performed to further investigate the effect of adenosine, acting through the A₁R, on blood pressure regulation and renin release in conscious animals.

MATERIALS AND METHODS

The local ethics committee for Uppsala University approved all procedures for this study. The experiments were carried out on female A₁R knockout (A₁R−/−) mice and their wild-type (A₁R+/+) littersates weighing 23–32 g. The A₁R−/− mice were generated as described by Johansson et al. (14). The mice used in the experiments were siblings from matings of third-generation A₁R+/− mice mixed on a C57BL, 129/OlaHsd background. The mice were genotyped with Southern blot analysis or with PCR. The animals were placed on standardized normal-salt (NS; 0.7% NaCl), high-salt (HS; 7.0% NaCl), or salt-deficient (SD; 0% NaCl) diets (Harland Scandinavia, Allerod, Denmark). The animals were allowed to equilibrate for 10


In the kidney, which plays an important role in the regulation of body fluid and blood pressure, stimulation of the adenosine A₁ receptor (A₁R) produces vasoconstriction of the afferent arterioles via an increase of calcium in the smooth muscle cells (9). This vasoconstriction causes a reduction in glomerular filtration rate and renal blood flow and has been found to have a key role in mediating the tubuloglomerular feedback (TGF) response (2, 20, 29).

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days on each diet before urinary excretion, plasma renin level, or blood pressure measurements were performed. A congenic mouse strain, customs generated by Jackson Laboratory from our A1R strain, was also used to investigate plasma renin concentrations (PRCs) and genetic differences concerning the Ren1 and Ren2 genes. These mice are congenic as judged by 140 gene markers spread over the genome.

**Telemetric blood pressure measurements.** Blood pressure was measured telemetrically with blood pressure transmitters (PA-C20; Data Science International, St. Paul, MN). For implantation of the blood pressure transmitters, the mice were anesthetized by spontaneous inhalation of isoflurane (Forene, Abbott Scandinavia, Solna, Sweden) and placed on a servo-controlled heating pad to maintain body temperature of 37.5°C. A midline incision (~2 cm) was made from the lower mandible to approximately the sternum. The blood pressure catheter was placed in the carotid artery and the transmitter body was placed subcutaneously along the right flank. The animals were allowed to recover for at least 7 days before blood pressure recordings were commenced. The computer program PC-Lab version 5.0 was used to sample calibrated values of blood pressure during the experiment (1). Data were collected for 5 s every 2 min for 1–5 days at a time. Daytime (12 h) and nighttime (12 h) blood pressure readings were pooled and used for analysis. The recorded data were further analyzed with a Microsoft Excel macro program.

**Plasma renin measurements.** Plasma renin levels were measured in both the A1R mice and the congenic strain. Immediately after anesthesia, a blood sample was taken from the carotid artery and centrifuged, and the plasma was frozen at –85°C. PRC was measured by radioimmunoassay of ANG I with the antibody-trapping technique (17). Briefly, 10 μl of plasma from each sample was serially diluted between 50- and 1,000-fold. Five microliters of each dilution were incubated n duplicates for 24 h together with rabbit ANG I antibody and renin substrate (~1,200 ng ANG I/ml) from 24-h nephrectomized rats (renin had been extracted from the substrate by affinity chromatography). The reaction was stopped by the addition of 1 ml cold barbital buffer, ANG I tracer was added, and a radioimmunoassay was performed. Only results with linearity in serial dilutions were accepted. Renin values were standardized with renin standards obtained from the Institute for Medical Research (MRC, Holly Hill, London, UK) and are expressed in standard Goldblatt units (GU).

**Urinary excretion measurements.** The mice were placed individually in metabolic cages for 24 h before excretion measurements were started. NS, HS, or SD diets and water were supplied ad libitum. Urine was collected under a 24-h period, and the urine volumes were determined gravimetrically. Urinary concentrations of sodium and potassium were obtained by flame photometry (FLM3; Radiometer, Copenhagen, Denmark). Osmolarity in the urine was measured by depression of the freezing point (model 3MO; Advanced Instruments, Needham Heights, MA).

