Increase of blood-brain barrier permeability to catecholamines by dimethyl sulphoxide in the neonate chick

Parenteral adrenaline or noradrenaline, because they cross a permeable blood-brain barrier in young chicks, produce sustained roosting or sleeping behaviour (Key & Marley, 1962; Spooner, Mandell & others, 1968; Hanig & Seifter, 1968). This phenomenon disappears within 6–8 weeks as the various components of the central nervous system mature (Waelsch, 1955; Lajtha, 1957). Several years ago, Brink & Stein (1967) showed that dimethyl sulphoxide (DMSO) facilitated the entry of [^{14}C]pemoline into the brain of rats. Recently, De La Torre (1970) has shown that DMSO increases the relative penetration of L-dopa and 5-HTP across the blood-brain barrier of the rat.

DMSO is an industrial solvent with skin-penetrating effects, and the ability to carry into the body toxic substances that are normally excluded (Stoughton & Fritsch 1964; Kligman, 1965; Narula, 1967). Since DMSO has both aqueous and lipid solubility characteristics that allow it to penetrate the central nervous system easily, it was chosen as a prototype compound for study of blood-brain barrier biogenic amine interaction in the neonate chick. We observed that DMSO intensified roosting induced by adrenaline and noradrenaline in the neonate, and therefore sought to determine whether this was associated with increased penetration of catecholamines into chick brain (Hanig, Morrison, & Krop, 1970).

One-day-old chicks housed in a temperature-controlled brooder were given free access to food and water and used within one week. Adrenaline or noradrenaline was dissolved in 0·9% NaCl or 50% DMSO—0·9% NaCl and administered (5 mg/kg, i.v.) into the jugular vein. This corresponded to a dose of 2·75 g/kg of DMSO which is well below the single dose toxicity for various species described by Smith, Hadidian & Mason (1967). Chicks were decapitated 10 min after adrenaline administration, but 2 min after noradrenaline because of its rapid turnover in the brain. Both amines in whole brain were estimated by an automated fluorimetric procedure (Hanig, Morrison & Krop, 1969).

The grossly observable behaviour of DMSO alone in chicks was minimal except for a transitory arousal that lasted for several seconds after injection, whereas those receiving adrenaline or noradrenaline with DMSO exhibited a roosting response that was more intensified than that observed with the same dose of either amine alone. Preliminary chemical studies showed no difference in endogenous amine concentra tions between animals treated with saline or those treated with DMSO alone (Hanig & others, 1970). Administration of adrenaline + DMSO gave a highly significant increase of 34·8% in concentrations of this amine in brain over controls receiving the same dose of adrenaline alone. Similarly, noradrenaline + DMSO treatment gave

Table 1. *Dimethyl sulphoxide (DMSO) increases penetration of adrenaline and noradrenaline across the blood brain barrier of the neonate chick.*

Treatment	Concentration of adrenaline or noradrenaline†	Change %	n
Adrenaline	0·381	—	16
Adrenaline + 50% DMSO	0·513*	+34·8	16
Noradrenaline	0·614	—	24
Noradrenaline + 50% DMSO	0·852*	+38·8	24

* Significantly different ($P < 0·001$) from adrenaline and noradrenaline treatments, respectively.
† Expressed as μg/g whole brain.

a highly significant increase of 38·8% in brain noradrenaline over those receiving only the amine (Table 1). Experiments still in progress indicate that DMSO plus dopamine intensify fixed staring and catatonia that occur after administration of this amine alone, although the associated amine brain levels have not yet been determined.

Results indicate that DMSO, a solvent having both polar and nonpolar characteristics, facilitates entry of adrenaline, noradrenaline and possibly dopamine across the blood-brain barrier. The occurrence of this phenomenon may, in part, be related to the ability of this solvent, acting as a carrier of biogenic amines, to traverse both aqueous and lipid phases or components of the barrier. These findings may have significance in conditions requiring brain amine replenishment.

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The involvement of plasma free fatty acids in (+)-amphetamine-induced hyperthermia in rats

Both hyperthermia and increased levels of plasma free fatty acids (FFA) are seen in animals after the administration of amphetamine. Gessa, Clay & Brodie (1969) attributed the hyperthermia in rats to a peripheral site of amphetamine's action, *viz.*, the increased plasma FFA. However, Hill & Horita (1970) reported hyperthermia in rabbits to be due to its central action. In mice, low doses of amphetamine cause *hypo*thermia and large doses *hyper*thermia (McCullough, Milberg & Robinson, 1970). The former is attributed to a central component and the latter to a peripheral component of amphetamine's activities. Since the question of the mechanism of amphetamine-induced hyperthermia is still unanswered, we now report that an increase of plasma FFA is not an integral part of the hyperthermic response.

Male Wistar rats (Harlan Industries, Indianapolis), 175–200 g were housed six per group in a cage (50 × 80 × 40 cm). After determining rectal temperatures with a thermistor probe (TRI-R), desipramine (10 mg/kg, i.p. of the salt) was administered, 15 min later (+) amphetamine (4·0 mg/kg, i.p. base), was administered. Rectal temperatures were read at 30 and 60 min after the drug was given. Orbital sinus