Morphology of 1-BP-exposed hippocampal formation

We performed a morphological analysis to determine whether exposure to 1-BP led to any structural damages in the hippocampal formation. If present, morphological changes such as loss of certain neuronal populations, could affect results in electrophysiological recordings and therefore might explain the abnormalities identified in the paired-pulse ratios. Both excitatory and inhibitory neuronal components were examined in detail by confocal laser scanning microscopy, and no apparent sign of structural damage was found in either component. As disinhibitory changes were consistent with results in the present as well as previous electrophysiological data (Fueta et al., 2002c), we made a quantitative analysis based on a modern stereological method, and confirmed the preservation of GABAergic neuronal subpopulations. This strongly suggests the possibility that 1-BP-induced changes in paired-pulse ratios were caused by functional derangement such as altered properties of membrane receptor proteins, but not by structural defects. If this is the case, it follows that functional derangement can be normalized again after withdrawal of toxic agents. In fact, this occurred in our clearance study in which paired-pulse ratios were indistinguishable between 1-BP-exposed animals 4 weeks after cessation of inhalation and controls.

The lack of structural defects and the reversal of hyperexcitability in 1-BP-exposed hippocampus are in sharp contrast with the results of kainic acid treatment, amygdala kindling animals, and pilocarpine models. For example, intracranial or systemic administration of kainic acid immediately induces seizures in the animals and is often used in experimental studies on epilepsy. In the acute phase of kainic acid-induced seizures, massive loss of principal neurons occurs particularly in the CA3 region, whereas sprouting of mossy fiber terminals that originate from target-deprived granule cells is a well-known phenomenon in the chronic phase (Tauck and Nadler, 1985; Cronin and Dudek, 1988). These histological abnormalities can be related to findings in postmortem examination of the brain of epilepsy patients, and are attributed to repeating episodes of seizures. However, mechanisms underlying origination of the hyperexcitable state of epileptic brains still remain obscure. In this respect, chronic inhalation of 1-BP can induce a unique hyperexcitable state that is free from structural depletions but is a preparatory stage for convulsions; animals finally manifested convulsions at the end of the 4th week in the case of 1500 ppm inhalation (Fueta et al., 2002c) and at the 14th week of 700 ppm inhalation (T. Ishidao, unpublished observations). More importantly, 1500 ppm 1-BP also induced a hyperexcitable state lacking morphological changes from the 1st though 3rd week, and it was only after the onset of convulsions that pyknosis was recognizable in the CA1 regions (T. Fukuda and T. Kasai, unpublished observations). It is uncertain to what extent the mechanisms of 1-BP-induced hyperexcitability have features common to pathogenesis in clinical seizures, but the characteristic proconvulsant state in 1-BP-exposed brains appears to have some aspects applicable to potentially diverse, clinical cases.

In conclusion, chronic inhalation of 1-BP (700 ppm) produced disinhibitory effects in the CA1 and DG of the hippocampal formation. Disinhibition in the DG was involved with an activation of NMDA receptors due to a reduced GABAergic inhibition, while that of the CA1 did not. The functional changes in both regions were not associated with morphological changes detectable by immunohistochemical techniques. Reversible disinhibitory effects after cessation of inhalation support the lack of morphological changes in the hippocampal formation.

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