Journal of Neuroscience Methods 233 (2014) 166–171

Contents lists available at ScienceDirect

Journal of Neuroscience Methods

journal homepage: www.elsevier.com/locate/jneumeth

Basic Neuroscience

Theoretical and practical applications of the intracerebroventricular route for CSF sampling and drug administration in CNS drug discovery research: A mini review

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HIGHLIGHTS

- Review of CNS disorders.
- Describes knowledge/applications underlying ICV route of CSF sampling and dosing.
- Bridging preclinical studies and human clinical studies.

ARTICLE INFO

Article history:
Received 11 May 2014
Received in revised form 6 June 2014
Accepted 9 June 2014
Available online 14 June 2014

Keywords:
Brain
Central nervous system
Intracerebroventricular
Rat
Cerebrospinal fluid (CSF)
Supraspinal
Intrathecal

ABSTRACT

Clinically, central nervous system (CNS) disorders account for more hospitalisations and prolonged care than almost all other diseases combined. In the preclinical setting, the intracerebroventricular (ICV) route for cerebrospinal fluid (CSF) sampling or dose administration in rodent models of human CNS disorders has potential to provide key insight on the pathobiology of these conditions. Low level neuroinflammation is present in >40% of patients with severe depression or schizophrenia and so comparative assessment of CSF composition between patients and rodent models of CNS disorders is potentially invaluable for hypothesis generation and for assessing rodent model validity. As molecules in the CSF have relatively low protein binding and are freely exchanged into the extracellular fluid of the brain parenchyma, supraspinal drug administration into the CSF can produce therapeutic drug concentrations in the brain. Direct administration of investigational agents into the CSF of the lateral ventricle of the brain enables intrinsic efficacy and adverse effect profiles to be evaluated without the confounding effects of drug metabolism, due to the low capacity of the CNS to metabolise exogenous compounds. It is our view that the ICV route for CSF sampling and for administration of novel drugs in development is under-utilised in preclinical research on CNS disorders. This is due to the high degree of technical skill and low margin for error associated with correct ICV guide cannula implantation in the rat. However, these technical challenges can be overcome by using standardised procedures and attention to detail during surgery and in the post-operative period.

Contents

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http://dx.doi.org/10.1016/j.jneumeth.2014.06.006
0165-0270/

1. Introduction

Despite considerable research advances in the past two decades, central nervous system (CNS) disorders that encompass developmental, psychiatric and neurodegenerative diseases, remain the world's leading causes of disability and account for more hospitalisations and prolonged care than almost all other diseases combined (de Lange, 2013; Misra et al., 2003). In the clinical setting, brain disorders and other chronic conditions such as persistent inflammatory and neuropathic pain where the pathobiology is underpinned by neuroplastic changes in the CNS (Woolf, 2011), cause enormous human suffering and a huge socioeconomic cost to patients, their care-givers and the general community.

It is estimated that approximately 13% of global disease is due to disorders of the brain, surpassing both cardiovascular diseases and cancer (Collins et al., 2011). In the European Union, disorders of the brain are the largest contributor to the all cause morbidity burden as measured by disability adjusted life years (Wittchen et al., 2011). Brain disorders represent approximately one third of the total disease burden in Europe (Olesen and Leonardi, 2003; Stoeckli, 2012). In 2010, it was estimated that the total annual direct and indirect costs of disorder of the brain was €798 billion (Gustavsson et al., 2011). During 2001–2003 in the USA, serious mental illness reportedly accounted for ~$193 billion per annum in lost earnings alone (Kessler et al., 2008) with 2006 estimates of a further $57.5 billion per annum for direct mental healthcare costs in the USA (Soni, 2009). Estimates by the World Health Organization indicate that approximately 22% of the world's primary care patients have debilitating chronic pain and that these individuals are approximately four times more likely to have co-morbid anxiety or depressive disorder compared with pain-free patients in the primary care setting (Alonso et al., 2011; Lepine and Briley, 2004). More recently, population surveys in many countries consistently show that at any given time, ~20% of people have severe/chronic pain (Blyth et al., 2001; Boulanger et al., 2007; Harifi et al., 2013; Langley, 2011; Ohayon and Stingl, 2012) with the prevalence of neuropathic pain accounting for ~10% in the United Kingdom (Torrance et al., 2006) and Brazil (de Moraes Vieira et al., 2012). Neuropathic pain is underpinned by well-documented neuroplastic changes in the CNS (Mika et al., 2013) and it is notoriously difficult to treat with no more than 40–60% of patients achieving partial pain relief with currently available analgesic/adjuvant drug treatments (Dworkin et al., 2007).

