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THE EFFECT OF SODIUM SALICYLATE ON CEREBRAL BLOOD FLOW AND METABOLISM

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1 The effect of intravenous sodium salicylate on cerebral oxygen consumption and cerebral blood flow and its response to hypercapnia was measured by the ^{133}Xenon intracarotid injection technique in ten baboons.

2 After an initial peak, the plasma salicylate level maintained a stable value for 2 h of 1 mmol/l with 50 mg/kg sodium salicylate and 2.5 mmol/l with 200 mg/kg sodium salicylate.

3 Sodium salicylate (50 mg/kg) produced no change in baseline cerebral blood flow (CBF) or cerebral oxygen consumption ($CMRO_2$) but the CBF response to hypercapnia was reduced by 41% during the first hour. During the second hour after salicylate administration, $CMRO_2$ increased by 26%, CBF at normocapnia increased by 31% and the CBF response to hypercapnia was 67% of the baseline value.

4 Sodium salicylate (200 mg/kg) increased $CMRO_2$ by 65%. There was no significant change in CBF at normocapnia or hypercapnia.

5 These results confirm that inhibitors of prostaglandin synthesis, which can cross the blood brain barrier in sufficient quantity, reduce the response of the cerebral circulation to hypercapnia. The difficulties in interpreting changes in the CBF CO_2 response in the presence of increases in $CMRO_2$ are discussed. It is suggested that the respiratory stimulation seen in salicylate intoxication is the result of a central metabolic stimulation.

Introduction

The response of the cerebral circulation to hypercapnia is blocked by indomethacin, an inhibitor of prostaglandin synthesis (Pickard & MacKenzie, 1973). It was suggested that carbon dioxide would produce cerebral vasodilatation only in the presence of an unspecified prostaglandin, yet the effects of the stable prostaglandins, prostaglandin E_2 (PGE_2) and $PGF_{2\alpha}$, on the cerebral circulation did not suggest that they fitted this role (Pickard, MacDonell, MacKenzie & Harper, 1977). To discover whether the effect of indomethacin on the CBF CO_2 response was shared by other inhibitors of prostaglandin synthesis, we have examined the actions on the cerebral circulation of salicylates, which are being proposed for use in the management of cerebrovascular disorders (Hass, 1977).

It was anticipated that salicylate effects would prove to be more complex than those of indomethacin; indomethacin blocks prostaglandin synthesis at much lower concentrations than those at which it affects other enzyme systems. With salicylates the effects are manifest at more similar concentrations (Flower, 1974). In a previous study, in human volunteers, we demonstrated that 1 g of sodium salicylate given intravenously reduced the CBF response to CO_2 by 26% (Pickard, Rose, Cooke, Blair & Strathdee, 1977).

In the present study, we have explored the effects of various plasma levels of sodium salicylate on cerebral blood flow and metabolism in the baboon.

Methods

Animals

Thirteen young healthy baboons (*Papio cynocephalus* and *Papio anubis*) of either sex, weighing approx. 10 kg were used for these experiments.

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Anaesthesia

Following sedation with phencyclidine (12 mg, i.m.), anaesthesia was induced with sodium thiopentone (7.5 mg/kg, i.v.). After endotracheal intubation, anaesthesia was maintained by half-hourly injections of phencyclidine (4 to 6 mg, i.m.) and muscular relaxation provided with suxamethonium chloride (6 mg/kg, i.m.) administered half-hourly. The animals were ventilated with 75% N_2O and 25% O_2 delivered by an intermittent positive pressure respiratory pump in open circuit. The use of this anaesthetic regime has been discussed in detail in a recent paper (Fitch, McGeorge & MacKenzie, 1978).

End-tidal CO_2 was continuously monitored with an infrared analyzer and controlled either by altering the stroke volume of the pump or by adding CO_2 to the inspired gas mixture. The Pa_{O_2} was always maintained above 80 mmHg. A catheter was inserted into the abdominal aorta via the femoral artery for the frequent measurement of P_{CO_2}, pH, P_{O_2}, oxygen content and haemoglobin concentration.

A fine catheter in the superior sagittal sinus was used to measure cerebral venous pressure and oxygen content. The oxygen contents of the samples of arterial and cerebral venous blood were measured with a Lex-O_2-Con oxygen Content Analyzer (Albury Instruments Ltd).

