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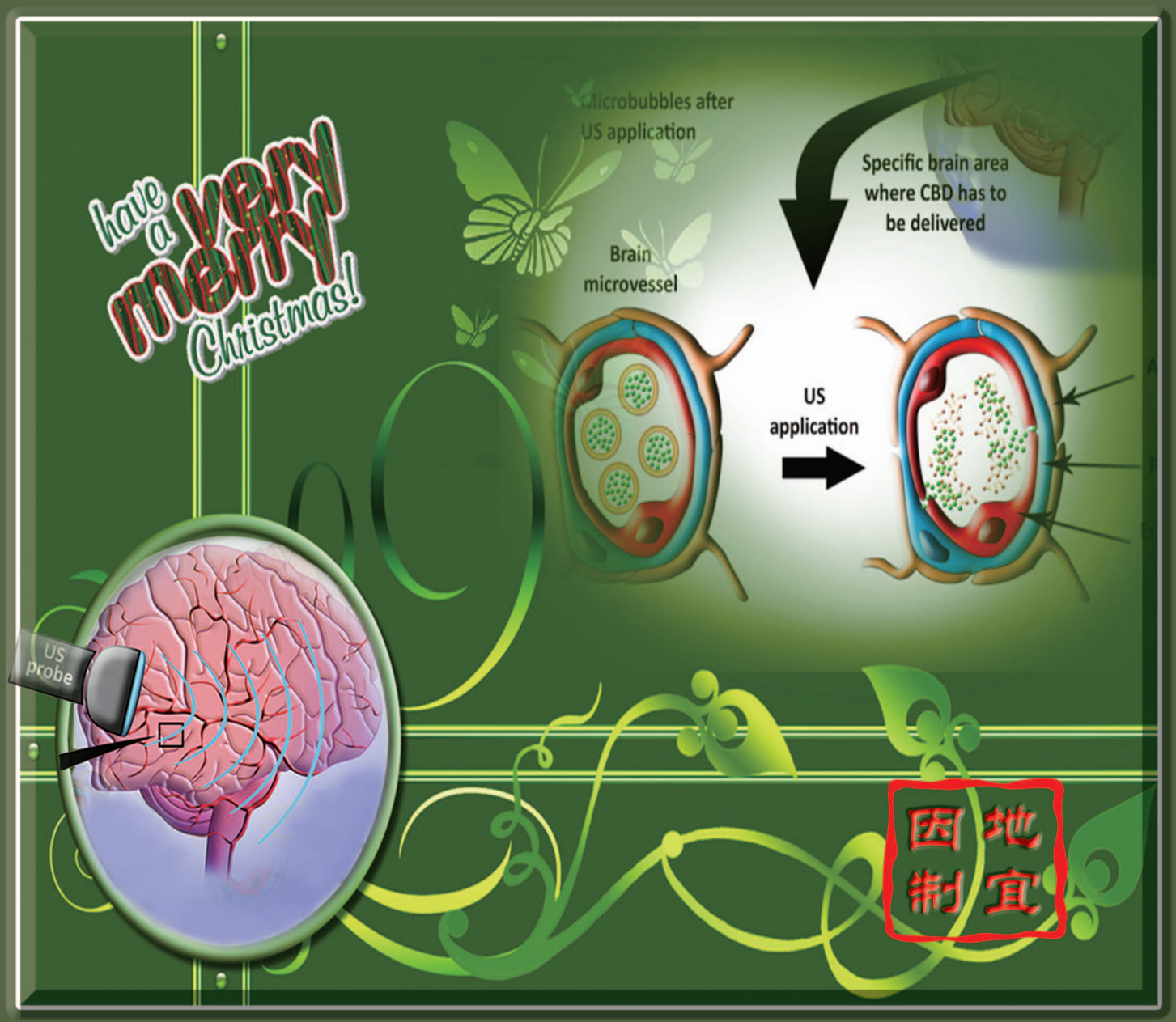

Targeting cannabidiol to specific areas of the brain: an ultrasound-based strategy Page 2248

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PERSPECTIVE

Targeting cannabidiol to specific areas of the brain: an ultrasound-based strategy

Brain diseases, ranging from central nervous system (CNS) disorders to brain cancers, are some of the most prevalent pathologies in the world. Despite the high incidence, many of these diseases lack successful treatments because of inadequate drug development in comparison to other therapeutic areas. In particular, even if many drugs have shown the potential to tackle some neurological disorders including Alzheimer's and Parkinson's diseases and many other associated CNS pathologies, their delivery in specific brain areas and in adequate concentrations represent the real obstacle to the treatment of these pathologies.