Based on the high prevalence and associated costs of CNS disorders and chronic pain in the general population, investment in drug development for new treatments for these large unmet medical needs should be flourishing. However, the reality is that many pharmaceutical companies have withdrawn investment from these therapeutic areas due to the perceived lack of validated drug targets and the failure of many clinical trials in the last decade (Stoeckli, 2012). By contrast, there has been a recent surge in multi-government interest in the societal burden of brain disorders (Poo, 2014). Herein, we highlight the unique value of the intracerebroventricular (ICV) route for CSF sampling and for efficacy assessment of novel drug treatments in preclinical research on CNS disorders.

2. Translational research bridging preclinical studies and human clinical studies

Molecules in the extracellular fluid of the brain parenchyma freely exchange into the CSF and *vice versa*. Hence, CSF sampling in relevant rodent models of human CNS disorders has the potential to provide mechanistic insight on disease pathobiology. On the other hand, ICV drug administration in rat models of CNS disorders to produce therapeutic concentrations in the CNS enables the intrinsic efficacy and adverse event profiles of novel drug treatments from discovery programmes to be assessed due to the low capacity of brain parenchyma to metabolise exogenous compounds (Hanna et al., 1990; Smith et al., 1999).

As already noted, CNS disorders account for more hospitalisations and prolonged care than almost all other diseases combined, despite enormous global research effort to date (Misra et al., 2003). Intriguingly, recent work implicates low level neuroinflammation in more than 40% of patients with severe depression or schizophrenia (Bechter et al., 2010). Hence, comparative assessment of CSF composition between rodent models of CNS disorders and patients with these clinical conditions with a focus on proinflammatory/anti-inflammatory profiles of cytokines, chemokines and other biomolecules of interest is warranted, not only for assessing the validity of rodent models of CNS disorders, but also for hypothesis generation and testing.

It is evident that key factors contributing to the poor track record for translation of findings from basic science research on CNS disorders to new therapeutics approved for patient use, are the poor validity of rodent models of these disorders and the narrow set of experimental conditions used for *in vivo* efficacy testing using these models (Jucker, 2010; Lowenstein and Castro, 2009). Hence, the failure of early phase clinical trials for lack of efficacy of novel drug treatments for CNS disorders compared with placebo is not too surprising, as the challenges associated with disease complexity were never evaluated during preclinical testing (Ledford, 2011; Lowenstein and Castro, 2009). Thus, major imperatives are to develop improved rodent models of CNS disorders that better mimic disease complexity in humans, and to improve the robustness of *in vivo* efficacy study designs in rodent models, by inclusion of a broader spectrum of disease readouts. Apart from inclusion of multiple behavioural endpoints and imaging to assess treatment efficacy in a panel of rodent models of CNS disorders that each recapitulate a different aspect of the human disease pathology, study designs incorporating CSF collection may have considerable benefit in addressing the >50% attrition of novel treatments due to lack of efficacy in phase 2 human clinical trials (Hurko and Ryan, 2005; Paul et al., 2010).

3. Intracerebroventricular dose administration

For *in vivo* research in rodents, the ICV and intrathecal (IT) routes are the two most commonly used central routes of drug administration. The former enables direct injection of test compound into the CSF in the lateral ventricle of the brain whereas the latter facilitates direct injection into the CSF in the spinal subarachnoid space. Following drug administration by the ICV and IT