Effect of Lithium on Aggression, Mania- and Permselective Membranes

The effect of lithium ions on behaviour has been established beyond doubt during the last decade. Lithium ions reduce aggressive behaviour in fish and rodents[1,2] and have been effective in the treatment of human mania[3–6] and beside this sometimes even of human depression[7–10]. Some biochemical reactions influenced by lithium have been discussed in a review[11], such as inhibition of carbohydrate transport[12,13] and influence on cyclic AMP metabolism[14] and on the combined effect with dopamine and vanillyl mandelic acid[15]. However, the impression remained that a basic link is still missing in the explanation of the physiological effect of lithium ions[11].

Behaviour is controlled by the nervous system. The excitation wave along the neurons and synaptic transmission takes place along and across the membranes of neuron and synapsis. It may therefore be pertinent that the lithium ion also has a strong effect on certain ion-permselective membranes which in some respects resemble neural membranes and may sometimes serve as their simplified model.

Permselective membranes selectively allow the passage of anions or cations according to whether the fixed ionic groups within them are positively or negatively charged. Such membranes made of polyethylene-phosphonic acid increase their resistance from a few ohms per cm^2 to some 100,000 ohms when they are transferred from an alkaline into an acid solution. However, their resistance is also increased a 1000 fold in the presence of lithium ions, even in 1*N* LiOH which is strongly alkaline[16,17]. Their phosphonic acid content determines how strongly and in which pH range resistance changes most quickly with pH. The strongest pH dependence is often in the physiological range of about pH 7.

The explanation of these phenomena is as follows: Phosphonic acids gradually deionize in acid media. Consequently they also lose swelling water, and this is the reason that the number of aqueous channels across the membrane and hence the conductivity decreases. We found that these membranes are more open to Na^+ than to K^+ in acid and neutral pH ranges[16]. This means that the size of the unhydrated ion determines permeability in this domain. To confirm this conclusion we also used Li^+, as the smallest alkali ion. Surprisingly, it was found to 'close' the membrane similarly to H^+, but even in strongly alkaline solutions. This must mean that the small Li^+ ion is attracted so strongly by the phosphanate ion that it loses its hull of hydrate water molecules and becomes attached to the phosphonate ions. The latter are thus deionised, and also lose their hydration water, so that the membrane shrinks and its conductivity decreases strongly. It should be remembered that inorganic Li_3PO_4 is also slightly soluble in water.

The physiological membranes which surround neurons and are responsible for their excitability always contain phosphate groups bound in their phospholipids. It seems more than probable that some of these phosphate groups react with Li^+ similarly to the phosphonate groups of our artificial membranes. Although spiking of nerves is only slightly impeded when Li^+ is substituted for Na^+ in the external solution around an axon[18], the recovery period after spiking is 10–25 times longer in Li^+ than in Na^+ solutions and it blocks impulse transmission in glanglia[19,20]. The simple ionic combination of Li^+ with phosphate sites in the phospholipid membrane is probably dependent on the species of phospholipid. One would assume that acidic lipids like phosphatidic acid, phosphatidyl-inositol or phosphatidyl-serine combine more strongly with Li^+ than the amphoteric species lecithin and phosphatidyl-ethanolamine in which the phosphate can be bound to ammonium or amino groups. This could allow different parts and actions of the neuron to be influenced by Li^+ to a different extent. But it seems very probable that Li^+ increases the electric resistance of some nerve membranes in the same way as it increases the resistance of our artificial membrane, and that nerve membranes which become sluggish in their electrophysiological behaviour ultimately also reduce more violent psychological effects.

Zusammenfassung. Nachweis, dass Li^+-Ionen den elektrischen Widerstand von permselektiven Membranen, welche Phosphatgruppen enthalten, stark erhöhen. Die beruhigende Wirkung der Li^+-Ionen bei psychischen Störungen könnte damit zusammenhängen.

D. KERTESZ and F. DE KÖRÖSY

Division of Chemistry, Negev Institute for Arid Zone Research, Beer Sheva (Israel), 2 May 1972.

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LSD Effects on Signal-to-Noise Ratio and Lateralization of Visual Cortex and Lateral Geniculate During Photic Stimulation

Signal-to-noise ratios and modulation period changes of visual cortex and lateral geniculate body have been described by TREHUB[1,2], during contralateral and ipsilateral photic stimulation. More recently this author[3] postulated, on the same experimental grounds, that the brain functions as a coherent signal detector.

