

Child-appropriate multiplex mass spectrometric assay solution to reliably monitor the maturing renin-angiotensin-aldosterone-system und the adjoining kinin-kallikrein-system in low sample volumes

Dr. Bjoern B. Burckhardt

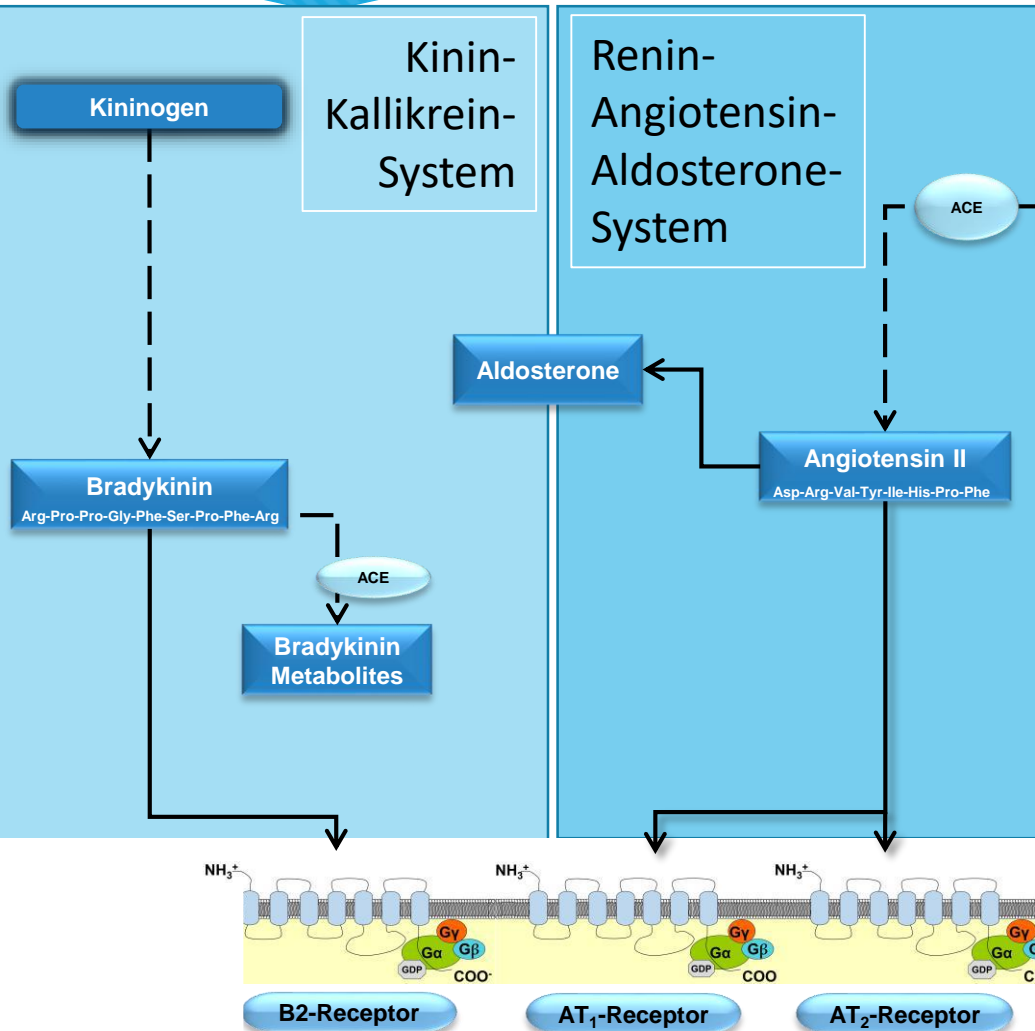
Institute of Clinical Pharmacy and Pharmacotherapy,
Heinrich Heine University, Germany

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Renin-Angiotensin-Aldosterone-System (RAAS) and Kinin-Kallikrein-System (KKS)