Cerebral blood flow

CBF was measured by the height/area method following the intracarotid injection of ^{133}Xenon via a cannula in the right linguofacial trunk (Høedt-Rasmussen, Sveinsdottir & Lassen, 1966). The remaining branches of the right external carotid artery were ligated and the scalp and temporalis muscle on the right removed in order to eliminate errors due to isotope clearance from any extracranial tissues. Clearance of ^{133}Xenon was recorded by use of a collimated, one-inch sodium iodide, thallium-activated, scintillation crystal.

Cerebral oxygen consumption ($CMRO_2$) was calculated from the product of CBF and the arteriovenous oxygen content difference.

Plasma salicylate estimation

Plasma levels were estimated by the method of Smith & Talbot (1950). Because of rather high blank values in sera from controls with this method, values below 0.5 mmol/l are of dubious significance.

Design of experiments

Following surgery an hour was allowed before any baseline measurements of CBF and $CMRO_2$ were made. The response to hypercapnia was then assessed. After return to normocapnia, sodium salicylate, dissolved in water, was infused intravenously over 10 min. Measurements of CBF and $CMRO_2$ were then repeated at frequent intervals for at least 2 h, at both normocapnia and hypercapnia. Statistical significance was assessed with Student's and paired t tests.

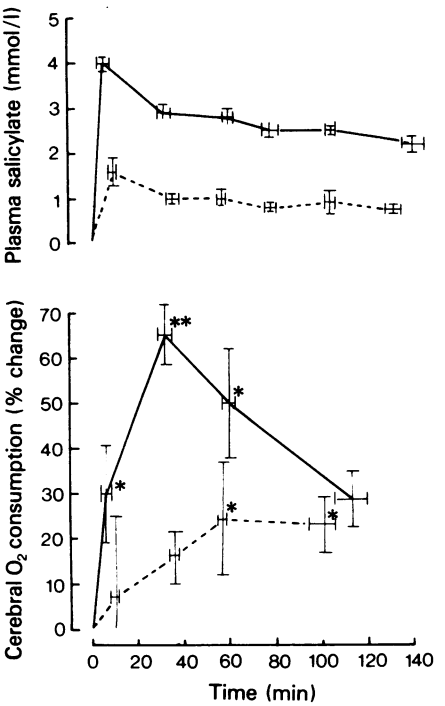

Figure 1 Changes in plasma salicylate level (a) and cerebral oxygen consumption (b) with time after intravenous administration of 50 mg/kg (dotted line) and 200 mg/kg (complete line) of sodium salicylate. The bars represent twice the s.e. (*$P < 0.05$; **$P < 0.01$).

Results

Plasma salicylate level

The peak value was recorded at 10 min; between 30 min and 2 h there was minimal decline in the plasma salicylate level with either dose (Figure 1).

Systemic effects

The sodium salicylate solution was administered intravenously over 10 min. In one animal, cardiac arrest ensued after only 100 mg/kg had been given. In

the experiments on the 10 animals described here, arterial blood pressure remained stable after salicylate administration (Table 1), but there were effects upon $Paco_2$, Pao_2 and body temperature.

End-tidal CO_2 increased after salicylate, especially at the higher dose: this was corrected by adjustment of the respirator. Pao_2 was unaffected by salicylate except for an inconstant and transient fall immediately following salicylate administration. At no time did the Pao_2 fall below 80 mmHg.

There was no consistent change in body temperature with 50 mg/kg salicylate. After 200 mg/kg salicylate, the temperature rose from baseline by a mean of 0.6 ± 0.2°C by 20 min and by 1.2 ± 0.3°C over the succeeding 2 h. We did not attempt to reduce this temperature rise except by removing the infra-red heaters normally used to maintain the animal's temperature.

Cerebral oxygen consumption

There was a very large increase (65%) in cerebral oxygen consumption after 200 mg/kg sodium salicylate, which lagged behind the plasma salicylate level (Figures 1 and 2). After 50 mg/kg sodium salicylate, the increase in cerebral oxygen consumption was less and was more delayed (Figures 1 and 2).

