Neuropharmacology 87 (2014) 125–134

Contents lists available at ScienceDirect

Neuropharmacology

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

Invited review

Current preclinical studies on neuroinflammation and changes in blood–brain barrier integrity by MDMA and methamphetamine

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ARTICLE INFO

Article history:
Available online 2 March 2014

Keywords:
Blood–brain barrier disruption
3,4-Methylenedioxymethamphetamine
Methamphetamine
Neuroinflammation
Basal lamina proteins
IgG extravasation

ABSTRACT

The blood–brain barrier (BBB) is essential in the maintenance of brain homeostasis both by preserving normal brain functioning and also by protecting the brain from exposure to a range of potentially harmful substances. This review presents some of the evidence of BBB disruption following exposure to the substituted amphetamines 3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy') and methamphetamine (METH), two drugs of abuse which are widely consumed recreationally by younger sectors of the population.

Both MDMA and METH have been shown to produce disruption of the BBB as reflected by IgG extravasation and Evans Blue leakage. In particular, METH decreases the expression of basal lamina proteins associated with an increase in matrix metalloproteinase activity. These changes in BBB integrity appear to be related to MDMA-induced activation of the mitogen-activated protein kinase (MAPK) JNK1/2.

The consequences of the disruption in the BBB by these two drugs remain to be established, but there is evidence in the literature that, at least in the case of METH, increased matrix metalloproteinase (MMP) activity may be related to increased behavioural sensitization and reward perhaps because of the modification of the passage of the drug into the CNS. In addition, the high incidence of AIDS-related neurologic disease in METH users may also be related to increased entry into the brain of virally derived neurotoxic products.

This article is part of the Special Issue entitled 'CNS Stimulants'.

1. Introduction

It is likely that every preclinical neuropharmacologist is aware of the existence of the blood–brain barrier (BBB) and its general importance to the normal functioning of the brain and its role in determining the concentration of drugs in that organ. However it is probably a truism that rather few factor in its fundamental role in determining the reliability of the experimental data being obtained and, crucially, its importance when designing the experiments in the first place.

The importance of quantitative pharmacology or pharmacokinetic–pharmacodynamic integration (PK–PD) in all preclinical studies has been emphasised in recent publications (Gabrielsson and Green, 2009; Gabrielsson et al., 2010). The use of PK–PD is standard in all drug discovery and development in the pharmaceutical industry and its use is considered mandatory by regulatory bodies. It requires an understanding of both the pharmacodynamic and pharmacokinetic properties of the drug. Pharmacodynamics is the study of the biological effects of the drug and the relationship of drug exposure to its effects, both wanted and adverse (basically, what the drug does to the body) while pharmacokinetics details the time course of the drug and its metabolism in the body (basically what the body does to the drug). Fusion of these data produces a clear understanding of the relationship between drug exposure and effect. Exposure is influenced by absorption, protein binding, metabolism and excretion and is not therefore merely the dose but the concentration of active drug in the body (Gabrielsson and Green, 2009).

A further major aspect of PK–PD is target engagement which is a complex event involving target exposure, target binding and expression of target pharmacology. Consequently dose size, exposure to the compound (pharmacokinetics), its interaction with the

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http://dx.doi.org/10.1016/j.neuropharm.2014.02.015
0028-3908/

target (affinity and efficacy, pharmacology) and the physiological response to the target–drug interaction all influence target engagement. In the case of drugs acting in the brain therefore a full understanding is only gained with knowledge of drug exposure of the target (receptor or enzyme for example), and this is controlled by the passage of the drug into the brain. That is, the ability of the drug to pass the BBB (Gabrielsson and Green, 2009; Gabrielsson et al., 2010).

Damage to the BBB will therefore impact in two ways. Firstly, damage will affect the normal functioning of the brain, thereby impairing homeostasis in the CNS. Second, damage to the BBB will alter the entry of drugs to the brain and probably enhance exposure to pharmaceutical agents. This latter effect could be particularly detrimental if recreational drugs are being repeatedly ingested as is the focus of this review, as any adverse effects of these compounds will be exacerbated by their further administration.

All the foregoing therefore makes it clear that it is vital both to understand the function of the BBB in influencing the response of an organism to any peripherally administered drug and also to understand the effect of BBB disruption on the functioning of that organism.

2. Blood–brain barrier physiology

It is beyond the scope of this article to detail the physiology of the BBB. However a brief overview is useful and excellent detailed reviews can be found elsewhere (Abbott et al., 2010; Daneman, 2012; Pardridge, 2012; Saunders et al., 2013). These reviews discuss in detail the information given briefly below.