### RESULTS

**Blood pressure.** Blood pressure was monitored telemetrically in conscious, unrestrained, and, insofar as possible, non-stressed animals. In this way, the pharmacological effects of anesthesia on blood pressure were avoided. Typical 24-h circadian variations in blood pressure could be observed in mice of the two different genotypes, with a higher blood pressure during active (nighttime) periods (Fig. 1). As seen in Table 1, the A1R –/– mice have an elevated blood pressure compared with their wild-type littermates on SD and NS diets.

The changes in blood pressure, depending on the amount of salt in the diets, were much more pronounced in the wild-type mice than in the knockout mice. On NS and SD diets, the daytime and nighttime blood pressures of the A1R +/+ were higher than those seen in the A1R –/– mice. On the HS diet, mREN1/mREN2 analysis. Animals were killed by decapitation, and the kidneys were removed. The kidneys were frozen in liquid nitrogen and stored at –80°C until isolation of total RNA.

Total RNA was isolated from renal tissues using RNA-Be (BIOZOL, Eching, Germany). Two micrograms of total RNA were denatured at 65°C, and cDNA synthesis was then performed with random hexamers at 42°C for 1 h with SuperScript first-strand synthesis system (Invitrogen, Karlsruhe, Germany). For PCR, oligonucleotides were designed with Vector NTI 8.0 (Invitrogen). The oligonucleotides are introns able to amplify both mREN1 and mREN2. Sequences of the oligonucleotides of mREN1/2 are sense, 5’-CCTTGCAACCTTCAGTCTCC-3’, and antisense, 5’-GCTGAGGAAACTCTGTGC-3’. PCR amplification was performed with a T1 thermocycler (Biometra, Göttingen, Germany). Cycling conditions were 95°C for 5 min, followed by 30 repeats of 95°C for 1 min, 55°C for 1 min, and 72°C for 30 s. To distinguish Ren1 and Ren2 restriction, analysis of the PCR amplicons was performed using the restriction enzyme HaeIII (Promega, Mannheim, Germany). The mREN1 amplicon contains a HaeIII recognition site, which is not contained in mREN2. Ten microliters of the PCR reaction were used for the digestion reaction. Digestion was performed for 4 h at 37°C. Samples were separated and visualized on a 1% agarose gel containing ethidium bromide.

**Statistics.** The results are presented as means ± SE. The data were tested for significance with the Student’s t-test for paired or unpaired observations. When multiple groups were compared, one-way ANOVA was employed. The Bonferroni test for pairwise multiple comparisons was used to allow for more than one comparison with the same variable. This states a significance level of P/M, where M is the number of comparisons to be made. Statistical significance was defined as P < 0.05.

### Table 1. Average day and night blood pressures measured telemetrically in A1R +/+ and A1R –/– mice on either an SD, NS, or HS diet

<table>
<thead>
<tr>
<th>Average Blood Pressure, mmHg</th>
<th>SD Diet</th>
<th>NS Diet</th>
<th>HS Diet</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A1R +/+</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Day</strong></td>
<td>87.0 ± 4.0†</td>
<td>92.2 ± 3.7</td>
<td>101.9 ± 1.0†</td>
<td>10</td>
</tr>
<tr>
<td><strong>Night</strong></td>
<td>94.3 ± 2.7†</td>
<td>101.1 ± 2.0</td>
<td>111.8 ± 1.2‡</td>
<td></td>
</tr>
<tr>
<td><strong>A1R –/–</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Day</strong></td>
<td>93.5 ± 1.3**†</td>
<td>99.3 ± 2.8**</td>
<td>101.3 ± 3.7</td>
<td>8</td>
</tr>
<tr>
<td><strong>Night</strong></td>
<td>105.0 ± 1.1*</td>
<td>111.1 ± 3.4*</td>
<td>113.2 ± 3.7</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SE; n = no. of mice. SD, salt deficient; NS, normal salt; HS, high salt; A1R, adenosine A1-receptor. *P < 0.05 vs. A1R +/+ on same diet; †P < 0.05 vs. NS diet of the same genotype.
However, there was no difference in blood pressure between the two groups. The SD diet caused a reduction in both daytime and nighttime blood pressure in the A1R+/+ mice. When the A1R+/+ were put on the HS diet, blood pressure was increased both day and night, reaching the same levels as in the A1R−/− mice. A decrease in blood pressure was observed in A1R−/− mice only when given the SD diet and then only during daytime. No significant changes in blood pressure were observed in A1R−/− mice placed on the HS diet.