Cerebral blood flow and its response to hypercapnia

The large early rise in cerebral oxygen consumption after 200 mg/kg sodium salicylate was not accompanied by a significant early increase in CBF at normocapnia (Table 1). During the second hour, CBF at normocapnia increased significantly with 50 mg/kg.

The responsiveness of the cerebral circulation to CO_2 has been observed to relate to the level of $CMRO_2$ (see Discussion). In this study, the CBF response to hypercapnia was impaired by 41% during the first hour after 50 mg/kg; this was the only time and the only dose of sodium salicylate with which cerebral oxygen consumption did not increase (Table 1, Figure 2).

The stimulation of the cerebral oxygen consumption which was observed at all other times did not potentiate the CBF CO_2 response: the ratio of CBF CO_2 response to $CMRO_2$ was depressed after salicylate (Figure 2). The ratio $(\Delta CBF/\Delta Paco_2)/CMRO_2$ in Figure 2 is a very contrived index: it is shown only to

Table 1 The effect of sodium salicylate on cerebral blood flow at normocapnia and hypercapnia

	$\frac{Paco_2}{(mmHg)}$	*Mean arterial blood pressure* (mmHg)	*Cerebral blood flow* (ml 100 g^{-1} min^{-1})	$\frac{\Delta CBF}{\Delta Paco_2}$
Baseline				
Normocapnia	39 ± 0.4	94 ± 6	51 ± 4	
Hypercapnia	55 ± 1	97 ± 5	100 ± 6	3.12 ± 0.26
Sodium salicylate (50 mg/kg) (5 animals)				
1st hour				
Normocapnia	38 ± 0.3	86 ± 4	56 ± 5	
Hypercapnia	53 ± 1	91 ± 4	84 ± 6*	1.84 ± 0.26**
2nd hour				
Normocapnia	39 ± 0.7	87 ± 9	67 ± 9*	
Hypercapnia	53 ± 2	96 ± 9	97 ± 9	2.08 ± 0.32*
Sodium salicylate (200 mg/kg) (5 animals)				
1st hour				
Normocapnia	39 ± 0.6	102 ± 8	56 ± 5	
Hypercapnia	55 ± 1	106 ± 4	104 ± 8	3.41 ± 0.29
2nd hour				
Normocapnia	40 ± 0.6	91 ± 10	64 ± 10	
Hypercapnia	56 ± 2	98 ± 10	109 ± 11	2.64 ± 0.50

Values are mean ± s.e. mean.
* $P < 0.05$; ** $P < 0.005$: comparison with baseline values.

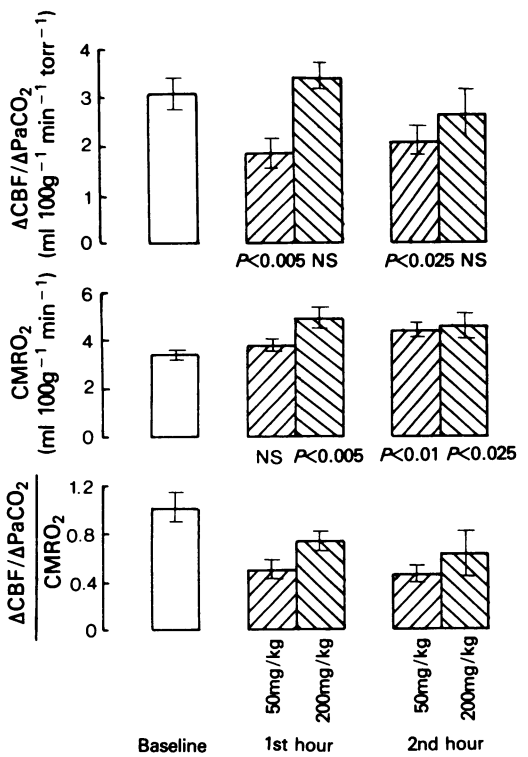

Figure 2 The effect of intravenous administration of 50 mg/kg and 200 mg/kg of sodium salicylate on the cerebral blood flow (CBF) CO_2 response, cerebral oxygen consumption ($CMRO_2$) and the ratio between the CBF CO_2 response and $CMRO_2$. The bars represent twice the s.e. mean.

highlight the reduction in CO_2 response relative to the $CMRO_2$.