The basic structure of the BBB is shown in Fig. 1 (Abbott et al., 2010). The capillary bed in the CNS is formed by endothelial cells which make the walls of the blood vessels. These endothelial cells form highly polarized cells held together by tight junctions at their margins which seal the aqueous paracellular diffusional pathway between the cells and limit the movement of molecules and ions. The parenchyma facing surface of the endothelium is incompletely surrounded by a layer of pericytes. The pericyte cells are involved in the regulation of angiogenesis, vascular tone and vascular remodelling. They are also involved in the functioning of the BBB.

The cerebral endothelial cells together with the pericytes are enclosed by, and are part of, the basement membrane which forms the perivascular extracellular matrix (Basal Lamina 1 or BL1). In addition there is an extracellular matrix of the glial end-feet bounding the brain parenchyma (BL 2). Foot processes from astrocytes surround the capillaries and this cell association is involved in providing the properties of the BBB including junctional and transport processes, possibly as a result of responding to neuronal function. The end feet also express the water channel aquaporin 4 which is a key regulator of water homeostasis in the brain.

Axonal projections from neurons onto arteriolar smooth muscle contain vasoactive neurotransmitters and peptides and regulate local cerebral blood supply and permeability. This association between brain function and vasculature is sometimes referred to as the neurovascular unit. Microglia are the immunocompetent cells of the brain.

The movement of solutes across the BBB can be either passive, that is, driven by a concentration gradient from plasma to brain with more lipid-soluble substances entering most easily, or may be facilitated by passive or active transporters in the endothelial cell membranes. There also exist specific transporters for essential nutrients. In addition there are energy-dependent efflux transporters (ATP-binding cassette transporters or ABC cassette transporters) within the endothelium which help limit the penetration of a wide variety of compounds.

Finally, the intraluminal surface of the endothelium is covered with a complex mixture of carbohydrates. This gylcolayx acts as the primary barrier which sieves in both a charge and size selective way thereby limiting the interaction of circulating molecules and cells with the endothelial cell itself.

3. Pathophysiology of the blood–brain barrier

There are data which indicate that dysfunction of the BBB is involved in the pathology of several major neurological diseases.

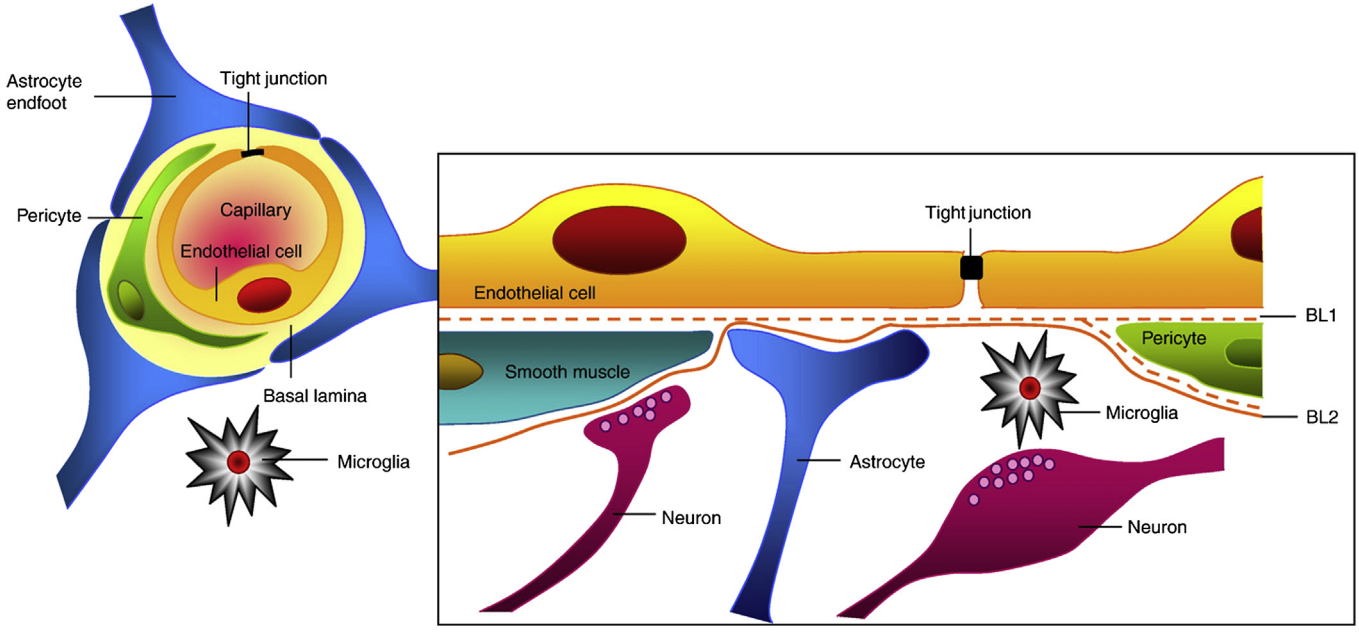

Fig. 1. Basic structure of the blood–brain barrier (BBB).
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