

**Possible role of prostanoids in migraine and other  
headaches evaluated in an experimental human model**

**Mulig rolle for prostanoider i migræne og andre hovedpine  
typer evalueret i en experimentel hovedpinemodel**

**PhD thesis**

Troels Wienecke, MD

Danish Headache Center and Department of Neurology  
Glostrup Hospital  
Faculty of Health Sciences  
University of Copenhagen  
Copenhagen  
Denmark

Hovedvejleder: Messoud Ashina

Medvejleder: Jes Olesen

Opponenter: Rami Burstein, Troels Stahelin Jensen, Niels Secher

## Summary in English

Prostanoids are products of the arachidonic acid cascade and highly relevant to the pathophysiology of migraine without aura. Inhibition of prostanoid synthesis is effective in the treatment of headache and migraine without aura, and headache is reported as adverse event during infusion of PGI<sub>2</sub>, PGE<sub>2</sub> and PGD<sub>2</sub>.

The aim of the present thesis was to explore the headache eliciting effect of the prostanoids prostaglandin I<sub>2</sub> (PGI<sub>2</sub>) (prostacyclin), prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) and prostaglandin D<sub>2</sub> (PGD<sub>2</sub>) in healthy subjects. In addition, explore the possible migraine triggering effects of PGI<sub>2</sub> in migraineurs without aura.

PGI<sub>2</sub>, PGE<sub>2</sub> and PGD<sub>2</sub> were infused intravenously in placebo controlled double blind cross-over studies. Headache intensity and associated symptoms were recorded according to the International Headache Society (IHS). Velocity in the middle cerebral artery ( $V_{MCA}$ ), and diameter in the superficial temporal artery (STA) and radial artery (RA) were measured with ultrasonography and regional cerebral blood flow (rCBF) using <sup>133</sup>Xe inhalation and Single Photon Emission Computerized Tomography (SPECT) to estimate relative changes in diameter of the Middle Cerebral Artery (MCA). PGI<sub>2</sub>, PGE<sub>2</sub> and PGD<sub>2</sub> induced a mild headache (median VRS 1-2) associated with vasodilatation in healthy subjects. In contrast to PGI<sub>2</sub> and PGE<sub>2</sub>, PGD<sub>2</sub> did not trigger a severe headache despite a large and prolonged vasodilatation. PGI<sub>2</sub> triggered a migraine like headache with associated dilatation in migraineurs without aura and 75% reported the headache to mimic a spontaneous migraine attack without aura. These findings support a role for prostanoids in the pathophysiology of migraine without aura. Sensitization of nociceptors might be central in the pathophysiology of migraine without aura.

## Summary in Danish

Prostanoider er produkter af arakidonsyre og meget relevanter i migrænenes patofysiologi. Hæmmere af prostanoid syntesen (NSAIDs) er effektive til behandling af hovedpine og migræne uden aura, og hovedpine er en kendt bivirkning ved infusion af PGI<sub>2</sub>, PGE<sub>2</sub> og PGD<sub>2</sub>.

Formålet med denne afhandling var at undersøge de hovedpine udløsende egenskaber af prostanoiderne prostaglandin I<sub>2</sub> (PGI<sub>2</sub>) (prostacyclin), prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) og prostaglandin D<sub>2</sub> (PGD<sub>2</sub>) på raske forsøgsparticipanter. Yderligere, at undersøge mulige migræne udløsende egenskaber hos migræne patienter uden aura.

PGI<sub>2</sub>, PGE<sub>2</sub> og PGD<sub>2</sub> blev givet ved intravenøs infusion i placebo kontrollerede dobbelt blinde cross-over forsøg. Hovedpine intensitet og associerede symptomer blev noteret jvf den internationale hovedpineklassifikation. Blodets hastighed i arteria cerebri media og diameter af arteria temporalis superficialis og arteria radialis blev målt ved ultralydsteknik og hjernens regionale blod flow ved hjælp af <sup>133</sup>Xe inhalation og Single Photon Emission Computerized Tomography (SPECT) for at estimere relative ændringer i arteria cerebri medias diameter. PGI<sub>2</sub>, PGE<sub>2</sub> og PGD<sub>2</sub> inducerer en mild hovedpine (median VRS 1-2) associeret med kardilatation hos raske forsøgsparticipanter. I modsætning til PGI<sub>2</sub> og PGE<sub>2</sub>, fremkalder PGD<sub>2</sub> ikke en kraftigere hovedpine pga større og længerevarende kardilatation. PGI<sub>2</sub> udløser en migrænelignende hovedpine associeret med kardilatation hos migræne patienter uden aura og 75% rapporterede at denne hovedpine lignende et spontant migræne anfald uden aura. Disse fund bekræfter at prostanoider spiller en rolle i migrænen uden aura patofysiologi. Sensitisering af nociceptorer kan være central i migræne uden auras patofysiologi.