**PRC.** There were clear differences in PRC in the A1R+/+ vs. the A1R−/− group on all the different diets (Fig. 2). Basal renin levels during the NS diet were much higher in the A1R−/− group (36.2 ± 8.4 mGU/ml) than in the A1R+/+ group (74.2 ± 0.008 mGU/ml). On the SD diet, PRC in the A1R+/+ group was 32.1 ± 12.6 mGU/ml and more than twofold greater in the A1R−/− group (82.0 ± 17.2 mGU/ml). On the HS diet, PRC was reduced in both groups; however, PRC remained significantly higher in the A1R−/− animals (A1R+/+, 13.7 ± 1.8 mGU/ml; A1R−/−, 38.5 ± 5.1 mGU/ml).

In the congenic mouse strain, there was no difference in PRC between the congenic A1R+/+ (A1R+/+ c) and the A1R−/− (16.1 ± 2.3 and 18.9 ± 7.4 mGU/ml, respectively). PRC in the congenic A1R−/− was also found to be significantly elevated (34.9 ± 8.3 mGU/ml) compared with the congenic A1R+/+ animals (P < 0.05).

**mREN1/mREN2.** The results of the restriction analysis (Fig. 3) show that the 129P2 and A1R−/− mouse strains express both Ren1 and Ren2, whereas C57BL/6 and A1R+/+ express only Ren1 in the kidney. Both renin genes were also present in the congenic A1R−/− mice.

**Urinary excretion.** On the NS diet, conscious A1R−/− mice had a greater sodium excretion rate than A1R+/+ mice (0.046 ± 0.008 and 0.027 ± 0.004 μmol·min⁻¹·10 g⁻¹, respectively) (Fig. 4). The SD diet caused a great reduction in sodium excretion rate in both the A1R+/+ and A1R−/− mice. Despite this reduction, the A1R−/− mice had a greater excretion rate than the A1R+/+ mice (0.014 ± 0.004 and 0.005 ± 0.001 μmol·min⁻¹·10 g⁻¹, respectively). On the HS diet, there was no significant difference in sodium excretion between the A1R−/− and A1R+/+ mice (0.123 ± 0.35 and 0.144 ± 0.02 μmol·min⁻¹·10 g⁻¹, respectively). The different diets did not seem to affect urinary potassium excretion in either group (Table 2). Urinary osmolar excretion was elevated in the A1R−/− animals on all of the different salt diets, probably as a consequence of increased sodium excretion. A1R−/− mice had an elevated diuresis on the SD and NS diets compared with the A1R+/+ mice. The HS diet caused an increased diuresis in both genotypes.

**DISCUSSION**

One of the aims of this study was to investigate the blood pressure in conscious A1R−/− mice, as two earlier studies addressing the role of the A1R in blood pressure regulation yielded inconsistent results (2, 29). The difference in effects on blood pressure could be because of the two different mouse strains used in these studies having different genetic backgrounds (129 × 1/129 S1 hybrid vs. 129OlaHsd mixed with C57BL/6). Another possible explanation is that different exons of the A1R gene had been targeted: the first coding exon in the congenic A1R−/− and the second exon in the normal A1R−/−. However, it is also possible that there might have been a second cause for the difference in blood pressure between the two groups. This could be a result of increased sodium excretion.
mice generated by Johansson et al. (14). Schweda et al. (25) found that the A1R+/− mice generated by Sun et al. possess two renin genes (Ren1d and Ren2), whereas wild-type mice only have one renin gene (Ren1′) (25). This is related to differences between the C57 and 129 mouse strains. The embryonic stem cells for the targeted disruption of the A1R were derived from the 129J mouse strain, which has two renin genes, designated Ren1′ and Ren2. When the A1R mutation is propagated in the mice with a C57BL/6 background (which has only one renin gene), the knockout will carry the 129J background in the area of the mutated gene and will therefore possess two renin genes: Ren1′ and Ren2 from the 129J background. In the present study, we found that our knockout mice, generated by Johansson et al. (14), also had two renin genes, whereas the corresponding wild-type animals had only one. A congenic C57BK/6 strain was also investigated in an attempt to alleviate this discrepancy. Even in this congenic strain, both renin genes were present in the knockout animal. However, there was no difference in PRC between the congenic A1R+/+ and A1R+/−, whereas the PRC in the A1R−/− mice was found to be twice as high as that in the congenic A1R+/+ mice. Lum et al. (16) recently found that mice with two renin genes have higher blood pressure than those with only one renin gene. Together, their results and ours may indicate that the number of renin genes is not important for the degree of renin production. The increased plasma levels seen in the A1R+/− mice could therefore be a direct consequence of the disrupted A1R gene in the knockout animals.

