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Modulation of the respiratory depressant effect of ethanol by 5-hydroxytryptamine

Most depressants of the central nervous system also depress respiration. We have measured respiratory depression induced in the mouse by alcohols, two barbiturates and an opioid using blood gas analysis (Hayashida & Smith, 1971) to determine whether their mechanisms of respiratory action differ. A strategy of neurotransmitter depletion and repletion was used.

Swiss-Webster female mice, 20–25 g, were used. Ethanol was diluted in normal saline to a concentration of 20% (w/v) and injected intraperitoneally (i.p.) in doses from 2 to 5 g kg^{-1}. These doses produced significant respiratory depression as indicated by a log-dose related rise in capillary blood P_{CO_2} and a fall in blood pH seen maximally 30 min after ethanol injection. (±)-Methadone (kindly donated by Mallinckrodt Chemical Works), sodium pentobarbitone, sodium phenobarbitone given in at least 3 doses for each drug were also injected 30 min before blood sampling. Reserpine (Serpasil) was given (i.p.) 4 h before other drugs. *p*-Chlorophenylalanine methyl ester was administered (300 mg kg^{-1}, i.p.) 4 h before ethanol injection. Blood was drawn into a 100 mm heparinized capillary tube without exposure to air from an incision made in the ventral surface of the proximal third of the tail. The blood was then transferred to a Radiometer blood micro system (BMS-3) and the pH and P_{CO_2} values displayed on a digital meter. The P_{O_2} values ranged from 75–90 mm Hg and were not dose-related to the depressant drug.

As shown in Table 1, ethanol significantly elevated capillary blood P_{CO_2} and lowered blood pH. Administration of reserpine or *p*-chlorophenylalanine (p-CPA) blocked the rise in P_{CO_2} normally induced by ethanol in a dose of 3 g kg^{-1} although blood pH remained depressed. The acidosis is probably attributable to the metabolic effect of the ethanol. The normal rise in P_{CO_2} induced by injections of various dosages of (±)-methadone or sodium pentobarbitone was however not blocked by the depletors of 5-hydroxytryptamine (5-HT). These findings suggest that 5-HT may specifically modulate the respiratory depression induced by ethanol.

Data also shown in Table 1 further implicate 5-HT; the respiratory-depressive effect of ethanol was restored in mice treated with reserpine and then injected intracerebrally with 10 μg of 5-HT. 5-HT was injected into the right cerebral hemisphere 15 min after ethanol in a volume of 10 μl using a microsyringe fitted with a guard to prevent penetration of the 25 gauge needle to a depth greater than 3 mm. Intracerebral injection of the saline vehicle or 5-HT alone did not produce any changes.

Since p-CPA inhibits tryptophan hydroxylase and prevents formation of 5-hydroxy-

Table 1. *Effect of reserpine* (2 mg kg^{-1}) *or* p-*chlorophenylalanine* (300 mg kg^{-1}) *on the respiratory depression induced by ethanol* (3 g kg^{-1}), *methadone* (10 mg kg^{-1}) *or sodium pentobarbitone* (40 mg kg^{-1}). 5-HT or 5-HTP was injected 15 min after ethanol. Figures in parentheses indicate number of animals. Values given as mean ±s.e.m.

Narcotic	Treatment	pH	P_{CO_2}
—	—	7·400 ± 0·005	25·9 ± 0·34 (67)
—	Reserpine	7·347 ± 0·010	24·3 ± 0·75 (19)
—	*p*-CPA	7·396 ± 0·007	25·6 ± 0·99 (10)
Ethanol, 3 g kg^{-1}	—	7·277 ± 0·004	33·6 ± 0·39 (70)
,,	Reserpine	7·255 ± 0·008	25·3 ± 0·68 (27)*
,,	*p*-CPA	7·299 ± 0·017	25·0 ± 0·84 (10)*
,,	Reserpine + 5-HT 10 μg i.c.	7·265 ± 0·016	33·3 ± 0·62 (10)
,,	*p*-CPA + 5-HTP 100 mg kg^{-1} i.p.	7·191 ± 0·015	32·6 ± 0·67 (10)
Methadone, 10 mg kg^{-1}	—	7·286 ± 0·010	38·1 ± 1·05 (16)
,,	Reserpine	7·249 ± 0·016	39·1 ± 1·60 (20)
,,	*p*-CPA	7·304 ± 0·016	37·1 ± 1·05 (10)
Pentobarbitone, 40 mg kg^{-1}	—	7·283 ± 0·014	38·6 ± 2·43 (9)
,,	Reserpine	7·212 ± 0·020	37·1 ± 1·77 (10)
,,	*p*-CPA	7·242 ± 0·017	36·0 ± 2·31 (10)

* $P < 0·01$ as compared to untreated experimental group.

tryptophan (5-HTP), injection of 5-HTP, 15 min after ethanol, should restore the respiratory-depressive effect of ethanol; Table 1 shows that it does.

We also examined the respiratory-depressive response to methanol, 7 g kg^{-1}, to isopropanol, 2 g kg^{-1}, and to propanol, 1 g kg^{-1}. In these doses the various alcohols produced respiratory depression equivalent to that produced by 3 g kg^{-1} of ethanol. Treatment with p-CPA prevented the expected rise in P_{CO_2} in each case, whereas high P_{CO_2} levels were unexpectedly found in mice treated with chloral hydrate, 450 mg kg^{-1} or paraldehyde, 1 g kg^{-1}. The respiratory depressant effect of heroin, 5 mg kg^{-1} or sodium phenobarbitone, 100 mg kg^{-1} also remained unaffected by p-CPA treatment.

Thus it would appear that certain alcohols, notably ethanol, require 5-HT to induce respiratory depression in the mouse. The reductive catabolite of 5-HT appears to play little or no role since the injection intracerebrally of as much as 128 μg of 5-hydroxytryptophol failed to restore the ability of ethanol to produce respiratory depression in mice pretreated with reserpine.

The finding that 5-HT mediates or modulates respiratory depression induced by a series of alcohols but not by two barbiturates or methadone suggests alcohols differ from two other kinds of narcotics at least in regard to respiratory depression. The failure of paraldehyde or chloral hydrate to share a common neurotransmitter mechanism with ethanol is surprising.

This study was supported by USPHS grants DA-00020-7 and AA-00257-4.

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September 27, 1974

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