In another series of experiments, compound A was administered at 10 and compound B at 2 mg/kg/day p.o. for 7 days each to 6 SH rats. The antihypertensive effect was observed on every treatment day; there was no evidence of tolerance development to either of the 2 compounds (figure 3).

By i.v. administration to anesthetized dogs, compound A at 2.5 mg/kg i.v. and compound B at 1 mg/kg i.v. lowered arterial pressure and peripheral vascular resistance. A pronounced increase in cardiac output was seen with both drugs at 2 min after treatment. Heart rate was slightly increased by compound B but not compound A. There was no significant change in right atrial pressure with either compound (table 2).

On isolated cat heart papillary muscles, compound A, 10 µg/ml, had slight positive inotropic activity. This effect was prevented by the β-adrenergic blocking agent, sotalol, 10 µg/ml 10 min prior to compound A or by pretreatment of cats with reserpine, 0.5 mg/kg i.p., 18 h prior to the test. Compound B at either 10 or 40 µg/ml had no effect on the contractile force (table 3). The positive inotropic effect of compound A was attributed to possible release of norepinephrine from cardiac storage sites.

Other exploratory experiments indicated that by intraarterial administration to anesthetized dogs, compounds A or B, 100 to 500 µg, transiently increased arterial blood flow. Neither of the 2 compounds had any ganglionic blocking, adrenergic neuron blocking or α-adrenoceptor blocking effects. In 2 cats with pithed spinal cord, compound A, 20 mg/kg i.v., lowered arterial pressure to an extent similar to that observed in normal cats. These experiments suggest that the hypotensive effect of compound A is likely to be independent of the autonomic nervous system and is possibly mediated by direct smooth muscle relaxant activity.

In preliminary toxicological studies, both compounds produced myocardial necrosis in dogs. In this respect, the 4-trifluormethylimidazoles were similar to directly-acting vasodilator drugs, e.g. hydralazine, diazoxide or minoxidil.

Our findings represent a discovery of a new class of vasodilator drugs which can conceivably be useful in the treatment of hypertension.

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Effects of chronic lithium administration on concanavalin A binding to plasma membranes from the corpus striatum of rat brain

D.J. Segarnick, L.J. Traficante[1], W.T. Maple and J.B. Ferguson

Bard College, Department of Biology, Annandale-on-Hudson, New York, (N.Y. 12504, USA), 4 September 1978

Summary. The effects of chronic in vivo lithium administration on mannose-containing components of plasma membranes from rat corpus striatum were examined by a ^{3}H-concanavalin A binding displacement method. No difference in Con A binding was observed between sodium or lithium-treated rats during a 1-month period.

Several diverse biological effects have been observed in association with the pharmacological action of the lithium ion (Li^+). These effects include depression of DNA polymerase activity[2], substitution for intracellular and extracellular cations[3], and altered metabolism of the catecholamines[4]. Furthermore, Li-induced changes in intracellular and extracellular function have initiated a number of theories of depression in association with the cell membrane[5]. Kline et al.[6] have reported observations by scanning electron microscopy on the choroid plexus of rats chronically treated with lithium which are compatible with possible alterations in surface glycoprotein hydration.

These potent neuropharmacologic actions of lithium have stimulated an examination of the effects of this ion on concanavalin A (Con A) binding in brain to examine possible structural changes in mannose-containing components of the cell membrane in a group of rats chronically treated with sodium or lithium.

Materials and methods. Male Sprague-Dawley rats weighing 160–200 g were maintained on Purina dry rat chow containing 0.21% (w/w) lithium or sodium in a 12-h light/dark cycle and were sacrificed at the end of 4 weeks. All animals treated attainer intracellular erythrocyte lithium levels between 0.4 and 0.8 meq/l.

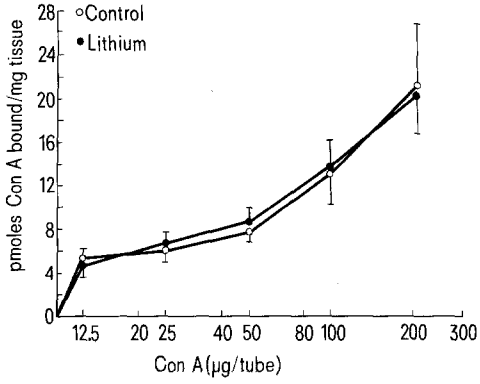
After sacrifice by decapitation, whole brains were rapidly placed into chilled physiological saline. The corpora striata were dissected over ice, weighed and gently homogenized in a Kontes-Duall glass-teflon tissue grinder in 75 vol. of a modified Krebs Ringer buffer solution consisting of 11 mM NaCl, 0.5 mM KCl, 0.1 mM $MgSO_4$, 0.2 mM $CaCl_2$, 0.1 mM NaH_2PO_4, 1 mM ascorbic acid, 0.5 mM EDTA, 1 mM glucose, 5 mM $NaHCO_3$ and 0.1% (w/v) bovine serum albumin. The solution is oxygenated for 15 min, and pH adjusted to 7.4. All buffers and tissue homogenates were kept at 0–4 °C.

