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Action of the 5-HT_{2A} Antagonist Amperozide on Alcohol-Induced Poikilothermia in Rats

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MYERS, R. D. AND M. LANKFORD. *Action of the 5-HT_{2A} antagonist amperozide on alcohol-induced poikilothermia in rats.* PHARMACOL BIOCHEM BEHAV **59**(1) 91–95, 1998.—Amperozide, a novel 5-HT_{2A} receptor antagonist that releases dopamine from mesolimbic neurons suppresses alcohol drinking in rats. Because serotonergic neurons are implicated in both the central mechanisms underlying thermoregulation and the reinforcing effects of alcohol, this study was undertaken to determine whether the poikilothermic effects of alcohol on body temperature (T_b) would be altered by amperozide. In adult male Sprague–Dawley rats kept at an ambient temperature of 22 to 24°C, a radio transmitter for continuous monitoring of T_b was first implanted intraperitoneally. Then, amperozide was given subcutaneously in a dose of 2.5, 5.0, or 10.0 mg/kg 30 min before an intragastric gavage of either 2.0 g/kg or 4.0 g/kg 20% ethyl alcohol (v/v). Amperozide blocked dose dependently the fall in T_b of the lower 2.0 g/kg dose of alcohol. However, only the higher 5.0 mg/kg and 10.0 mg/kg doses of amperozide prevented the initial thermolytic action of the higher 4.0 g/kg dose of alcohol. Further, the 10.0 mg/kg dose of amperozide given prior to the control saline gavage evoked a hyperthermic response in the rats that persisted for 5 h. These results suggest that the antagonism of 5-HT_{2A} receptors on central serotonergic synapses involved in thermoregulation acts to counteract the potent thermolytic effects of alcohol at an ambient temperature that is below thermoneutrality. © 1998 Elsevier Science Inc.

Amperozide Alcohol Hypothermia Hyperthermia Serotonin Ethanol 5-HT_{2A} receptors Dopamine Hypothalamus Thermoregulation

AS is typical of any anesthetic agent, alcohol is a potent poikilothermic drug whose action on body temperature (T_b) is dependent clearly on the ambient temperature of the organism (3,6,18,28). Clinically it is well known that a severely intoxicated person can succumb readily to heat stroke in the extreme heat of a hot tub or a summer athletic event, or to deep hypothermia when exposed to the intense cold of a frigid environment. Consequently, by manipulating the ambient temperature of the individual, sharp deflections in T_b resulting in hyper- or hypothermia following an anesthetizing dose of alcohol can be averted entirely (18). Thus, the viewpoint that alcohol is simply a hypothermic agent is an inaccurate assumption (22,29) because the external, ambient temperature will determine entirely the T_b of the animal in response to an incapacitating dose of alcohol (18).

Serotonin (5-HT), dopamine (DA) and norepinephrine (NE) have long been implicated in the hypothalamic mechanisms controlling T_b (17,21). In relation to their role in the thermolytic action of alcohol, 5-HT, DA, and NE receptor antagonists injected centrally fail to prevent the decline in T_b at room temperature; however, the Ca^{2+} chelating agent, EGTA, reverses the fall in T_b caused by alcohol in rats at a room temperature below thermoneutrality (22). Other studies have shown that central and peripheral 5-HT receptors may play a crucial role in a drug induced fall in T_b at an ambient temperature below thermoneutrality (1,8,32). In fact, 5-HT_{2A} receptors are thought to underlie thermogenesis and a rise in T_b (8,14,26,33) as well as malignant hyperthermia (12), whereas 5-HT_{1A} receptors are believed to be responsible for a drug induced hypothermia (7,15,16,27).

