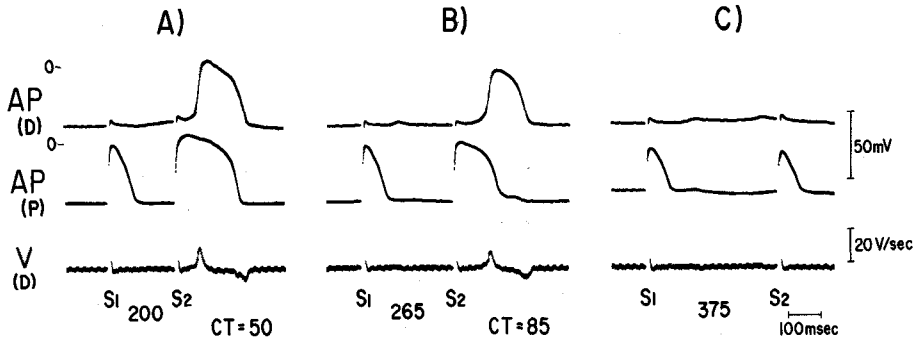


Fig. 2. Facilitated conduction in premature responses in high K-high Ca solutions. A basic and a premature AP which were recorded at distal (D, top trace) and proximal points (P, middle trace) are shown in a pair. In bottom trace rising velocity (V) of APs recorded at D is illustrated. See text for additional explanation.

coupling interval was increased to 265 msec, R_2, which was smaller than in A, was conducted to D with increased conduction time (figure 2, B). When S_2 was applied at a interval of 375 msec, R_2 as well as R_1 was blocked. In consequence of this supernormal conduction, the minimal coupling interval with propagated responses was shortened to 173±11 msec in high K- high Ca solutions from 239±9 msec in control. If extracellular accumulation of potassium ions occurs in the patient's heart muscle, the above-mentioned phenomenon may well be related to the genesis of Wedensky effect and bradycardia-dependent conduction disturbance, although another mechanism, oscillatory potentials[10], may play some role in such depolarized fibres. Moreover, the supernormal response may be involved in the genesis of extrasystoles, because the decreased minimum coupling interval with propagated responses, as well as delayed conduction, favours the occurrence of reentry[11].

1 We thank Dr Rikuo Ochi, Department of Physiology, Juntendo University, who critically reviewed the manuscript.
2 L.S. Gettes and H. Reuter, J. Physiol. *240*, 703 (1974).
3 W. Trautwein, T.F. McDonald and O. Tripathi, Pflügers Arch. *354*, 55 (1975).
4 M. Kohlhardt, H. Krause, M. Kubler and A. Herdey, Pflügers Arch. *355*, 1 (1975).
5 P.F. Cranefield, The conduction of the cardiac impulse. Futura, Mt. Kisco 1975.
6 T. Sano, T. Sawanobori and M. Hiraoka, J. molec. Cell. Cardiol. *9*, suppl., 18 (1977).
7 A.J. Pappano, Circulation Res. *27*, 379 (1970).
8 H. Iinuma and K. Kato, Eur. J. Cardiol. *7*, 465 (1978).
9 H. Iinuma and K. Kato, J. Electrocardiol. *11*, 15 (1978).
10 G.W. Beeler and H. Reuter, J. Physiol. *268*, 177 (1977).
11 E. Carmeliet, in: Re-entrant arrhythmias, p. 15. MTP Press, Lancaster 1977.

The effects of dopaminergic blocking agents on the glucose tolerance test in 6 humans and 6 dogs[1,2]

F. Lechin[3], E. Coll-García, B. van der Dijs, A. Bentolila, F. Peña and C. Rivas

Departamento de Fisiopatología, Instituto de Medicina Experimental, and Departamento de Bioquímica, Escuela de Bioanalisis, Facultad de Medicina, Universidad Central de Venezuela, Caracas (Venezuela), 9 October 1978

Summary. Pre-treatment with low doses of sulpiride, an atypical dopaminergic blocking agent, but not haloperidol, a classical dopaminergic blocking agent, decreased tolerance to glucose and increased blood serotonin levels in 6 normal humans and 6 normal dogs investigated.

The administration of 2 different kinds of dopaminergic blocking agents (haloperidol + sulpiride) were successfully used in the treatment of more than 1500 headache, and other psychosomatic patients. A high percentage of the diabetics included in that casuistic showed significant reductions in their fasting serum glucose levels[4,5]. It was also found that haloperidol and sulpiride, administered separately, induce opposite effects on distal colon motility[6] and on whole blood serotonin levels[5]. For these reasons, we decided to investigate the effects of both drugs on the glucose tolerance test.