Binding of ^{3}H-labeled Con A (New England Nuclear, Boston, Mass. USA) to cell plasma membranes was measured by a method similar to that described by Cuatrecasas et al.[7] for fat cells. Tissue homogenate (containing 60 µg protein) was added to each assay tube containing 0.5 ml of the Krebs Ringer buffer, 2×10^4 cpm ^{3}H-Con A, and various amounts of unlabeled Con A (figure). Incubations were carried out in an ice bath for 90 min, after which each assay mixture was filtered over a Whatman glass fibre filter (GF/B) and the filter washed with an additional 10 ml of the ice-cold buffer. Total binding of the labeled lectin was measured as the excess over tubes containing no tissue. The molecular weight used for Con A was 100,000. Total

specific lectin binding was reversed by the addition of 50 mM α-methyl-d-mannoside. All assays were run in duplicate. Glass fibre filters were each suspended in 10.0 ml of Aquasol scintillation fluid (New England Nuclear) for determination of incorporated ^{3}H.

Results and discussion. The displacement of ^{3}H-labeled Con A bound to rat striatal membranes by various quantities of unlabeled Con A occurs in a dose-dependent manner from 25 to 200 µg Con A per assay (figure). Saturation of binding sites was not observed at the highest concentration of Con A studied (200 µg/assay). Cuatrecasas et al.[7] have reported similar results for fat cells where levels of 1 mg/ml were required to approach saturation. In addition, the Con A binding profile shown in the figure is similar to that described by Carter et al.[8] for the binding of Con A to rat liver plasma membranes. The figure shows that Con A binding to striatal cell-surface components does not differ for the sodium or lithium treated groups for all animals tested at the end of the 4-week period. We conclude that chronic lithium treatment does not appear to alter mannose-containing cell-surface glycoproteins or glycolipids in this brain region under the conditions studied. However, it is not possible to conclude that there are no effects on membrane components which do not contain mannose, or components which contain mannose but where the carbohydrate residue is not susceptible to Con A binding because of steric hindrance.

Although previous reports[6] indicate that possible alterations in cell-surface glycoproteins may occur in rat choroid plexus during chronic lithium administration, our present results do not indicate any significant alterations in cell-surface components susceptible to Con A binding in rat corpus striatum. Further studies of this nature should be carried out in other brain regions along with additional lectins which have different carbohydrate specificities, i.e., wheat germ agglutinin.



Binding of concanavalin A to cell-surface components in rat corpus striatum. Data reported as mean±SE, n=8 for each group of lithium and sodium (control) treated rats for a 1 month period. ○, control; ●, lithium.

1 To whom all reprint requests and communications should be addressed: Neuropsychopharmacology Research Unit, Department of Psychiatry, New York University Medical Center, 550 First Avenue, New York, New York 10016. We thank Dr S. Gershon of this research unit for his encouragement and support during these studies.

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β-Adrenoceptor blocking drugs, heart rate and genetic hypertension development in rats[1]

C. Richer, N. Venturini-Souto[2] and J.F. Giudicelli

Département de Pharmacologie, Faculté de Médecine Paris-Sud, 15, rue de l'Ecole de Médecine, F-75270 Paris Cédex 06 (France), 4 September 1978

Summary. In spontaneously hypertensive rats (SHRs) chronically treated during their growth with β-adrenoceptor blocking drugs, no correlation was found between the reduction in heart rate and the prevention of genetic hypertension development.

Chronic administration of some β-adrenoceptor blocking drugs, e.g. propranolol, metoprolol and atenolol[3,4] to young spontaneously hypertensive rats (SHRs) has been shown to prevent to a large extent genetic hypertension development (GHD). This effect suggests that the high level of sympathetic activity[5] and the subsequent elevated heart rate (HR) observed in young SHRs might play an important role in GHD. We now report the effects of chronic administration of 7 different β-adrenoceptor blocking agents on GHD and HR in SHRs.

8 groups of 5-week-old male SHRs (Charles River) were used. (ystolic blood pressure (SBP) was determined in the conscious animals by the indirect tail-cuff method (DMP Narcobiosystems Inc.) on their 40th day of life and then at 8, 12, 16 and 20 weeks of age at least 20 h after the last drug administration. HR was obtained from the pressure tracings. Starting from the 40th day of life, the different groups of rats (untreated controls n=36, treated n=12) were given orally by gavage (1 ml/100 g b.wt) every day at the same time for 14 weeks, either distilled water (controls) or atenolol (200 mg/kg), propranolol (100 mg/kg), nadolol (100 mg/kg), penbutolol (100 mg/kg), pindolol (20 mg/kg), acebutolol (100 mg/kg) and the acetyl metabolite of acebutolol (Ac-acebutolol) (100 mg/kg). All doses refer to the base. Treated/control animals ratios (±SEM) for SBP and HR values were then calculated for each drug at each time of measurement and the difference between these ratios and unity was analyzed statistically.

In the control group, SBP values were 129.4±2.6, 161.0±2.7, 183.9±3.8, 198.4±2.9 and 204.4±4.1 mm Hg at the ages of 40 days, 8, 12, 16 and 20 weeks. The corresponding HR values were: 475.2±13.5, 472.1±12.0, 473.4±18.9,