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LETTER TO THE EDITOR

Epigenetics and pharmaco-epigenetics in the primary headaches

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I wish to thank Dr. Schürks for his appreciative comments [1] on my review published in the *Journal of Headache and Pain* [2]. This review was based on a presentation given at a master course on headache in Rome, (incompletely) summarizing evidence for genetic mechanisms in the primary headaches and briefly presenting our proposal of the primary headaches as integrated behaviours having an evolutionary meaning and pain as a signal of homeostatic unbalance. This novel view of the primary headaches with a discussion on the relevant imaging studies was better detailed elsewhere [3], and represents an elaboration of precedent bio-behavioural theories of migraine [4, 5]. Modelling the primary headaches as behavioural disorders helps to explain their important co-morbidities (to be really construed as intrinsic features of the diseases), and sets up also a framework useful for future genetic studies, since, as Schürks rightly emphasizes that it can accommodate those environmental aspects (lighting conditions, dietary factors and lifestyles, socio-economic status, etc. [6, 7]) that are so important for pathogenesis. Thus, epigenetic mechanisms seem to be particularly interesting for migrainologists, whereas their importance is being increasingly recognized in psychiatric and developmental disorders of the nervous system. Epigenetic mechanisms have yet even to be taken into consideration in the primary headaches, even though some preliminary evidence may be gleaned by studies of twins raised together and apart from their infancy [8]. While this study found that several putative risk factors (schooling, education, marital status, smoking status and alcohol consumption) showed no association with migraine with aura, this was a retrospective study and one that investigated situations mostly arising later in life [8]. Epigenetic mechanisms can be more easily investigated prospectively in the setting of neonatal/paediatric medicine, for instance, by studying the child attachment patterns and psycho-social conditions and how they relate to the chance of developing migraine later in life.

Schürks expands our (epi)genetic model to include the hypothesis of a pharmaco-epigenetic determination of drug treatment response, and suggests that epigenetic modifications may explain for instance patients' responses to analgesics and triptans that change over time and upon frequency of usage (e.g. medication overuse) and that therefore are hard to explain by simple alterations in the genetic code [1]. Schürks' hypothesis is surely a most welcome consideration and extension of the model, and one that I most enthusiastically endorse. To this, I wish to add another suggestion that indeed preventative therapies, such as tricyclic antidepressants, calcium channel inhibitors, anti-epileptics and lithium salts, also used widely in the prophylaxis of migraine and other headaches, work by modifying those epigenetic mechanisms involved in headache determination at the individual level. Indeed, we still do not know how these therapies work, and their timing of action, often requiring several weeks or even months for the pharmacological effect to develop, is difficult to explain with a direct or an indirect action on neurotransmitter receptors. Valproate, an anti-epileptic drug also used in the migraines, has been indeed shown to modify epigenetic programming in the experimental animal [9]. Hypotheses are not however facts, and whether epigenetic mechanisms contribute to the pathogenesis of the primary headaches needs to be specifically addressed by appropriate studies. Here, I take again the opportunity of thanking Dr. Schürks for his thoughtful comments.

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Conflict of interest None.

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