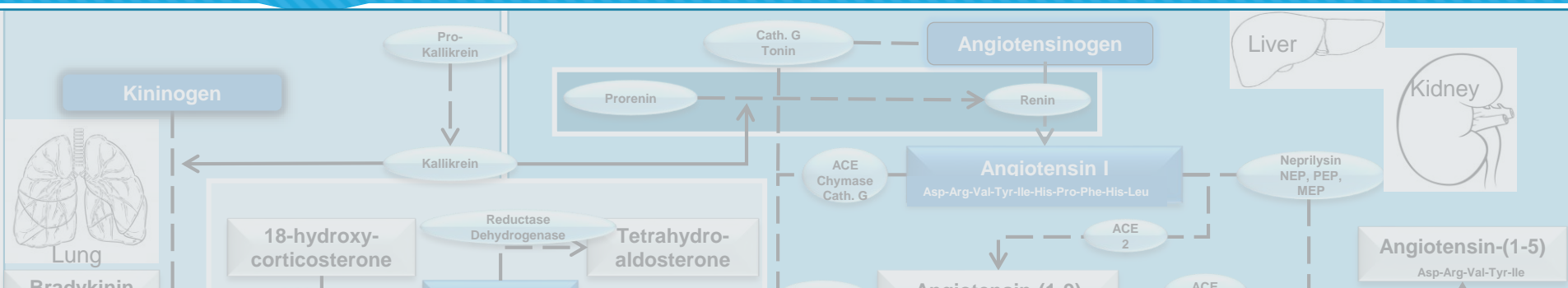


Furthermore, these systems undergo substantial developmental changes during childhood

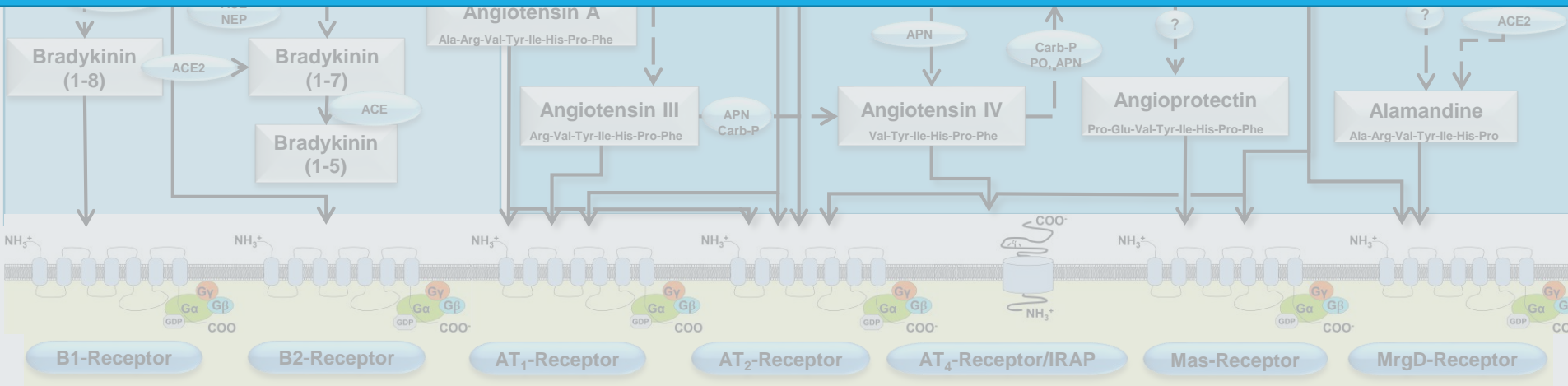
Both systems are involved in e.g.

- **Cardiovascular** (*hypertension, heart failure, ischemic stroke*)
- **Renal** (*renal disease, adrenal insufficiency*)
- **Endocrinological** (*Diabetes mellitus*)
- **Neurodegenerative** (*Alzheimer, Parkinson*)
- **Neuropsychiatric** (*epilepsy, depression*)
- **Inflammatory** (*Morbus Crohn, Colitis ulcerosa*)
- **and respiratory diseases**

There is so much more to know...



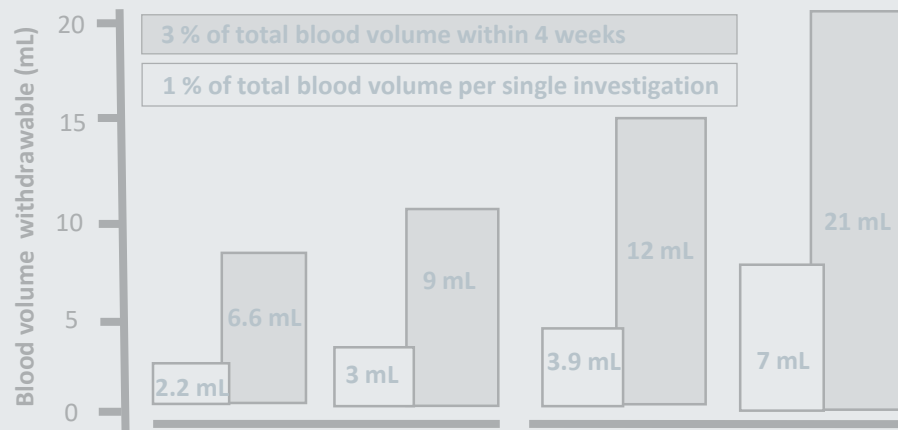
The investigations of those complex biochemical parameters are often limited by the blood volume available.