Discussion

These results confirm our previous work showing that when an inhibitor of prostaglandin synthesis crosses the blood brain barrier in sufficient quantity, it impairs the response of the cerebral circulation to hypercapnia (Pickard & MacKenzie, 1973). Sodium salicylate reduced the CBF response to CO_2 at 50 mg/kg (plasma level 1.0 mmol/l) but had no immediate effect on baseline CBF in the baboon. This confirms our earlier study in human male volunteers when a plasma salicylate level of 0.9 mmol/l also produced a significant reduction in the CBF CO_2 response (Pickard *et al.*, 1977b).

Prostaglandin synthesis in the rabbit brain is inhibited by 50 mg/kg of sodium salicylate (Cranston, Hellon & Mitchell, 1975). Whilst sodium salicylate and aspirin are equipotent as inhibitors of prostaglandin synthesis *in vivo*, neither is as potent as indomethacin (Flower, 1974). This is in keeping with our observation that salicylate does not impair the CBF CO_2 response as much as indomethacin.

Unlike indomethacin, however, sodium salicylate increases cerebral oxygen consumption. This has not been observed previously *in vivo* although Fishgold, Field & Hall (1951) detected a similar increase in oxygen consumption in rat brain slices. It seems unlikely that the $CMRO_2$ changes we observed are due to the changes in temperature which occurred. Hyperthermia does increase cerebral oxygen consumption, although the effect is small; the increase in $CMRO_2$ is only about 5% per degree centigrade and there is a comparable increase in CBF (see Siesjö, 1978 for review). Furthermore, our results show that the increases in $CMRO_2$ and body temperature follow very different time courses after salicylate administration. A similar increase in oxygen consumption and local acidosis within the central respiratory centres might explain the central respiratory stimulation of salicylate intoxication (at 2 to 3 mmol/l plasma salicylate levels) which remains an enigma (Woodbury, 1970).

As $CMRO_2$ increased with salicylate, so the reduction in CBF CO_2 response became less marked. This suggests that two mechanisms are competing: a direct effect of CO_2 on the arteriolar smooth muscle cell (blocked by indomethacin and partially by salicylate) and a possible enhancement of the CO_2 response as a consequence of increasing $CMRO_2$, which is produced by salicylate but not by indomethacin. Fujishima, Scheinberg, Busto & Reinmuth (1971) demonstrated that the acute response of CBF to changes in $Paco_2$ depended on the $CMRO_2$: if $CMRO_2$ was depressed with barbiturate, the CBF response to $Paco_2$ changes was depressed. This has been confirmed by Grubb, Raichle, Eichling & Ter-Pogossian (1974). Unfortunately, until the present one, there has been no study of the effect of an elevation in $CMRO_2$ on the CO_2 response. Therefore, we do not know if the relationship between $CMRO_2$ and CO_2 response is also present when $CMRO_2$ is increased. It will be interesting to explore the effect of another agent which stimulates $CMRO_2$, such as amphetamine, on the CBF CO_2 response. Fujishima *et al.* (1971) explained the interaction between $CMRO_2$ and CBF CO_2 response by suggesting that CO_2 had both a direct vascular effect and as yet an unknown neurogenic-metabolic effect. By contrast, Grubb *et al.* (1974) believed that changes in $CMRO_2$ were always associated with parallel changes in CBF: by some unspecified mechanism, the vasoconstriction associated with low CBF then reduced the response to CO_2. On the other hand, *in vitro* studies have demonstrated that, when tone is increased, the relaxant effect of reducing

pH on middle cerebral arteries is potentiated (Pickard, Simeone & Vinall, 1976). This is the reverse of what Grubb *et al.* postulated.

Another factor which complicates the interpretation of the changes in CBF CO_2 response with salicylate is the enhanced transfer of salicylate across the blood brain barrier with hypercapnia (Goldberg, Barlow & Roth, 1961). This effect is small for the hypercapnic time-period and arterial pH change noted in these baboons, less than 20% increase in transfer after 1 h of continuous hypercapnia, extrapolating from Goldberg *et al.* (1961). Furthermore, the $CMRO_2$ at normocapnia was not significantly different from that at hypercapnia.