Recently, the diphenylbutylpiperazine-carboxamide derivative, amperozide, was shown to possess a unique profile of pharmacological properties that make it a possible candidate for the treatment of alcoholism. This 5-HT_{2A} receptor antagonist reduces alcohol drinking in chemically induced or genetic drinking rats without such side effects as the suppression in feeding (23,24). Following its sustained delivery, amperozide suppresses alcohol consumption long after its administration is terminated (24). In view of its action on alcohol drinking, this project was undertaken to determine whether amper-

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ozide would alter the thermolytic action of alcohol in the rat. In the present experiments, amperozide was administered to Sprague–Dawley rats in efficacious doses just prior to the administration by intragastric gavage of two thermolytic doses of alcohol. The ambient temperature of the room was 22 to 24°C, which is below the thermoneutral level for the rat (18), so that alcohol would cause a clear-cut hypothermic response.

METHOD

Male Sprague–Dawley rats (n = 13), 90 days old at the beginning of the experiments, were housed in individual plastic cages and kept on a 12 L:12 D cycle, with lights on at 0700 h. Purina rat chow and water were provided to each animal ad lib. for the duration of the experiment. All experimental procedures used in this study were approved by the internal animal use committee of the School of Medicine and were in strict compliance with the guidelines of the National Institutes of Health for the care and use of laboratory animals.

Surgical Procedures

After each rat was anesthetized with 60 mg/kg of sodium pentobarbital injected intraperitoneally, an AM radio transmitter (Mini-Mitter, Sunriver, OR) was implanted in the peritoneal cavity following aseptic surgical procedures (11). Temperature signals from the transmitter were relayed to a computer-linked receiver, so that the core T_b of the rat was recorded continuously. Following a postoperative period of 6–7 days, each rat was acclimatized to the experimental conditions whereby no restraint was required. The baseline T_b of the rats prior to the administration of vehicle or amperozide was 36.9 ± 0.1°C.

Experimental Design

All experiments were carried out in a laboratory room with an ambient temperature of 22–24°C. A 20% (v/v) solution of alcohol was prepared daily with 95% reagent grade alcohol (AAPER) in tap water. Following procedures described earlier (22), one of the two doses of 2.0 and 4.0 g/kg alcohol was administered by intragastric gavage so that the resultant volume delivered varied with body weight of each rat in a range between 4.0 to 6.0 ml and 10.0 to 13.0 ml, respectively. To administer either the control 0.9% saline or 20% solution of alcohol intragastrically, the animal was held in a upright position and a 15 ga Harvard intubation needle was lowered slowly through the esophagus to the stomach. Then either fluid was administered equivolumetrically following identical procedures. All rats were fully sated prior to the experiments, which were carried out at weekly intervals to prevent the development of tolerance to the effects of alcohol.

The solution of amperozide HCl was prepared daily in sterilized 0.9% saline at pH 4.5–5.0. The drug or control saline vehicle was administered subcutaneously in a randomized sequence and in one of three doses, 2.5, 5.0, or 10.0 mg/kg, as based on the findings of Kimura (10) and others (23,24). Each rat was given a dose of alcohol of either 2.0 or 4.0 g/kg by intragastric gavage to determine the extent of fall in its T_b, because the ambient temperature was kept below the thermoneutral level to evoke its thermolytic effect (22). Amperozide was always administered in a given dose to the rat 30 min prior to the intragastric gavage with either dose of alcohol.

Data Analysis

The computer-derived data were plotted at 15-min intervals over the first 2.0 h and then at 1.0-h periods over the next 5.0 h. The values were then calculated as means and standard errors for all groups in terms of deviation in °C from baseline T_b. The data then were analyzed using the Stat-Mate software program using a one-way analysis of variance followed by post hoc Student–Newman–Keuls test when appropriate. A p-value of <0.05 was considered statistically significant.

RESULTS

Amperozide given by the subcutaneous route in doses of 2.5, 5.0, or 10.0 mg/kg antagonized the loss of body heat in the rats following the intragastric administration of alcohol. As shown in Figs. 1 and 2, both the 2.0 g/kg (n = 8) and 4.0 g/kg (n = 12) doses of alcohol (ETOH) alone caused a marked decline in T_b from the pregavage baseline values. An intragastric gavage of the lower and higher doses of alcohol reduced T_b by a mean of 0.45 ± 0.07°C and 0.42 ± 0.07°C, respectively; the maximum decline in T_b of 1.0°C occurred at intervals of 3.0 to 4.0 h. Following the alcohol gavage, the rats exhibited piloerection, motor incoordination and ataxia of varying intensity and duration.