Pharmacodynamics in paediatrics

Still in recent paediatric trials

- often only 1 pharmacodynamic parameter monitored
- same assays as for adult trial applied
- requiring too much blood volume



Innovative and reliable bioanalytical tools are highly required, which facilitates the comprehensive investigation of those endogenous peptides in small human sample volumes.

Pharmacokinetics, pharmacodynamics, safety and efficacy study of LCZ696 in children (1 month to < 18 years) with heart failure (Novartis; on-going)

- Sampling of Plasma B-type natriuretic peptide (BNP), plasma N-terminal pro-brain natriuretic peptide (NTproBNP). **The 24 hour post dose is optional depending on blood volume restrictions**

A study to investigate increasing doses of Sodium Zirconium Cyclosilicate (SZC) in children under 18 years old who have high blood potassium levels (Hyperkalaemia) (Astra Zeneca; initiated)

- Serum aldosterone (S-Aldo) **at the end** of the maintenance phase

Bioanalysis tailored for paediatrics

The developed multiplex platform bases on:

- High-performance liquid chromatography coupled to mass spectrometry
 - *to overcome limitations of immunoassay determination*
- Small sample volume (Plasma / serum)



Tailored multiplex mass spectrometric assays successfully established to support the maximum knowledge gain from human blood samples

- applicable to healthy and diseased population

- High-throughput approach
 - *to allow implementation in clinical setting*
- Fully validated according to EMA / FDA bioanalytical guidelines and embedded into GCLP-compliant environment



Multiplex bioanalytical mass spectrometric platform established

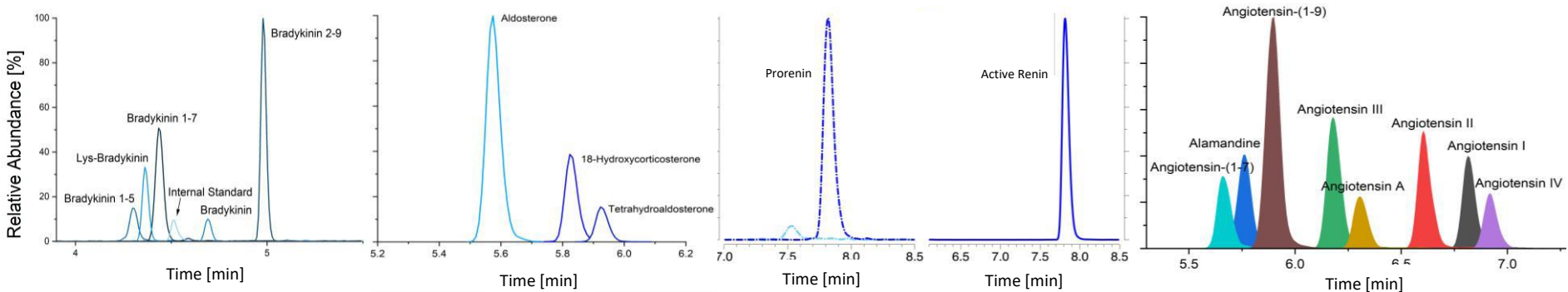
Allows for the comprehensive investigation of:

7 parameter
in the KKS

- Bradykinin
- Bradykinin (1-5)
- Bradykinin (1-7)
- Bradykinin (1-8)
- Bradykinin (2-9)
- Lys-Bradykinin
- 6-keto prostaglandin F1 α

14 parameters
in the RAAS

- 18-Hydroxy-Corticosterone
- Aldosterone
- Tetrahydro-Aldosterone
- Prorenin
- Active Renin
- Alamandine
- PRA
- Angiotensin I
- Angiotensin II
- Angiotensin III
- Angiotensin IV
- Angiotensin A
- Angiotensin (1-7)
- Angiotensin (1-9)



KKS: Kinin-Kallikrein-System; RAAS: Renin-Angiotensin-Aldosterone-System



Conclusion

Multiplex bioanalytical LC-MS/MS platform

- Comprehensive monitoring of two important regulation systems
 - *Enables deeper and coherent insight into etiology and pathology*
- Tailored for application in all paediatric age groups
 - *Allows repeated determination even in neonates without infringing ethical considerations*
- Facilitates better understanding of important diseases in paediatrics
 - *Leading to a more rational and focused pharmacotherapy*
- Empowers identification of new promising drug targets



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Heinrich Heine
Universität Düsseldorf



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