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DEVELOPMENT OF MULTITARGET DRUGS FROM L-3-N-BUTYLPHALIDE AND THE DERIVATIVES

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ABSTRACT

L-3-n-Butylphalide (l-NBP) was isolated from seeds of Apium graveolens L. by the Institute of Materia Medica, CAMS in the 1980s. It was showed to be effective in anti-epilepsy. Soon it was synthesized as a racemic form, dl-3-n-butylphalide (dl-NBP) and demonstrated that dl-NBP had the similar pharmacological effects compared to l-NBP. In early 1990s dl-NBP was found to be potent in protection of brain injury from cerebral ischemia in animal models. Preclinical studies demonstrated that dl-NBP might improve micro-circulation of brain, inhibit blood platelets aggregation, protect the structure and function of mitochondria and against the neuronal apoptosis. In 1999 dl-NBP was approved by SFDA for clinical trial. It was approved as a new drug for acute ischemic stroke in 2005. Due to the properties of dl-NBP, it is difficult to be used for intravenously because of its hydrophobicity. Dl-NBP can only be made into soft capsule. Thus, dl-NBP is limited to use in the clinic for serious stroke patients. Therefore a prodrug of dl-NBP was designed as dl-PHPB. It is a white crystal powder with a good hydrophilicity. Dl-PHPB can be simply made into a variety of dose formulations such as tablets, capsules and injections. Pharmacokinetic study demonstrated that dl-PHPB is fast and completely converted into dl-NBP in vitro and in vivo of animal experiments. The bioavailability of dl-PHPB was 50 to 100% higher than dl-NBP after orally given to rats and dogs. The pre-clinic study showed that PHPB had a same or better effect in treatment of ischemic stroke of rat MCAO model and no more side-effect and toxicity was seen compared with dl-NBP. Dl-PHPB was approved by the SFDA for clinic trial in 2009. Furthermore, we found recently that l-NBP had very interesting effect except its anti-stroke. L-NBP may reduce the levels of beta-amyloid and tau phosphorylation in cell lines, brains of aged rats and transgenic mice model of Alzheimer's disease. The targets of l-NBP for above effects might be PKC related signal transduction system and the GSK3βas well as CDK5, respectively. L-NBP may improve the cognitive ability was also seen in AD animal models. Therefore, l-NBP appears to be promising as a multitarget drug for the prevention and/or treatment of Alzheimer's disease. It has completed the phase I clinic trial. Conclusion: Our study showed a good example of drug development from nature products/Chinese medicine.