As shown in Fig. 1, the low (n = 9), medium (n = 8), and high (n = 7) doses of amperozide given to the rats 30 min prior to the 2.0 g/kg gavage of alcohol prevented the thermolytic response to alcohol (ETOH). The mean changes in T_b after the three doses of amperozide followed by the alcohol gavage were +0.28 ± 0.05°C, +0.45 ± 0.05°C, and +0.59 ± 0.04°C, respectively. The mean increases in T_b from the pretreatment baseline values following each dose of amperozide was significantly higher than that in which the alcohol gavage was given alone, $F(3, 398) = 70.23$, $p < 0.01$.

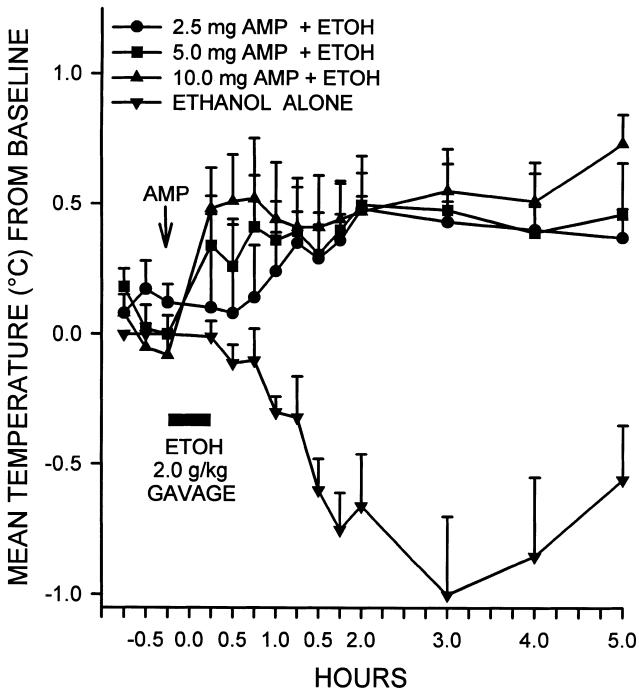

FIG. 1. Mean changes (± SE) from baseline T_b (°C) of rats after injection of amperozide (AMP) subcutaneously in a dose of 2.5, 5.0, or 10.0 mg/kg 30 min prior to intragastric gavage of 2.0 g/kg 20% (v/v) ethyl alcohol (ETOH). The control dose of ETOH was 2.0 g/kg 20% given alone (n = 8). AMP 2.5 (n = 9); AMP 5.0 (n = 8); and AMP 10.0 mg/kg (n = 7). Bar at zero time on abscissa indicates interval of intragastric gavage of each group. Mean baseline T_b = 36.9 ± 0.1°C.

As presented in Fig. 2, the same doses of amperozide prior to the gavage with 4.0 g/kg alcohol (ETOH) also blocked the alcohol induced decline in T_b. The mean changes in the T_b of rats treated with 2.5 mg/kg ($n = 5$), 5.0 mg/kg ($n = 5$), and 10.0 mg/kg ($n = 5$) of amperozide were -0.14 ± 0.07°C, $+0.12 \pm 0.07$°C, and $+0.57 \pm 0.07$°C, respectively. Because a slight hypothermia followed the lowest dose of amperozide, the data were analyzed in terms of groups. Thus, the mean T_b values following pretreatment with amperozide in a dose of 5.0 or 10.0 mg/kg were significantly higher than those in which only the alcohol gavage was given, $F(1, 11) = 28.0$, $p < 0.01$, $F(1, 11) = 94.1$, $p < 0.01$. However, the effect on the T_b of the rats of the 2.5 mg/kg dose of amperozide was not significantly different from that of the 4.0 mg/kg dose of alcohol.

