

TRANSLATIONAL BOTULINUM TOXIN RESEARCH: COMPARING BT DRUGS

Dirk Dressler

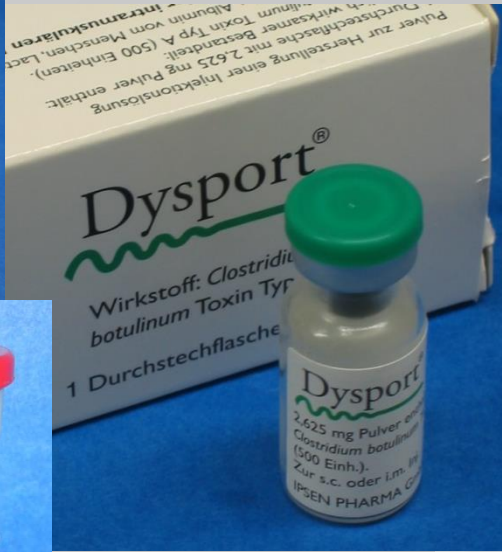
**Movement
Disorders Section
Department
of Neurology
Hannover
Medical School**

**Hannover
Germany**

肉毒毒素转化医学研究：不同肉毒毒素的比较

WHAT IS TRANSLATIONAL RESEARCH?





COMPARING BT DRUGS 肉毒毒素的比较

- all BT drugs are different ('unique'), but they can be compared
- however, this comparison is *complex* and has to be *multidimensional*
- dimensions of BT drugs comparison are:

mode of action

作用机制

duration of action

作用时间

diffusion

弥散

potency/adverse effects

效力/不良反应

potency labelling

效力特点

antigenicity

抗原性

stability

稳定性

composition

组成

manufacturing

生产过程

manufacturer

生产商

MODE OF ACTION 作用机制

- all BT-A drugs have the same MOA
- BT-A drugs and BT-B drugs have different MOA
 - SNAP cleavage site
 - binding potential to motor and autonomic synapses

- 所有的A型肉毒毒素为相同的作用机制
- A型肉毒毒素与B型肉毒毒素作用机制不同
 - 突触相关膜蛋白的结合位点不同
 - 与运动和自主神经突触结合的结合力不同

DURATION OF ACTION 作用时间

- all BT-A drugs have same DOA
- daxibotulinumtoxinA claims longer DOA
- BT-B and BT-A seem to have same DOA
- different BT types have different DOA

- 所有A型肉毒毒素有相同的作用时间
- A型肉毒毒素与B型肉毒毒素有相同的作用时间
- 不同类型的肉毒毒素作用时间不同

POTENCY AND ADVERSE EFFECTS 效力及不良反应

- **all BT-A drugs have same potency and AE**
reported differences are due to incomparable dosages
- **BT-B drugs have more autonomic AE**
- **BT-A and BT-B drugs seem to have same potencies**

- 所有A型肉毒毒素有相同的效力及不良反应
目前报道的差异来源于剂量问题，其不可比较
- B型肉毒毒素有更多的自主神经不良反应
- A型肉毒毒素与B型肉毒毒素有相同的效力

POTENCY LABELLING 1 效力的特征

- **BT potency labelled can be defined international definition (MU)**
 - however: definition of MU seems to be incomplete
- **BT potency can be measured against external standard**
 - however: there is no external standard
- **hypothesis for incomparability ONA vs ABO:**
 - different measurement assays
 - correct vial filling, but incomplete retrieval after reconstitution
 - insufficient HSA content
- 肉毒毒素效力定义
 - 国际定义（小鼠单位，mouse unit），但是有局限
- 效力可通过外部标准评价，但目前没有通用的外部标准
- 不可比性的假说 OnabotulinumtoxinA 对比 AbobotulinumtoxinA
 - 评估的试验不同/配制导致的药品差异/人血清白蛋白

POTENCY LABELLING 2 效力的特征

- **potency measurement**

animal assays

lethality assay (致死试验)

mouse diaphragm assay (小鼠膈肌试验)

cell based assay (细胞试验)

human assays

motor function: EDB test, SCM test, frowning test

autonomic function: sweat test

clinical comparisons

cross-over designs (交叉设计)

randomised head-to-head comparisons (随机对照)

historical comparisons (回顾性比较)

problem: sensitivity of the test system/measurement system

存在问题: 实验系统/评估系统的敏感度

ANTIGENICITY 抗原性

- **complexing proteins**
 - **purity of the botulinum neurotoxin component**
specific biological activity (SBA)
 - **assays**
 - clinical monitoring**
 - BT antibody test**
 - functional assays: lethality assay, mouse diaphragm assay**
 - structural assays: ELISA, RIPA**
 - 复合蛋白（毒素辅助蛋白）
 - 毒素神经毒素部分的纯度
特异性生物学活性
 - 试验
 - 临床检测
 - 毒素抗体测试
- 功能测定：致死试验/小鼠膈肌试验
结构测定：ELISA,RIPA