Material and methods. 4 consecutive oral glucose (100 g) tolerance tests (30-day intervals) were performed on 6 healthy volunteer humans (30–36 years old and 60–65 kg) and on 6 normal adult mongrel dogs (1.7 g/kg) weighing 25–30 kg. Peripheral blood samples were withdrawn for glucose[7], insulin[8], and serotonin[9] determinations at 0, 30, 60 and 120 min. Whole blood serotonin levels were assessed at 0 and 60 min only. All experiments began at 08.00 h, after 12 h (humans) and 16 h (dogs) fasting periods.

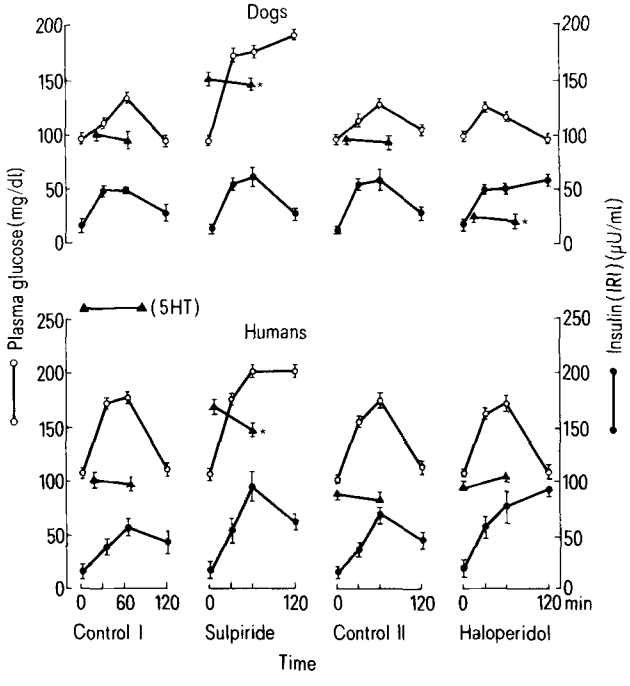
In 3 human subjects and 3 dogs, oral sulpiride (50 mg and 25 mg every 8 h, respectively) was administered for 8 days before the 2nd test; whereas oral haloperidol (0.5 mg and 0.3 mg every 8 h, respectively) was administered 8 days before the 4th test. In the 3 other human subjects and dogs, the sequence of the drug periods was inverted. Drug doses were similar to those employed in the treatment of headache patients[4]. In all the subjects and dogs, placebo was administered before the 3rd tests (control II). The humans did not change their habits during the duration of the investigation. They suffered no intercurrent diseases or oscillations of body weight during that time. No side effects were registered and no other drug was taken during the experimentation periods.

Dogs employed in the present study were maintained (under controlled conditions) in the home of one of us, where they ate their routine dog food (Perrarina). No

oscillations in body weight were registered during the experimentation periods. The dogs showed neither anxiety nor psychomotrix agitation during experiments, and no changes in their behaviour were observed during or after the drugs' administration periods.

Results. At the dosage level employed in the present study, sulpiride decreased and haloperidol increased tolerance to oral glucose (figure). The present study also shows that sulpiride, but not haloperidol, increases blood serotonin levels. This latter drug reduced blood serotonin levels in the dogs, but not in the human subjects. On the other hand, despite the changes registered in glucose tolerance, neither glucose nor IRI fasting serum levels were affected by pre-treatment with dopaminergic blocking agents. No significant variations in the glucose tolerance and blood serotonin levels were observed during control I and control II tests.

Discussion. Some proven facts need to be invoked in order to find explanations for our results. a) Dopamine and serotonin fluorescences have been found over the insulin granules in beta-cells and both monoamines disappear during insulin secretion[10,11]; hence, it is probable that they play a physiological role in this process. b) Serotonin stimulates basal, and inhibits glucose-induced insulin secretion[12,13]. c) Sulpiride and haloperidol produce opposite effects on distal colon motility[6]. This antagonism between both anti-dopaminergic drugs is in line with that obtained in the present study. From these facts, it is reasonable to think that the decrease in glucose tolerance induced by sulpiride could be mediated by the concommitant rise in blood 5HT levels provoked by this drug. However, our findings could be related also to the 2 antagonistic dopamine-receptors found at the central nervous system level, one of which, but not the other, was blocked by haloperidol[14]. On the other hand, assuming that low doses of this drug block pre-synaptic receptors, preferentially, a release of dopamine and/or noradrenaline would be induced[15-18]. On the contrary, sulpiride, an atypical neuroleptic drug, would block post-synaptic dopamine receptors only[19,20].



8 days of sulpiride, but not of haloperidol, pre-treatment impaired oral glucose tolerance test and raised blood serotonin (5HT) levels in 6 normal humans and 6 normal dogs. No drugs were administered before control I test. Placebo was administered before control II test. Means±SEM. Serotonin was assayed at 0 and 60 min, only. Changes in 5HT are expressed in percentage. $P < 0.001$. Statistical significance against zero-mean values at control I test (100%).