The T_b response to each of the three doses of amperozide injected subcutaneously 30 min prior to an intragastric gavage of the saline control solution is shown in Fig. 3. Although no significant changes in T_b from the baseline values occurred, during the 5 h interval after 2.5 mg/kg ($n = 7$) and 10.0 mg/kg ($n = 10$) amperozide were administered, the T_b rose nominally by 0.35 ± 0.07°C and 0.37 ± 0.06°C, respectively, whereas the 5.0 mg/kg dose of amperozide caused a mean decline of less than 0.2°C ($n = 6$). However, these group changes were not significantly different from each other (Fig. 3).

DISCUSSION

The present results demonstrate that the 5-HT_{2A} antagonist, amperozide, given systemically, acts to prevent the poikilothermic decline in T_b when alcohol is administered intragastrically to rats kept at an ambient temperature of 22 to 24°C, which is below their thermoneutral temperature of ≈30°C (18). Further, the systemic injection of amperozide tended to induce a hyperthermic response over the test interval of 5.0 h. This gradual rise in the T_b of the animals would seem to reflect circadian thermogenesis, because the T_b of two of the three saline control groups also tended to increase above baseline levels over the 5-h test interval. It is notable that the average T_b response to the 2.0 and 4.0 g/kg doses of alcohol could not be differentiated as has been demonstrated in earlier experiments (18). One explanation of this finding is the fact that the animals in the present study were not food deprived, as was done previously (22). Consequently, the gastric absorption of alcohol may have been somewhat compromised by the presence of food in the stomach.

Based on the effects of 5-HT receptor agonists and antagonists on peripheral cardiovascular processes, one would theoretically expect that amperozide could enhance the thermolytic action of alcohol. Although conflicting evidence does exist on the role of the 5-HT subtypes of receptors in peripheral vasomotor responses, different observations generally favor a differentiation of the 5-HT_1 and 5-HT_2 receptors in the vasoconstrictor action of 5-HT itself. Essentially, 5-HT_1 receptors are implicated in the contractility of basilar and coronary arteries in the dog and rabbit (25) as well as in human arteries (5). For example, studies with the 5-HT_2 receptor antagonist, ketanserin, indicate that 5-HT_1 rather than 5-HT_2 receptors are activated by 5-HT to contract human basilar arteries (30). Ketanserin blocks not only the constrictor effects

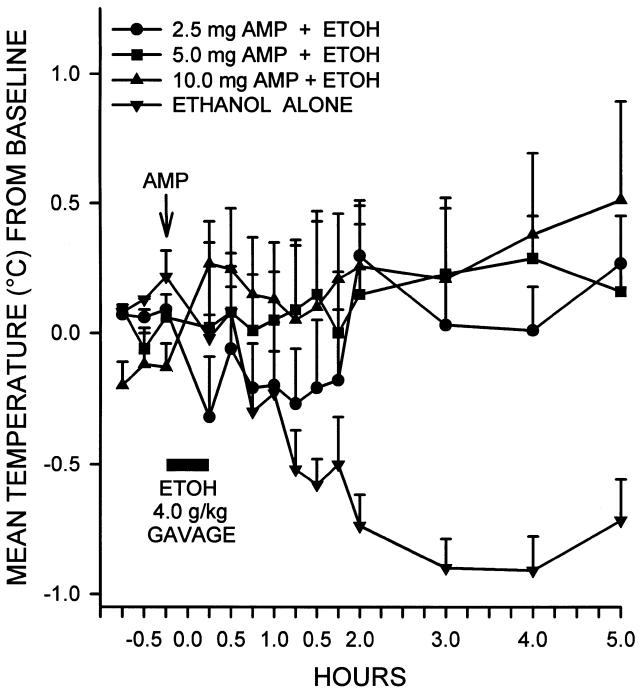

FIG. 2. Mean changes (± SE) from baseline T_b (°C) of rats after injection of amperozide (AMP) subcutaneously in a dose of 2.5, 5.0, or 10.0 mg/kg 30 min prior to intragastric gavage of 4.0 g/kg 20% (v/v) alcohol (ETOH). The control dose of ETOH was 4.0 g/kg 20% given alone ($n = 12$). AMP 2.5 ($n = 5$); AMP 5.0 ($n = 5$); and AMP 10.0 mg/kg ($n = 5$). Bar at zero time on abscissa indicates interval of intragastric gavage of each group. Mean baseline $T_b = 36.9 \pm 0.1$ °C.