STABILITY 稳定性

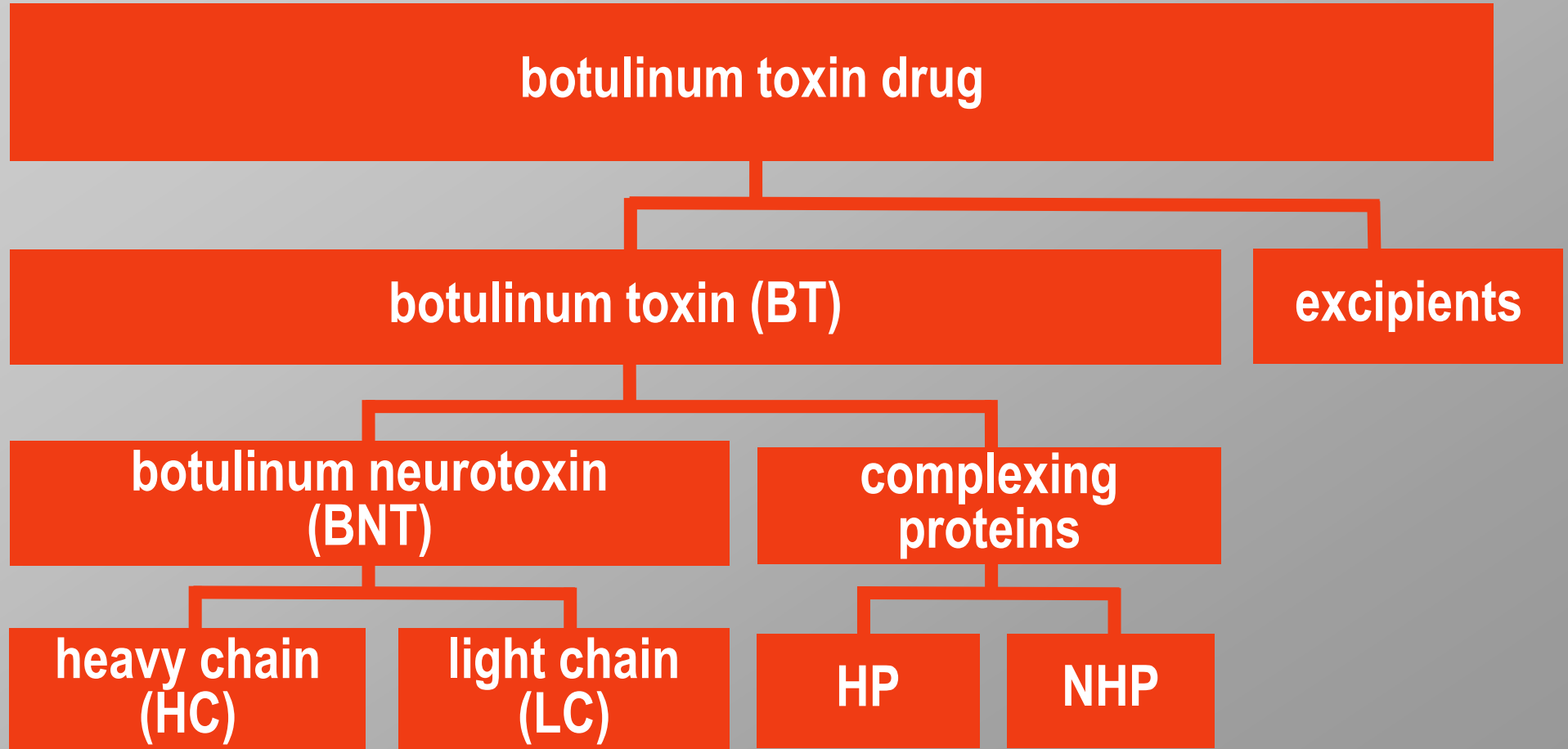
- **stability clearance is different between BT-drugs**
storage temperatures
shelf life
- **real stability may also be different**
- 不同肉毒毒素稳定性不同
 储存温度不同
 保质期不同
- 真实的稳定性也不同

DIFFUSION 弥散

- no differences between BT-A drugs
- no differences between BT-A drugs and BT-B drugs

- 不同肉毒毒素弥散无差异
- A型肉毒毒素与B型肉毒毒素弥散无差异

COMPOSITION 1 组成



HP: 血凝素部分 NHP: 非血凝素部分

COMPOSITION 2 组成

- **BT type**
- **complexing proteins**
- **excipients**
 - bovine gelatine, human serum albumin**
 - stabilisation: liquid, non-liquid**
 - pH value**

- 肉毒毒素种类
- 复合蛋白
- 辅料（赋型剂）
 - 牛明胶/人血白蛋白
 - 液态/非液态
 - pH值

MANUFACTURING (生产)

- **quality of manufacturing process**

 - chemical purity

 - immunological purity

 - control of potency

 - consistency of potency

- **documentation of manufacturing process**

 - GMP, FDA/EMEA**

 - 生产制造过程质量

 - 化学提纯

 - 免提提纯

 - 效力控制

 - 效力的一致性

 - 生产过程的记录

MANUFACTURER (生产商)

- **cooperative and accessible**
- **supportive for training and research projects**
- **providing sufficient registrations**
- **solid development program**

expanding indications

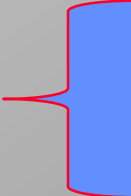
expanding registrations

developing products

researching new products

- 合作
- 支持学习及研究项目
- 提供有效的注册

• 发展计划



- 扩大适应症
- 扩大注册
- 发展产品
- 开发新产品

SUMMARY

- translational BT research is the bridge between basic science and clinical practise
- it also allows to compare BT drugs
- BT drug comparison is *complex* and has to be *multidimensional*
- the most important ones are potency labelling and antigenicity
- BT drug comparison will become more and more important as many new BT drugs are under development

- 转化肉毒毒素研究是基础研究及临床实践的桥梁
- 目前仍然允许比较肉毒毒素
- 肉毒毒素的比较复杂，且具有多维性
- 最重要的是效力的特点以及抗原性
- 肉毒毒素药物将会随着更多新药的产生变得越来越重要



谢谢



END