The reason for this is twofold. First, the presence of the blood-brain barrier (BBB) ensures that the brain is separated by the systemic circulation. Indeed, the BBB is a well-known complex anatomical structural barrier that plays a pivotal role in protecting the parenchyma of the CNS from potential toxicants and dangerous elements that could be present in the blood circulation (Branca et al., 2019b). For this reason, the BBB is the main obstacle that prevents most systematically administered drugs from entering the CNS. In these instances, the link of lipid groups to the polar ends of the therapeutic molecules were used to enhance drug delivery across the BBB. Similarly, ligands, involved in the specific interactions with endothelial transporters, were often incorporated into the therapeutic agents for the initiation of receptor-mediated transcytosis at BBB endothelium. Despite these strategies, many studies have reported that less than 1% of total injected dose reaches the brain by intravenous administration because the BBB hinders about 95% of drug delivery (Dong, 2018).

Secondly, the inabilities to deliver relevant doses of the therapeutic and to maintain a high targeting efficiency to diseased regions, make difficult to achieve effective therapies in the CNS. Linking lipids to therapeutics also did not help to sort out the problem of targeting a specific area: this process allows drugs to increase their hydrophobicity facilitating their distribution throughout the brain rather than in a specific region. To overcome the BBB hindrance, the use of the lipophilic molecule of cannabidiol (CBD) has been suggested. CBD has been demonstrated to bind to various receptors located on the brain endothelium environment, and some authors have clearly demonstrated that the decoration of lipid nanocapsule with CBD can overcome the BBB impermeability to deliver therapies for CNS diseases (Aparicio-Blanco et al., 2019).

The CBD molecule is the non-psychoactive extract component of the officinalis plant *Cannabis sativa* (about 40% of extract), that has been used for many years in the past both for medicinal and recreational purposes. In addition to its tolerability in humans (up to 1500 mg/d are well tolerated), CBD also lacks in affecting mental processes, e.g. cognition or affect, and exhibits a broad spectrum of potential therapeutic properties in neurological disorders such as psychosis, epilepsy, anxiety and sleep, and in neurodegenerative disease such as Alzheimer's, Parkinson's and Huntington's diseases (Izzo et al., 2009).

The mechanisms responsible for the wide range of CBD potential neuroprotective effects are not completely understood. In the last decade, many data demonstrated that multiple pharmacological targets are involved. Although CBD has a very low affinity for cannabinoid receptors, some of its effects seem to involve the cannabinoid receptor types 1 and 2, the most abundant neuromodulatory receptors in the brain and in the immune system, respectively (Long et al., 2005). CBD activates the transient receptor potential vanilloid channel-1, serotonin receptor 5-HT1A, or modulate G protein-coupled receptors. CBD may also interact with transcription factors, such as the G-protein coupled receptor 55 and the nuclear receptors of the peroxisome proliferator-activated receptor family (Calapai et al., 2020). The beneficial effects of CBD on brain disorders have also been associated with its capacity of modulating pro-inflammatory cytokines and brain-derived neurotrophic factor expression (Bih et al., 2015). Recently, *in vitro* and *in vivo* studies showed that CBD prevents the oxidative stress-dependent cell death probably acting as an endoplasmic reticulum stress attenuator and preserving the cellular redox potential (Branca et al., 2019a).

All these effects clearly indicate that CBD represents a new opportunity for the treatment of several disorders and make CBD activity of interest for a variety of medical purposes and therapeutic approaches. On this regard, we recently published *in vitro* data demonstrating that CBD is able to ameliorate the cadmium-induced neuronal toxicity (Branca et al., 2019a), thus making CBD a reasonable candidate to protect neurons from heavy metal-induced neuronal toxicity.

However, although many molecules such as ion channels, receptors, transporters, and enzymes have been suggested as likely CBD target, studies demonstrating which of these molecules underlie each specific therapeutic effect are scarce. Moreover, it would be of paramount importance to identify novel mechanistic pathways through which CBD exerts its properties; these findings will have important implications for understanding the mechanism of the CBD therapeutic effects.

Another important aspect to be considered is the different route of CBD administration.

