Butylidenephthalide 對抗清醒的正常老鼠因 cromakalim 引起的降壓及心悸反應

Butylidenephthalide antagonizes cromakalim-induced depressor and tachycardiac responses in conscious normotensive rats

中文摘要

Cromakalim（BRL 34915）作用於血管是一種有別於胰島 β-細胞上之 ATP-敏感的鉀通道亞型開啓劑具都是一些屬於 sulfonylurea 的口服降血糖藥如 tolbutamide 及 glibenclamide (GCB)等，其它就很少有報告。

本研究以間接血壓測定法（cuff method）監測，發現川芎抗痙主成分 butylidenephthalide (Bdph) 30 mg/kg 腹腔注射預投與清醒老鼠 30 分鐘，結果其作用類似 4-aminopyridine (4-AP, 0.4 mg/kg, i.p.)及 GBC (10 mg/kg, i.v.),能有意義地使 cromakalim 的對數齊量-降壓及心悸反應曲線向右移動，投藥組的半致效量有意義地比對照組大，但兩組間的最大降壓作用及心悸反應，統計上無意義差，因此對 cromakalim 有競爭性的對抗作用。這種對抗似乎很有選擇性，因 Bdph (30 mg/kg i.p.)預投與 30 分鐘，不能有意義的影響 prazosin (α1 adrenergic receptor antagonist)及 clonidine (α2 adrenergic receptor agonist)對清醒老鼠的降壓及心跳反應，也不能有意義地影響 Bay K 8644 的升壓作用及心悸反應，然而 nifedipine (1 mg/kg, i.v.)能有意義地抑制 Bay K 8644 (0.03?0.1 mg/kg, i.v.)的升壓作用,也能有意義地對抗 Bay K 8644 (0.03?0.3 mg/kg, i.v.)的心悸反應。

綜合以上結果，Bdph (30 mg/kg, ivp.)類似 4-AP (0.4 mg/kg, i.p.)及 GBC (10 mg/kg, i.v.)是一種 ATP 一敏感的鉀通道亞型阻斷劑，能對抗 cromakalim 的降壓作用及心悸反應，當 cromakalim 投與前或不存在時，它們並不影響清醒正常老鼠之血壓及心跳，可能是因此種鉀通道亞型不開啓時，本身不具活性。

英文摘要

Cromakalim (BRL 34915), is an opener of ATP-sensitive potassium channel subtype which has been reported to be distinct from that of pancreatic islet β-cells, has potent blood pressure lowering effect. Nowadays, few blockers have been repored, except the well known oral sulfonylurea antidiabetic agents, such as tolbutamide and glibenclamide (GBC) etc.

An indirect cuff method was used to determine the systolic pressure and heart rate of conscious normotensive rats in this study. The intraperitoneal pretreatment of synthetic butylidemephthalide (Bdph), the most potent antispasmodic constituent

found in the neutral oil of Ligusticum wallichii FRANCH., at a dose of 30 mg/kg for 30 min, similar to 4-aminopyridine (4-AP, 0.4 mg/kg, i.p.) and GBC (10 mg/kg, i.v.), significantly rightward shifted the log dose-depressor and -tachycardiac response curves of cromakalim. The median effective doses (ED50) of test group were significantly greater than those of control (vehicle) group. There was no significant difference between the maximal depressor responses of both two groups. So was the maximal tachycardiac reponses. Therefore, Bdph may competitively antagonize cromakalim. This antagonism appears so selective, because that the 30 min pretreatment of Bdph (30 mg/kg, i.p.) could not significantly affect the depressor and cardiac responses of prazosin ($\alpha 1$ adrenergic receptor antagonist) and clonidine ($\alpha 2$ adrenergic receptor agonist). It also could not significantly affect the pressor and tachycardiac responses of Bay K 8644. However, nifedipine (1 mg/kg, i.v.) could significantly inhibit the pressor effect of Bay K 8644 (0.03~0.1 mg/kg, i.v.) and the tachycardiac effect of Bay K 8644 (0.03~0.3 mg/kg, i.v.)

The above results suggest that Bdph (30 mg/kg, i.p.), similar to 4-AP (0.4 mg/kg, i.p.) and GBC (10 mg/kg, i.v.), may be a blocker of ATP-sensitive potassium channel subtype, which could antagonize the depressor and tachycardiac responses antagonize the depressor and tachycardiac responses of cromakalim. However, in the abscence of or before administration of cromakalim, they did not affect the systolic pressure and heart rate, because they are inactive when the ATP-sensitive potassium channel is not opened.