on the contractile influences of pyruvate, we suggest, as a working hypothesis, that such action could be associated with a faster rate of the metabolism of pyruvate, a substrate which, when accumulated readily, depresses the developed tension of isolated rat atria[1,3]. Indeed, the effects of catecholamine depletion, β-adrenergic blocking agents and catecholamines on the myocardial metabolism of fatty acid[15,16] could result in changes of the tissue levels of A-CoA, a metabolite known as a controller of the activity of pyruvate dehydrogenase[17] and thereby as a regulator of the rate of entry of pyruvate in the tricarboxylate cycle[18,19].

Résumé. La réduction de l'amplitude de la tension contractile auriculaire produite par le DL-propanolol ou par le MJ 1999 ne peut être considérée uniquement comme une conséquence du blocage des récepteurs β-adrénergiques. D'autre part, l'action inotropique des drogues citées est nettement différente suivant que les oreillettes se trouvent dans un milieu contenant de la glucose ou du pyruvate. La dépression contractile provoquée par l'agrégat du pyruvate fut nettement moindre dans les oreillettes déplétionées de cathécholamines ou en présence de DL-propanolol ou du MJ 1999.

M. F. GIMENO, J. A. CLUSELLA and A. L. GIMENO

Segunda Cátedra de Fisiología, Facultad de Medicina, Universidad Nacional de Buenos Aires, and Instituto de Fisiología, Facultad de Ciencias Médicas, Universidad Nacional de Córdoba, Santa Rosa 1075 Córdoba (Argentina), 18 February 1970.

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On the Mechanism of Amphetamine Potentiation by Iprindole

Recent studies with tyrosine hydroxylase inhibitors have suggested that amphetamine is an indirectly acting sympathomimetic amine whose central action depends upon the uninterrupted synthesis of catecholamines[1-3]. Desipramine (DMI) and other tricyclic antidepressants which block the uptake mechanism for norepinephrine in central norepinephrine fibers[4,5] have been shown to enhance and to prolong the central effects elicited by amphetamine in the rat[6-9]. The enhancement and the prolongation of the action of amphetamine after the administration of DMI-like antidepressants appears to be the consequence of an inhibition of the metabolism of amphetamine[10-14]. Iprindole, a new tricyclic antidepressant, does not appear to block the uptake of norepinephrine through the neuronal membrane but nevertheless strikingly enhances many central effects of amphetamine[15]. The present studies were undertaken to determine whether these actions of iprindole might also be the consequence of a modification of the distribution or metabolism of amphetamine.

Male Sprague-Dawley rats (180–220 g) were used. Amphetamine was administered i.v. as the sulfate salt and iprindole was injected i.p. as the hydrochloride 30 min before the administration of amphetamine. D-Amphetamine-H^3-sulphate (generally labeled, 4.23 c/mmol) was obtained from the New England Nuclear Corporation. The drug was assayed by a modification of the method of AXELROD[16] as previously described[10]. Psychomotor stimulation was measured in Williamson activity cages over a period of 10 h.

A single dose of iprindole enhances and strikingly prolongs the psychomotor activity elicited by D-amphetamine (Figure 1). For example, in rats pretreated with iprindole (2 mg/kg), D-amphetamine (2 mg/kg) elicited a marked psychomotor stimulation as long as 9 h after its administration. In animals which had not been pretreated with iprindole the action of the same dose of amphetamine persisted for only 2 h, with the maximum activity occurring at 1 h. Iprindole given alone did not evoke a measurable stimulation. It is noteworthy that a five-fold increase in the dose of iprindole did not increase the potentiation and prolongation of the action of amphetamine.

The measurement of H^3-D-amphetamine in brain revealed that the levels of D-amphetamine decreased logarithmically (Figure 2) in both control and iprindole pretreated animals. In animals pretreated with iprindole, the brain levels of D-amphetamine were not only higher than those of control animals but declined at a slower rate ($t\text{-}^1/_2$ for amphetamine approximately 1 h, $t\text{-}^1/_2$ for iprindole and amphetamine approximately 4 h). The analysis of the homogenates of the bodies of these animals showed that pretreatment with iprindole not only resulted

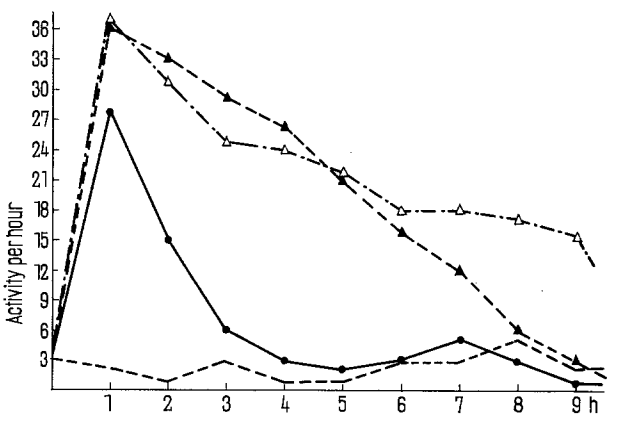

Fig. 1. Effect of iprindole on psychomotor stimulation elicited by D-amphetamine. ●—●, D-amphetamine; △—△, iprindole (2 mg/kg) + D-amphetamine; ▲—▲, iprindole (10 mg/kg) + D-amphetamine; ---, iprindole (10 mg/kg). Psychomotor activity is expressed as integrated counts per hour. Each value represents the mean of 6–10 animals. Iprindole was given i.p. 30 min before D-amphetamine (2 mg/kg per i.p.).

