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Alkyl-substituted phenyl-amino derivatives of 7-nitrobenz-2-oxa-1,3-diazole as uncouplers of oxidative phosphorylation and antibacterial agents: involvement of membrane proteins in the uncoupling action

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ABSTRACT

In search for new effective uncouplers of oxidative phosphorylation, we studied 4-aryl amino derivatives of a fluorescent group 7-nitrobenz-2-oxa-1,3-diazol (NBD). In our recent work (Denisov et al., Bioelectrochemistry, 2014), NBD-conjugated alkyl amines (NBD-C_n) were shown to exhibit uncoupling activity. It was concluded that despite a pK_a value being about 10, the expected hindering of the uncoupling activity could be overcome by insertion of an alkyl chain. There is evidence in the literature that the introduction of an aryl substituent in the 4-amino NBD group shifts the pK_a to neutral values. Here we report the data on the properties of a number of 4-arylamino derivatives of NBD, namely alkylphenyl-amino-NBD (C_n-phenyl-NBD) with varying alkyl chain C_n. By measuring the electrical current across planar bilayer lipid membrane, the protonophoric activity of C_n-phenyl-NBD at neutral pH grew monotonously from C_1- to C_6-phenyl-NBD. All of these compounds increased the respiration rate and reduced the membrane potential of isolated rat liver mitochondria. Importantly, the uncoupling action of C_6- and C_4-phenyl-NBD was partially reversed by glutamate, diethyl pyrocarbonate (DEPC), 6-ketocholestanol and carboxyatractyloside, thus pointing to the involvement of membrane proteins in the uncoupling activity of C_n-phenyl-NBD in mitochondria. The pronounced