It has recently been shown that sulpiride effects are mediated by the central serotonergic system[21]. This finding, along with the fact that sulpiride pre-treatment induced similar effects to those provoked by captivity[22] (both factors impaired tolerance to glucose and raised blood serotonin levels), supports the hypothesis of a central mechanism. In addition to that, the facts that both increased and defective insulin secretion can be induced by manipulations of brain catecholaminergic mechanisms[23,24], are in line with the central hypothesis.

Our findings support those showing that carcinoid syndrome patients had glucose intolerance, impaired insulin secretion and elevated serum serotonin levels[25]. Although chronic pre-treatment with sulpiride lowers GH and raises prolactin in humans[26], and the latter hormone impairs tolerance to glucose[27], hyperinsulinaemia is registered in these subjects. Further studies are required to shed light on the role of other hormones (GH, ACTH, cortisol, catecholamines, glucagon, etc.) with the dopaminergic blockade-induced changes of glucose tolerance.

1 Acknowledgment. The authors are grateful to Dr P.J. Randle, Dept. of Biochemistry, School of Medicine, Oxford University, for his helpful advices and for revision of the manuscript.

2 This work was supported by a grant of the Consejo de Desarrollo Científico y Humanístico de la Universidad Central de Venezuela.

3 Correspondence should be addressed to: Dr F. Lechin, Apartado 80.983, Caracas 108, Venezuela.

4 F. Lechin, B. van der Dijs, E. Lechin, F. Peña and A. Bentolila, Headache *18*, 69 (1978).

5 F. Lechin, B. van der Dijs and E. Lechin, in: The Autonomic Nervous System. Physiological Basis of Psychosomatic Therapy. Editorial Científico-Médica, Barcelona, España (1979).

6 F. Lechin and B. van der Dijs, J. clin. Pharmac., in press (1979).

7 J.G. Reinhold, Standard Meth. clin. Chem. *1*, 65 (1953).

8 C.N. Hales and P.J. Randle, Biochem. J. *68*, 137 (1963).

9 G.W. Ashcroft, T.B.B. Crawford, J.K. Binns and E.J. MacDougall, Clin. chim. Acta *9*, 364 (1964).

10 L.E. Ericson, R. Hakanson and I. Lundqvist, Diabetologia *13*, 117 (1977).

11 I. Lundqvist, R. Ekholm and L.E. Ericson, Diabetologia *7*, 414 (1971).

12 F. Lechin, E. Coll-García, B. van der Dijs, F. Peña, A. Bentolila and C. Rivas, Acta physiol. latinoam. *25*, 339 (1975).

13 J.M. Feldman and H.E. Lebovitz, Endocrinology *86*, 66 (1970).

14 A.R. Cools, H.A.J. Struyker and J.M. Van Rossum, Eur. J. Pharmac. *37*, 283 (1976).

15 S.A. McMillen and P.A. Shore, J. Pharm. Pharmac. *29*, 780 (1977).

16 M.A. Lazner and I.S. De La Lande, J. Pharm. Pharmac. *26*, 62 (1974).

17 J. Del Rio and J. Madroñal, Eur. J. Pharmac. *39*, 267 (1976).

18 S.Z. Langer, Br. J. Pharmac. *60*, 481 (1977).

19 P. Jenner, P.N.C. Elliott, A. Clow, C. Reavill and C.D. Marsden, J. Pharm. Pharmac. *30*, 46 (1978).

20 G.U. Corsini, M. del Zompo, S. Manconi, M.P. Piccardi, P.L. Onali and A. Mangoni, Life Sci. *20*, 1613 (1977).

21 B. Costall and R.J. Naylor, J. Pharm. Pharmac. *30*, 257 (1978).

22 F. Lechin, E. Coll-García, B. van der Dijs, A. Bentolila, F. Peña and C. Rivas, Experientia *35*, 876 (1979).

23 S.A. Metz, J.B. Halter and R.P. Robertson, Diabetes *27*, 554 (1978).

24 S.A.E. Darwish and B.L. Furman, Eur. J. Pharmac. *41*, 531 (1977).

25 J.M. Feldman, J.W. Plonk, C.H. Bivens and H.E. Lebovitz, Diabetes *24*, 664 (1978).

26 D.H. Mielke, D.M. Gallant and C. Kessler, Am. J. Psychiat. *134*, 12 (1977).

27 R. Landgraf, M.M.C. Landgraf-Leurs, A. Weissman, R. Hörl, K. von Werder and P.C. Scriba, Diabetologia *13*, 99 (1977).