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Whats's new in pharmacotherapy of neurological disorders?

Pharmacological fMRI and EEG for the development of novel analgesic compounds. André MOURAUX. Chargé de recherches FNRS. Laboratoire d'algologie – Unité READ. Université Catholique de Louvain.

Functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) have been introduced in pharmacological studies with the aim to measure the modulation of brain activity by drugs acting directly on the central nervous system (CNS) or indirectly on its afferent input. By providing novel and specific biomarkers which could substitute or complement clinical endpoints, this approach is thought to have the potential to contribute to the early clinical stages of drug development, and, in particular, to the development of novel analgesic compounds. Here, we shall (1) examine the ability of these methods to investigate the actions of drugs on the CNS, (2) review the studies of analgesic drugs which have already used these techniques, and (3) discuss potential caveats in interpreting modulations of fMRI and EEG activity as reflective of drug-induced changes in neuronal activity.

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Brain awareness week. What's new in drug treatment of neurological disorders? March 21, 2009. What's new in Amyotrophic Lateral Sclerosis (ALS)? Roland POCHET. Lab Histology, Neuroanatomy and Neuropathology, Fac. Médecine, Université Libre de Bruxelles.

Amyotrophic Lateral sclerosis (ALS) which is the most elusive neurological disorders but also the most common Motor Neuron Disease (MND) with a crude incidence between 0,6 and 2,6 per 100.000 population leading to a lifetime risk of developing ALS of 1 per 800.

The time from symptom onset to the date of diagnosis is often over a year with a terminal condition necessitating early access to palliative care services. The diagnosis is based upon clinical criteria that include the presence of upper motor neuron (UMN) and lower Lower Motor Neuron (LMN) signs. No single diagnostic test can confirm or entirely exclude ALS and should include electrophysiological test. The use of motor evoked potentials (MEP) recording following transcranial stimulation of motor cortex helps in demonstrating UMN involvement. Neuroimaging may exclude other conditions causing UMN and/or LMN. Computational neuroanatomy techniques such as voxel-based morphometry and diffusion tensor imaging hold promise in understanding ALS pathophysiology and developing surrogate markers for disease progression usable in clinical trials.

There is clear evidence that ALS and frontotemporal lobar dementia (FTLD) overlap, clinically, radiologically, pathologically and genetically which is reinforced by the recent discovery that TDP-43 is a major component of ubiquitinated

inclusions in both FTLD and in ALS. The presence of cognitive decline illustrate that ALS is a multisystem disorder. Therefore, cell therapy seems the most promising approach. Already the use of embryonic stem cells to generate a supply of human motor neurons has been achieved which offers insights and screening methods especially in the case of sporadic ALS considering that induced pluripotent stem cells carry the precise constellation of genetic information associated with person's condition.

Anti-migraine drugs: perspectives. Jean SCHOENEN. Dept of Neurology & GIGA-Neurosciences. Liège University.

