Comparative in vivo pharmacology of dopidines

A novel class of compounds discovered by phenotypic screening

Akademisk avhandling som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet, kommer att offentligen försvaras i sal Ivan Östholm, Medicinaregatan 13, fredagen den 2 oktober 2015 kl. 13:00 av

Susanna Holm Waters
Examinerad läkare

Fakultetsopponent: Professor Per Svenningson, Institutionen för klinisk neurovetenskap, Karolinska Institutet, Stockholm

Avhandlingen baseras på följande arbeten:

I. Tedroff J, **Waters S**, Barker R, Roos R, Squitieri F, on behalf of the EHDN Registry Study Group. Antidopaminergic Medication is Associated with More Rapidly Progressive Huntington's Disease. Journal of Huntington's disease 2015; 4(2): 131–140.

II. **Waters S**, Svensson P, Kullingsjö J, Pontén H, Andreasson T, Sunesson Y, Sonesson C, Waters N. *In vivo* systems response profiling and multivariate classification of CNS active compounds: Exploring dopaminergic stabilizers, antipsychotics and a novel class of cortical enhancers. Manuscript, 2015.

III. **Waters S**, Ponten H, Edling M, Svanberg B, Klamer D, and Waters N. The dopaminergic stabilizers pridopidine and ordopidine enhance cortico-striatal Arc gene expression. Journal of Neural Transmission 2014; 121(11): 1337-1347.

IV. **Waters S**, Ponten H, Klamer D, and Waters N. Co-administration of the Dopaminergic Stabilizer Pridopidine and Tetrabenazine in Rats. Journal of Huntington's Disease 2014; 3(3): 285-298.

UNIVERSITY OF GOTHENBURG

Göteborg 2015

Comparative in vivo pharmacology of dopidines

A novel class of compounds discovered by phenotypic screening

Susanna Holm Waters
Department of Pharmacology
Institute of Neuroscience and Physiology
Sahlgrenska Academy at University of Gothenburg

ABSTRACT

Dopidines are a novel class of dopamine (DA) modulating compounds, developed to provide improved treatment of a range of neurodegenerative and psychiatric disorders that are currently managed to a large extent with antidopaminergic medications. The overall aim of the present work was to investigate the *in vivo* pharmacology of dopidines, as compared to other classes of monoamine modulating compounds. A further aim was to explore the long term effects of antidopaminergic medication in Huntington's disease (HD), a neurodegenerative disorder characterized by motor, behavioural, and cognitive symptoms.

Data from REGISTRY, an observational study on patients with HD, were analysed by means of principal component analysis, bivariate regression, and multiple regression, to assess the potential impact of antidopaminergic medications on motor and functional outcomes. The further studies were based on preclinical studies, performed in rats. Multivariate analysis was applied on *in vivo* systems response profiles - systematically collected dose response data on monoaminergic neurochemistry and behavioural activity - elicited by a range of monoamine modulating compounds, including *i.a.* dopidines, antipsychotics, antidepressants, and procognitive agents. These data were used to create multivariate maps providing a comprehensive overview of similarities, trends and clusters among the compounds, and their effects *in vivo*. Further, the effects of dopidines and a set of reference compounds, on *Arc* mRNA expression, a marker of synaptic activity, were investigated. Pharmacological interaction studies were performed with one of the dopidines, pridopidine, and tetrabenazine, comparing pridopidine's effects with those of the DA D2 antagonist haloperidol. Outcome measures were locomotor activity, striatal DA indices, and *Arc* mRNA.

In patients with HD, antidopaminergic medication was associated with more severe motor and functional impairment, and a faster progression rate. This finding could not be explained by factors such as age, disease duration, or CAG repeat length. While *e.g.* selection bias underlying the findings cannot be ruled out, the concern is raised that current antidopaminergic medications may be detrimental in HD. This signal warrant further investigation, in HD as well as in other neurodegenerative disorders, where such treatment is common practice.

The *in vivo* profiling indicated that dopidines form a distinct pharmacological class, with antipsychotic and tentatively procognitive properties, but lacking psychomotor depression. The pattern of *Arc* gene expression distinguished the dopidines further from other DA modulating agents. The dopidines displayed effects suggesting synaptic activation in the frontal cortex, which is proposed to contribute to their characteristic psychomotor stabilizing effects, both in terms of efficacy in reducing locomotor activity in hyperactive states, but also with regards to their ability to relieve hypoactivity. Alleviation of hypoactivity was expressed also in a partially monoamine-depleted state induced by tetrabenazine. This has implications regarding potential benefits of co-administering tetrabenazine and pridopidine in patients with HD, and further suggests dopidines could be therapeutically useful in other neuro-degenerative disorders. Based on these findings, and previously published data, a tentative model of the *in vivo* mode of action of this class of compounds at the level of major neuronal pathways disrupted in HD, is outlined.

Keywords: Phenotypic screening, systems pharmacology, antipsychotics, dopamine, Arc, frontal cortex, striatum, Huntington's disease

ISBN 978-91-628-9501-3 (print)
ISBN 978-91-628-9502-0 (pdf)
http://hdl.handle.net/2077/39542