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EFEITOS DO CARVEDILOL E DO SEU METABOLITO BM-910228 NA PEROXIDAÇÃO LIPÍDICA E NA BIOENERGÉTICA MITOCONDRIAL

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SUMÁRIO

Tanto o carvedilol como o seu metabolito, o BM-910228, inibem a peroxidação lipídica mitocondrial induzida por adição de ADP/Fe^{2+} em mitocôndrias isoladas de fígado de rato. Os valores de IC_{50} desta inibição, obtidos através da monitorização do consumo de oxigénio, foram de 10.7 μM para o carvedilol e de 0.33 μM para o BM-910228. Tanto o carvedilol como o BM-910228 inibem completamente a peroxidação lipídica para concentrações de 40 e 1 μM, respectivamente. O estudo da inibição de peroxidação lipídica foi efectuado utilizando 3 metodologias diferentes: monitorização do consumo de oxigénio, monitorização do potencial eléctrico transmembranar ($\Delta\psi$) e produção do malonildialdeído. Os resultados obtidos pelos diferentes métodos confirmaram o poder antioxidante do carvedilol e do BM-910228 na mesma gama de concentrações.

Este efeito protector estará relacionado com a actividade de "scavenger" de radicais referenciada anteriormente para o carvedilol. No entanto outras hipóteses são levantadas. Quer o carvedilol quer o BM-910228 poderão agir formando uma barreira estérica ao complexo de iniciação. O carvedilol também poderá promover a inibição da peroxidação lipídica através da diminuição da produção de radicais livres como resultado do seu efeito depressor do $\Delta\psi$ mitocondrial.

Na sequência do efeito do carvedilol na diminuição do $\Delta\psi$ estudámos a acção do carvedilol e do BM-910228 na bioenergética mitocondrial. O carvedilol promove a diminuição do $\Delta\psi$ mas, para as concentrações em que inibiu completamente a peroxidação lipídica, não afectou significativamente o funcionamento das mitocôndrias de fígado de rato.

Neste trabalho foi possivel identificar dois efeitos diferentes do carvedilol no funcionamento mitocondrial: um efeito na cadeia transportadora de electrões e um outro efeito no "leak" membranar a protões. Por outro lado, o carvedilol não afectou o normal funcionamento do sistema fosforilativo mitocondrial, ou seja, não afectou a ATPsintase e os transportadores de nucleótidos e de fosfato inorgânico.

Estudámos também o efeito do BM-910228 na bioenergética mitocondrial para concentrações inibitórias da peroxidação lipídica. Verificou-se que o BM-910228 não promove efeitos significativos no funcionamento das mitocôndrias. Estes resultados

revelam que o BM-910228 poderá contribuir significativamente para os efeitos terapêuticos conhecidos do carvedilol.

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