Table I. Signal characteristics during contra, ipsi, bilateral photic stimulation at 12 c/sec

Cerebral structure	Before LSD			Following LSD		
	S′/N	S/N	S^2/N^2	S′/N	S/N	S^2/N^2
RGB						
Contra	1.04	0.04	0.0016	1.17	0.17	0.0289
Ipsi	0.91	−0.09	0.0081	1.07	0.07	0.0049
Bi	0.99	−0.01	0.0001	1.18	0.18	0.0324
LGB						
Contra	1.08	0.08	0.0064	1.78[a]	0.78	0.6080
Ipsi	1.04	0.04	0.0016	1.04	0.04	0.0016
Bi	0.93	−0.07	0.0049	1.37[a]	0.37	0.1370
LCtx						
Contra	0.95	−0.05	0.0025	1.55[a]	0.55	0.3000
Ipsi	0.97	−0.03	0.0009	1.05	0.05	0.0025
Bi	0.76	−0.24	0.0580	1.86[a]	0.86	0.7400

S/N, signal-to-noise ratio; S^2/N^2, signal-to-noise power ratio. Cerebral structures: right (RGB) and left (LGB) lateral geniculate bodies, left visual cortex (LCtx). [a] $p < 0.01$, as compared with 'before LSD' S′/N mean value (t-test).

Previously one of us (ETEVENON[4–6]) investigated on rabbits the effects of photic stimuli presented contralaterally, ipsilaterally or bilaterally and the changes observed after administration of lysergamide[4,5] (LSD-25, 5 γ/kg, i.v.), D-amphetamine sulphate[6] (1 mg/kg, i.v.) or pentobarbital[6] (3 mg/kg, i.v.).

Methods. Photic stimulation was delivered via fiber optics and hemispheric goggles. Unfiltered tungsten light sources (4 mW; 430 ft.-candles) were interrupted by mechanical shutters triggered by a Grass stimulator S4 at the chosen frequency (3; 7 or 12 c/sec). The integrated-raw EEGs were computed for right and left geniculate bodies (RGB, LGB) and right and left visual cortices (RCtx, LCtx). The 20 sec integrated EEG preceding each stimulation was taken as a control period (N) for the following 20 sec stimulation period (S′). The following results are based on 10 acute experiments with curarized rabbits placed under artificial respiration.

Results. Mean ratios of S′/N were computed. Student's t-test 'following vs. before LSD' reveals significant changes after LSD, during contralateral and bilateral stimulation (Table I). The control period N was taken as noise and the signal S evaluated by the difference between S′ and N. Values of signal-to-noise ratio (S/N is equal to S′/N minus 1) and signal-to-noise power ratio (S^2/N^2 is S/N squared) were computed (TREHUB[2]) with the relative signal-to-noise power ratio (R) for contralateral vs. ipsilateral stimulation (Table II).

Table II. Relative ratios R between signal-to-noise power ratios, for contralateral vs. ipsilateral stimulation

Cerebral structure	$R = (S^2/N^2)_1/(S^2/N^2)_2$ Contra = 1; Ipsi = 2	
	Before LSD	Following LSD
RGB	0.2	5.9
LGB	4.0	380.0
LCtx	2.8	120.0
Lateralization		
LGB/RGB	20.0	64.0
LCtx/RGB	14.0	20.3

Following LSD administration, the signal-to-noise ratio as well as the signal-to-noise power ratio increase during contra and bilateral stimulation for RGB, LGB and LCtx structures (Table I). Furthermore, the relative ratio R (contra/ipsi) between signal-to-noise power ratios is increased more than 50 times following LSD (Table II). We observed a discrepancy between right and left responses to contralateral stimulation. In 80% of the rabbits after contralateral stimulation, the left response was greater than the right response and this was reversed for 20% of the animals. The relative ratio LGB/RGB, between S/N values, doubles after contralateral stimulation before LSD and increases 2.3 times more after LSD. A 'lateralization index' may also be expressed by the ratios LGB/RGB and LCtx/RGB between R values and indicated a very marked increase following LSD administration (Table II).

Discussion. The homolateral non-decussating fibers in rabbits are estimated to 1% (SMYTHE[7], POLYAK[8]). The relative ratio R has been theoretically related to the 10% uncrossed optic nerve fibers in the rat (TREHUB[2]). The range of R values before LSD is consistent with the above hypothesis (Table II). Furthermore, a specific lateralization seems to modulate the contralateral effect. Following LSD, contralateral stimulation increases signal-to-noise values as well as lateralization index. After contralateral stimulation, amphetamine increases also the lateralization of visual areas, whereas pentobarbital decreases it towards control prestimulation values and ipsilateral stimulation effects[6]. Despite the fact that we have not used filtered EEG (through a narrow band-pass filter centered on the stimulation frequency), but raw EEG before integration, our results are coherent with TREHUB's results and such technique appears to be valuable in studying drug-effects.