Migraine is a disorder with a complex pathophysiology and various subtypes. Schematically one can distinguish "acute therapy", i.e. symptomatic treatment of the migraine attack, and "preventive therapy", i.e. continuous long-term treatment aiming at reducing attack frequency and intensity. Since more than 10 years, triptans are the mainstay in acute treatment. They are agonists of 5-HT1B/D receptors which are present in the trigeminovascular system where the migraine headache originates, on vessels (B), presynaptic distal and proximal nerve endings (D) and in suprasegmental areas including the endogenous pain control systems (B + D). There are shortcomings of triptans with regard to safety (they induce mild constriction of coronary arteries) and clinical efficacy (high recurrence rates, incomplete effect of oral triptans, class specific chest symptoms..). The vascular effects can be avoided with specific 5-HT1D and with 5-HT1F agonists. One of the former (PNU-142633) was ineffective in one trial. Among the latter, LY-334370 was effective but showed hepatotoxicity in animals. LY-573144 (Col-144) which has no toxicity, had dose-related efficacy in an i.v. phase 2 trial and is going into an oral phase 3 study. Besides 5-HT, a number of transmitters and receptors are involved in trigeminovascular nociception. CGRP is one of the most interesting as it raises in jugular vein blood during migraine attacks and its receptor (calcitonin receptor-like receptor coupled to RAMP1) is abundant in the trigeminal system. Olcegepant (BIBN 4096 BS), a peptide CGRP-R antagonist, had dose-dependant efficacy in an i.v. acute trial with a 2 h-responder rate close to that reported for injectable sumatriptan. Telcagepant (MK-0974), an oral CGRP-R antagonist, had, at 300 mg, similar efficacy as 5 mg zolmitriptan. The advantage of the "gepants" is their excellent tolerability and absence of vascular effects, but their global efficacy does not seem to be superior to that of the triptans. Phase 2 oral trials have just been completed for the follow-up drugs of olcegepant and telcegepant. NO donors are known to induce migraine-like headache several hours after administration. In a small study, L-NMMA, a non specific NOS inhibitor, was able to abort migraine attacks. However, a preventive RCT with an iNOS inhibitor, GW274150, was negative. MTR-106 was recently to be effective as an acute treatment in a small phase-II trial; its mode of action which is not completely elucidated, seems to involve inhibition of NO overproduction. A proof-of-concept study was positive for for an adenosine A1 receptor agonist, but this was not followed by other studies. A phase II study of a vanilloid receptor antagonist (VR1) has just been completed. Animal experiments suggests that nociceptin and the NOP receptor, the cannabinoid receptor CB1 and the orexin A receptor may be interesting targets for migraine treatment. Glutamate and its receptors play a seminal role not only in trigeminal nociception, but also in cortical excitability. LY-293558, a mixed AMPA/kainate receptor antagonist was found effective in acute migraine. On the other hand, ADX 10059, a negative allosteric modulator of mGlu-r receptors was superior to placebo in an acute phase I study, and is now going into a phase II preventive trial.

With regard to preventive trials, there are unfortunately few new findings. The efficacy of topiramate in migraine prevention has been extended to chronic migraine and medication overuse headache, although the score in the latter does not exceed 30%. As other anti-migraine preventives, topiramate was shown to have disease-modifying effects, as amelioration after a 6 months treatment was maintained in the majority of patients switched to placebo, though at the expense of increase in attack frequency in 30% of them. We have shown that lamotrigine is unique among other anti-migraine drugs, such as valproate or riboflavin, in that it is able to inhibit cortical spreading depression in animals after a 4 week treatment; in line with this, it has also selective clinical efficacy on the migraine aura. Tonabersat, a gap-junction modulator, which also inhibits CSD, seems to have the same profile, as it was not effective in the prevention of migraine without aura, but was so in a small cross-over study of migraine with aura. Finally, in a pharmacogenetic study we have shown that migraineurs who respond to riboflavin, have at majority polymorphisms in the non-coding region of mitochondrial DNA which classify them as belonging to non-H haplogroups, while non-responders belong at majority to the H-haplogroup, where mitochondrial oxphos activity is supposed to be greater.

To summarize, the next progress in the treatment of migraine attacks will undoubtedly come from the CGRP receptor antagonists, the "gepants". Compared to the triptans, they are probably not more effective, but have better tolerability and vascular safety. Regarding preventive treatments, improvement and progress will come from more precise targeting of individual pathophysiology and pharmacogenetics.

What's new in multiple sclerosis?

New epidemiological data show that the prevalence of multiple sclerosis is increasing in all countries where it is endemic and particularly in women, with a sex incidence ratio currently approaching 3 to 3,5.

For the past decade, treatment of multiple sclerosis has been limited to interferon β, glatiramer acetate with partial efficacy and subcutaneous or intra-muscular administration.

Natalizumab, a humanised monoclonal antibody against α4 integrin, has shown a higher efficacy and is usually well tolerated, but with an increased risk, particularly of progressive multifocal encephalomyelitis (currently 8 cases for > 20.000 patients treated more than 1 year).

Other monoclonal antibodies are currently studied in multiple sclerosis: alemtuzumab, daclizumab, rituximab, ocrelizumab..., some of which have been shown to have superior efficacy compared to Interferon b.

On the other hand, several oral therapies are currently in phase III studies (cladribine, FTY 720 or fingolimod, BG00012 a fumarate derivative, teriflunomide..) with promising results.

Although the adverse event profile of these drugs seems acceptable in rather short term studies (2-3 years), their long term benefit risk ratio will need to be carefully monitored in the coming years.