Adenosine, acting through the A1R, has an important role in modulating the release of renin. Renin release from the juxtaglomerular granular cells is stimulated by adenylyl cyclase. Because A1Rs are negatively coupled to adenylyl cyclase by inhibitory G proteins, lack of activation of the A1R increases renin release. Exogenous adenosine and A1R agonists attenuate the release of renin (15, 20, 26), as does adenosine released from macula densa cells (12), whereas antagonism of A1Rs enhances renin release (23). A more recent study by Schweda et al. (25) showed that the A1R has a tonic inhibitory effect on the renin system. Chronic blockade of adenosine receptors with the nonselective antagonist 8-cyclopentyl-1,3-dipropylxanthine leads to an activation of the renin-angiotensin system, raising the plasma levels of renin and causing an increase in blood pressure (19, 28). Indeed, as in these earlier studies with adenosine receptor blockers, the A1R−/− animals also showed an increased PRC that could be responsible for the observed increase in blood pressure.

Renin release mediated by the macula densa cells can be influenced by at least two different mechanisms (21). First, when the tubular fluid load at the macula densa site in the distal tubule is decreased, a condition known to increase renin release, calcium concentration in the macula densa cells increases (24). This activates macula densa cell phospholipase A2 to release arachidonic acid and produce prostaglandins, most likely PGE2, which is known to stimulate renin release (22). Second, decreased electrolyte uptake into and transport away from the macula densa cells will reduce ATP metabolism and the formation of adenosine. The lower concentration of adenosine around the afferent arteriole will reduce smooth muscle cell calcium (9), leading to decreased vascular tone and a diminished adenosine-mediated inhibition of renin release from this vessel. The latter mechanism could explain the present findings of increased renin release in the A1R−/− animals.

Not only was blood pressure elevated in the knockout mice, but they also had an increased sodium excretion compared with their wild-type counterparts. The increased sodium excretion and diuresis could be caused by the abolished TGF and adenosine’s direct effect on sodium reabsorption in the tubular epithelial cells (31, 32). The TGF response, which plays an important role in maintaining fluid balance in the body, is mediated by adenosine, acting via the A1R (2, 29). When the glomerular filtration rate is elevated, the macula densa cells sense the increased fluid and solute delivery to the distal tubule. The increased solute concentration at the macula densa site corresponds to an increased transport of sodium through

Table 2. Diuresis, potassium and osmolar excretion in A1R+/+ and A1R−/− mice on either an SD, NS, or HS diet

<table>
<thead>
<tr>
<th>Genotype</th>
<th>SD Diet</th>
<th>NS Diet</th>
<th>HS Diet</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuresis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A1R+/+</td>
<td>0.14±0.03</td>
<td>0.15±0.02</td>
<td>0.29±0.02†</td>
<td>8</td>
</tr>
<tr>
<td>A1R−/−</td>
<td>0.24±0.02*</td>
<td>0.26±0.03*</td>
<td>0.36±0.04†</td>
<td>9</td>
</tr>
<tr>
<td>Potassium</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A1R+/+</td>
<td>0.05±0.01</td>
<td>0.05±0.01</td>
<td>0.04±0.01</td>
<td>8</td>
</tr>
<tr>
<td>A1R−/−</td>
<td>0.07±0.01</td>
<td>0.06±0.01</td>
<td>0.06±0.01</td>
<td>9</td>
</tr>
<tr>
<td>Osmolar</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A1R+/+</td>
<td>0.37±0.09</td>
<td>0.45±0.07</td>
<td>0.57±0.04</td>
<td>8</td>
</tr>
<tr>
<td>A1R−/−</td>
<td>0.55±0.08*</td>
<td>0.67±0.09*</td>
<td>0.75±0.08*</td>
<td>9</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = no. of mice. BW, body weight. *P < 0.05 vs. A1R+/+ on same diet; †P < 0.05 vs. NS diet of the same genotype.