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After LSD[9], the observed decrease in mean EEG integrated values (proportional to the standard-deviation of EEG over the 20 sec integration epoch) and in variability coefficient computed between integrated values (inversely proportional to the signal-to-noise ratio[10]) confirms the present findings of signal-to-noise increase. This would indicate not only an increase in signal effects, especially during contralateral stimulation, but also a decrease in background EEG activity taken as a noise indicator.

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Résumé. L'administration de LSD augmente les effets de la stimulation contralatérale, la latéralisation et le rapport signal-sur-bruit. Ces résultats sont en accord avec le modèle de fonctionnement cérébral considéré comme un détecteur cohérent en parallèle.

P. ETEVENON and J. R. BOISSIER

Unité de Recherche de Neuropsychopharmacologie, INSERM
2, rue d'Alésia,
F-75 Paris 14e (France),
20 January 1972.

The Role of Melanoblasts in Melanophore Pattern Polymorphism of *Xiphophorus* (Pisces, Poeciliidae)

Species and species hybrids in the genus *Xiphophorus* (which includes *Platypoecilus*) may develop pigment cell patterns, which consist of extremely varied numbers of macromelanophores. These can be correlated to the genetic constitution of an animal[1,2]. Since melanophores[3,4] and melanocytes[4] are rarely, if ever, observed in division stages, one must suppose that genes influencing melanophore numbers act at an earlier level of pigment cell differentiation. Therefore, melanoblast[4] densities in adult animals of diverse genotypes[5] from pure species and from species crosses have been studied. For practical reasons, counts were restricted to melanoblasts which are attached to scales. Because of the heterogeneity of distribution, only maxima[6] and minima[6] are given in the Table.

The relationship between genotypes and melanoblast densities is considered based at first on the maximal values, since it has been determined that average numbers for whole animals generally approach them. Densities of about 200 melanoblasts per mm² (Figure 1) are found in members of pure species (see 1–3, 5, 6, 10, 11 in the Table) as well as in hybrids of different genotypes (see 12–14, 16–18 in the Table). The phenotypes within this group vary extremely, from animals bearing no macromelanophore spots (see 1, 3, 14, 17 in the Table) to melanoma or premelanoma bearing animals (see 12, 13 in the Table). From these counts there seems to be no correlation between the number of detectable melanoblasts and the melanophore promoting constitution of a genotype, the degree of which is indicated by more or less extended melanophore concentrations.

Additional results must be taken into consideration for cases of lower maxima (see 4, 7–9, 15 in the Table), which seem not to agree with this general conclusion. Actually, all numbers given have to be regarded as minimal counts only.

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[6] Maxima are normally found in the ventral ridge, the back beneath the dorsal fin and the throat. Minima often occur in the region of the middle line.

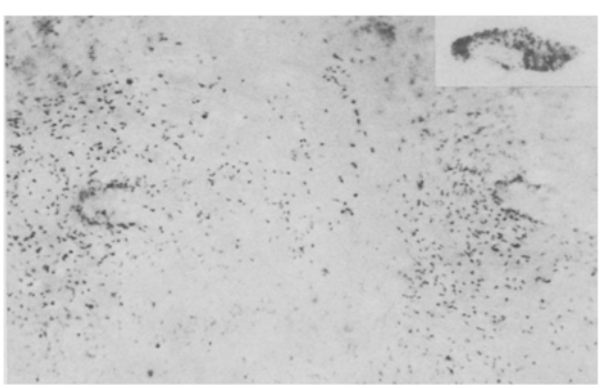

Fig. 1. Dense concentration of melanoblasts (approximately 200/mm²) on scales in situ covering the belly of an adult *X. helleri*/*maculatus* hybrid. Each small dot represents one melanoblast (see insert), except in single cases of very small melanophores. (The whole fish was fixed[11] at 4 °C for 2 h and rinsed thoroughly overnight. Dopa incubation[11] was done for 5–6 h with one change of solution after 1–2 h). × 20; insert × 650.

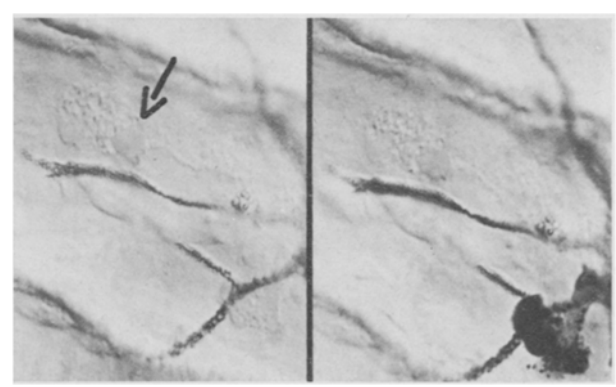

Fig. 2. Part of a scale of *X. helleri* before (left) and after Dopa incubation (right). 2 melanoblasts have been stained, 2 other ones (arrow) have remained colourless. Interference contrast, × 900.