In the context of salicylate administration for cerebrovascular disease, it is important to be clear about the reasons for its use. If aspirin is given purely for its antiplatelet effect, then only small doses are required (Moncada & Vane, 1978). Such small doses have no cerebrovascular effects in man (Pickard *et al.*, 1977b). High dosage salicylate, given in the belief that 'more means better', would stimulate cerebral oxygen consumption, limit CO_2 responsiveness and further stress the limited energy supply in ischaemic areas.

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Note added in proof

We have now demonstrated that prostacyclin will reverse the effects of indomethacin on the cerebral circulation of the baboon (Pickard, unpublished observations).

References

CRANSTON, W.I., HELLON, R.F. & MITCHELL, D. (1975). A dissociation between fever and prostaglandin concentration in cerebrospinal fluid. *J. Physiol.*, **253**, 583–592.

FISHGOLD, J.T., FIELD, J. & HALL, V.E. (1951). Effect of sodium salicylate and acetylsalicylate on metabolism of rat brain and liver in vitro. *Am. J. Physiol.*, **164**, 727–733.

FITCH, W., MCGEORGE, A.P. & MACKENZIE, E.T. (1978). Anaesthesia for studies of the cerebral circulation: a comparison of phencyclidine and althesin in the baboon. *Br. J. Anaesth.*, **50**, 985–991.

FLOWER, R.J. (1974). Drugs which inhibit prostaglandin biosynthesis. *Pharmac. Rev.*, **26**, 33–67.

FUJISHIMA, M., SCHEINBERG, P., BUSTO, R. & REINMUTH, O.M. (1971). The relation between cerebral oxygen consumption and cerebral vascular reactivity to carbon dioxide. *Stroke*, **2**, 251–257.

GOLDBERG, M.A., BARLOW, C.F. & ROTH, L.J. (1961). The effects of carbon dioxide on the entry and accumulation of drugs in the central nervous system. *J. Pharmac. exp. Ther.*, **131**, 308–318.

GRUBB, R.L., RAICHLE, M.E., EICHLING, J.O. & TER-POGOSSIAN, M.N. (1974). The effects of changes in $PaCO_2$ on cerebral blood volume, blood flow and vascular mean transit time. *Stroke*, **5**, 630–639.

HASS, W.K. (1977). Aspirin for the limping brain. *Stroke*, **8**, 299–301.

HØEDT-RASMUSSEN, K., SVEINSDOTTIR, E., & LASSEN, N.A. (1966). Regional cerebral blood flow in man determined by intra-arterial injection of radioactive inert gas. *Circulation Res.*, **18**, 237–247.

MONCADA, S. & VANE, J.R. (1978) Unstable metabolites of arachidonic acid and their role in haemostasis and thrombosis. *Br. med. Bull.*, **34**, 129–135.

PICKARD, J.D., MACDONELL, L.A., MACKENZIE, E.T. & HARPER, A.M. (1977a). Prostaglandin-induced effects in the primate cerebral circulation. *Eur. J. Pharmac.*, 43, 343–351.

PICKARD, J.D. & MACKENZIE, E.T. (1973). Inhibition of prostaglandin synthesis and the response of baboon cerebral circulation to carbon dioxide. *Nature, New Biol.*, **245**, 187–188.

PICKARD, J.D., ROSE, J.E., COOKE, M.B.D., BLAIR, I. MCL. & STRATHDEE, A. (1977b). The effect of salicylate on cerebral blood flow in man. *Acta neurol. scand.*, **56**, *Suppl.* **64**, 422–423.

PICKARD, J.D., SIMEONE, F.A. & VINALL, P. (1976). H^+, CO_2, prostaglandins and cerebrovascular smooth muscle. In *Ionic Actions on Vascular Smooth Muscle*, ed. Betz, E. pp. 101–104. Berlin: Springer-Verlag.

SIESJÖ, B.K. (1978). *Brain Energy Metabolism.* New York: Wiley & Sons.

SMITH, M.J.K. & TALBOT, J.M. (1950). A method for the rapid estimation of salicylates in serum or plasma. *Biochem. J.*, **46**, V.

WOODBURY, D.M. (1970). Analgesic-antipyretics, anti-inflammatory agents, and inhibitors of uric acid synthesis, In *The Pharmacological Basis of Therapeutics*, 4th Edition, ed. Goodman, L.S. & Gilman, A. pp. 314–329. New York: MacMillan Co.

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