Many pharmacokinetic studies have focused on the different path by which CBD can be taken into the body (i.e. subcutaneous, oral, inhalational, intravenous and intraperitoneal) and concluded that the highest CBD levels in the brain are reached after oral administration (Calapai et al., 2020). Although the lipophilic nature of CBD enables it to traverse the BBB, oral administration most often lack efficiency, does not allow reaching therapeutic dose in a specific brain region and is linked to drug-mediated toxicity. This scenario makes it necessary to devise a non-invasive, transient, and regionally selective brain CBD delivery method in order to restrict delivery into target areas, minimizing the toxicity-dependent systemic distribution of the therapeutic.

To this end, ultrasound (US)-mediated delivery, also known as sonography, allows spatially confined delivery of drugs into target areas. This approach has emerged as a non-invasive, and safe diagnostic medical imaging technique that uses sound waves to produce dynamic visual images of organs, tissues, tumors, cysts or blood flow (e.g. splenic blood flow by echo-colour-doppler assistance) inside the body (Ward et al., 2014). In addition, a parallel study has shown the non-invasiveness of this approach that makes US-induced BBB opening a novel and attractive means to perform localized CNS therapeutic agent delivery (McMahon et al., 2019).

Moreover, such a technique, can be used alone or in combination with different nanocarriers (polymer nanoparticles, liposomes, micelles, and microbubbles), to deliver different molecules, drugs or genes to a target site (such as various tissues and organs, including tumor tissues, kidney, cardiac, skeletal muscle, and vascular smooth muscle), with minimal loss of the initial dose (Beccaria et al., 2020).

Interestingly, many researchers are combining these applications for treating a variety of diseases and this approach was validated both by *in vitro* and *in vivo* experiments. On this regard, one of the new and intriguing emerging aspects about the US application for specific target, especially for brain drug delivery, is their combination with microbubbles. Microbubbles are spheroidal bubbles, typically ranging from 0.5 μm to 10 μm in diameter, with a gas core used to deliver drugs and able to vary their size upon interaction with US. Thus, the application of US to a specific area could provide highly efficient to target drug-loaded microbubbles to that area. This safe and non-invasive strategy has been used successfully to deliver treatments across the BBB to a specific area of the brain (Yang et al., 2019). Such an application is of great interest given the properties of the BBB. This unique and dynamic structure at the interface between the cerebral circulation and the brain tissue, that is essential for maintaining the microenvironment within the brain, displays a highly selectivity nature that in turn makes difficult to reach specific brain areas with the appropriate pharmacological intervention. Also, the targeted delivery of therapeutics to specific brain area have the potential to prevent damages to neighboring areas, an important side effect of many therapies. Therefore, the US application in a specific cerebral area, related to a particular CNS pathology, allows the breaking of the microbubbles containing CBD in the brain microvessels. This, in turn, induces the presence of a greater free fraction of CBD in the area irradiated by US that will facilitate its diffusion through the BBB to target the region of interest (**Figure 1**).

However, at this time not much is known on the US-mediated gene and protein expression. Does US cause a stress response (similar to heat shock) that may enhance or interfere with the action of drugs? Is this response similar for all cells and does it differ for various ultrasonic frequencies and intensities? These and other questions need to be addressed.

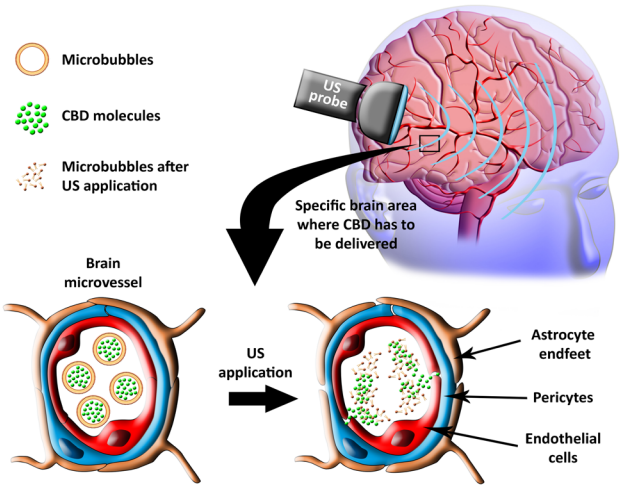

Figure 1 Representative image of microbubbles CBD-loaded and delivered in specific brain area by US application.
US waves are directed to the brain region where CBD needs to be carried; when the CBD-loaded circulating microbubbles are hit by the US waves, they break and release the CBD exactly in the brain region where the waves have already partially opened the BBB. BBB: Blood-brain barrier; CBD: cannabidiol; US: ultrasound.

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