in higher body levels of amphetamine but also increased the biological halflife of the drug (Figure 3). Since pretreatment with iprindole resulted in both a sustained increase in the concentration of D-amphetamine in brain as well as in a marked increase in the body levels of D-amphetamine, it may be concluded that iprindole, like DMI and other tricyclic antidepressants, inhibits the metabolism of D-amphetamine in vivo. Since iprindole does not block the uptake of norepinephrine[15], the results of the present studies indicate that the potentiation of amphetamine by iprindole is a consequence of this metabolic interaction. Moreover, the results of the present studies further emphasize the importance of metabolic considerations in the proper interpretation of drug interaction studies[17].

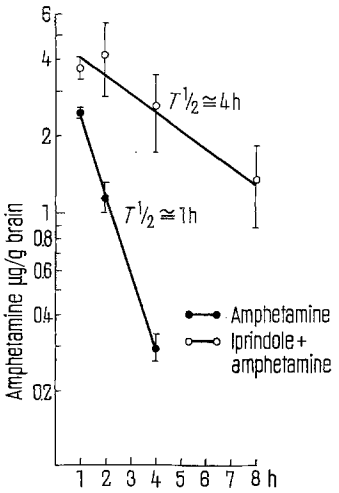

Fig. 2. Effect of iprindole on brain levels of D-amphetamine. Iprindole (10 mg/kg) was given i.p. 30 min before the administration of D-amphetamine (3 mg/kg per i.p.). Each point represents the mean value of 4 animals. Vertical bars indicate the standard deviation of the mean.

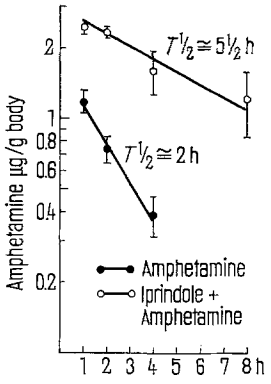

Fig. 3. Effect of iprindole on body levels of D-amphetamine. For details, see legend Figure 2.

Zusammenfassung. Iprindol verstärkt und verlängert die psychomotorische Aktivität von D-Amphetamin in der Ratte, eine Potenzierung, die mit erhöhter Konzentration und verlängerter Halbwertszeit von D-Amphetamin in Gehirn und Körper einhergeht. Iprindol scheint ähnlich wie die Antidepressiva der Imipramin-Klasse den Stoffwechsel von Amphetamin in vivo zu hemmen.

K. W. MILLER, J. J. FREEMAN, J. V. DINGELL and F. SULSER

Psychopharmacology Research Center, Department of Pharmacology, Vanderbilt University School of Medicine, Nashville (Tennessee 37203, USA), 23 February 1970.

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Die Wirkung von Theophyllin auf den cellulären Ca-Stoffwechsel des Warmblüterherzens[1]

Die positiv inotrope Wirkung von Theophyllin wird wie die von Adrenalin an isolierten Meerschweinchenvorhöfen durch Vorgabe von zweiwertigen Mangan-Ionen abgeschwächt[2]. Da Mn^{++} den an verschiedenen Herzpräparaten während der Erregung messbaren[3–5] Ca-Einstrom unterdrückt[6], wurde aus diesen Befunden geschlossen, dass die kontraktionskraftsteigernde Wirkung von Theophyllin zumindest teilweise über einen erhöhten Einstrom von extrazellulärem Ca während des Erregungsprozesses zustande kommt. Um diese Hypothese weiter zu prüfen wurde an isolierten Präparaten aus Warmblüterherzen 1. der Einfluss von Theophyllin auf den zellulären ^{45}Ca-Umsatz sowie 2. auf Kontraktionskraft und gleichzeitig auf Ca-abhängige Membranpotentialänderungen untersucht, denen, wie in vorangehenden Untersuchungen[7,8] gezeigt wurde, wahrscheinlich ein Ca-Einstrom in die Myokardzelle zugrunde liegt.

Methode. 1. Isolierte linke Meerschweinchenvorhöfe (mit 170 Imp/min gereizt oder ruhend) wurden 60 min lang in Tyrodelösung mit 0,45 m*M* $CaCl_2$ äquilibriert und anschliessend für 2–60 min in ^{45}Ca-haltiger Tyrodelösung ($[Ca]_e$ 0,45 m*M*) ohne und mit 5×10^{-4} g/ml Theophyllin