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the macula densa cells and an increased ATP utilization by the basolateral Na\(^+\)-K\(^+\)-ATPase. This will increase the demand for ATP in these cells, leading to hydrolysis of ATP to ADP and adenosine (30). Adenosine can then diffuse out of the cells into the interstitium, where it can stimulate A\(_1\)Rs on the afferent arterioles, causing vasoconstriction and a decrease in glomerular filtration rate. When the TGF response is absent, the increased solute load in the distal tubules cannot be adjusted, resulting in an increased solute excretion and diuresis. Two independent studies have shown that the TGF response is completely abolished in the A\(_1\)R\(^{-/-}\) mice, providing evidence that adenosine mediates the signal in the TGF mechanism (2, 29).

Another important function of the TGF is to regulate the delivery of electrolytes to the late distal tubule and collecting duct. The later segments are responsible for fine tuning of electrolyte reabsorption, keeping the plasma levels within certain limits. Their salt transport capacity is limited, however, and, if delivery of electrolytes is too large, reabsorption will not be sufficient and both water and electrolytes will be lost. As stated earlier, the increased natriuresis and diuresis could be a direct effect of the absence of TGF response, but it could also be because of the lack of A\(_1\)R along the nephron. We have also shown that the A\(_1\)R\(^{-/-}\) mice, under anesthesia, also have an elevated sodium excretion, a phenomenon also seen during A\(_1\)R blockade (2). In the present study, urinary excretion was measured in conscious mice freely moving in metabolic cages. Sodium excretion was higher in A\(_1\)R\(^{-/-}\) than in A\(_1\)R\(^{+/-}\) mice on both the SD and NS diets but not on the HS diet. Because the proximal tubule reabsorbs \(\sim 60\%\) of the filtered fluid and solute load, small changes in the rate of reabsorption will have a large effect on the amounts excreted. Although adenosine promotes sodium transport in the renal tubular cells, the exact mechanism has not been identified. A\(_1\)Rs have, however, been localized in the proximal tubule of the nephron (27). Wilcox et al. (32) could show in micropuncture studies in rats that A\(_1\)R inhibition inhibits proximal tubular reabsorption and disrupts the glomerulotubular balance. Studies in humans have also shown that an A\(_1\)R inhibitor causes a dose-dependent diuresis and natriuresis (6, 7). The increased renal excretion of sodium, seen in the A\(_1\)R\(^{-/-}\) mice, is most likely due to a combination of the absence of the TGF response and a reduction in sodium reabsorption along the nephron.

Paradoxically, although our A\(_1\)R\(^{-/-}\) mice had an increased sodium and fluid excretion, they still had elevated blood pressure compared with the A\(_1\)R\(^{+/-}\) mice. One would expect that increased urinary excretion would lead to decreased blood pressure in animals given an SD diet. However, this may be compensated by the activation of the renin-angiotensin system. Even though changes in salt intake did affect plasma renin levels, the A\(_1\)R\(^{-/-}\) mice had at least twofold higher plasma renin levels than the A\(_1\)R\(^{+/-}\) mice, indicating that the A\(_1\)R tonically inhibits renin secretion. Our results also show that an increase in dietary salt content diminishes PRCs to approximately the same extent in both the A\(_1\)R\(^{-/-}\) and A\(_1\)R\(^{+/-}\) mice. If adenosine were necessary for macula densa-mediated renin secretion, then the stimulator effect of a low-salt diet and the inhibitory effect of an HS diet on renin secretion would be greatly attenuated or blocked altogether in A\(_1\)R\(^{+/-}\) mice.

Together, our results confirm that adenosine, acting through the A\(_1\)R, plays an important role in regulating TGF and blood pressure, renin release, and sodium excretion.

ACKNOWLEDGMENTS

We thank Professor Göran Begström for assistance with the metabolic cages, Dr. Cecilia Lövdahl for help in the breeding of mice for the study, and Eva Irenius for help genotyping. Janet Holmén provided valuable linguistic assistance.

GRANTS

This study was financially supported by the Swedish Research Council (project no. 14X-2553, K2003-04X-03522-32, 2553, and 3522), the Swedish Heart Lung Foundation, the Wallenberg foundation, Wallenberg consortium North, the Ingabrit and Arne Lundberg Foundation, and Biovitrum Partners.

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