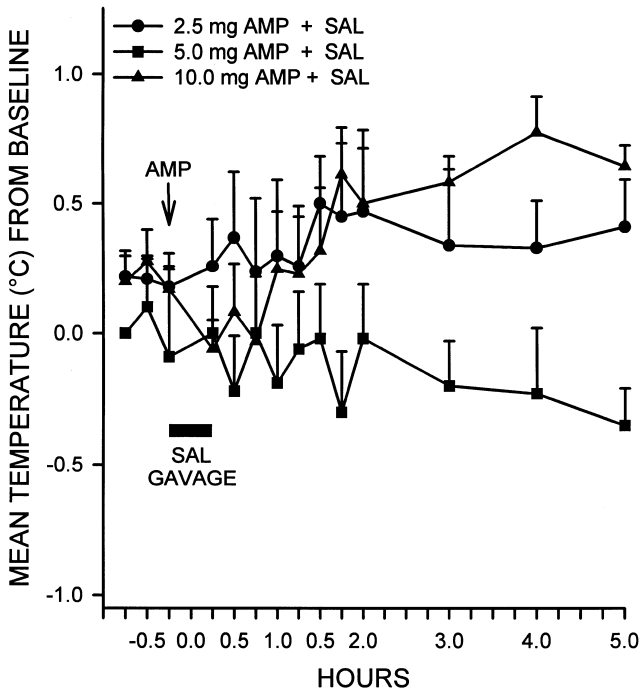

FIG. 3. Mean changes (± SE) from baseline T_b (°C) of rats after amperozide (AMP) injection subcutaneously in a dose of 2.5, 5.0, or 10.0 mg/kg 30 min prior to intragastric gavage of control 0.9% saline. AMP 2.5 ($n = 7$); AMP 5.0 ($n = 6$); and AMP 10.0 mg/kg ($n = 10$). Bar at zero time on abscissa indicates interval of intragastric gavage of each group. Mean baseline $T_b = 36.9 \pm 0.1$ °C.

of 5-HT itself on the rat aorta (2,35), but also the activation of indirect sympathomimetic effects (31). Thus, because alcohol exerts an intense vasodilatory action to cause a profound loss in body heat, a 5-HT_{2A} receptor blocking agent would be expected to enhance alcohol-induced poikilothermia rather than attenuate it. Nevertheless, 5-HT_{2A} receptor antagonists do differ in their respective pharmacological actions, as exemplified by their divergent actions on alcohol drinking (19).

Pharmacological studies of drugs given systemically show that the hypothermia generated by a 5-HT_{1A} agonist can be blocked by a 5-HT_{1A} antagonist (9). Nevertheless, different 5-HT_{1A} antagonists can retard the hypothermia induced by a 5-HT_{1A} agonist to varying degrees (34), which would indicate that diverse subtypes of 5-HT_{1A} receptors mediate the thermolytic action of a given 5-HT_{1A} agonist. In terms of the potent poikilothermic effect of alcohol, either the 5-HT_{1A} presynaptic or postsynaptic class of receptors (4) or 5-HT_{1B} receptors (13) conceivably could mediate the action of alcohol in severely impairing the thermoregulatory mechanism to evoke the sharp fall in T_b of the rat.

Each of these results may solely reflect a peripheral action of an agonist or antagonist of 5-HT receptors. For example, when injected centrally in a low dose, 5-HT itself produces a dose-dependent rapid rise in T_b in virtually all species (21). However, 5-HT injected similarly in high doses produces a fall in T_b, presumably because 5-HT neurons responsible for thermogenesis are incapacitated by the saturation of their receptors (17,21). Further, a drug that primarily blocks a subtype of 5-HT receptor may nevertheless possess other properties that would affect central functions differentially. For example, amperozide suppresses alcohol intake under different preference situations, whereas a similar 5-HT_{2A} antagonist, ketanserin, does not attenuate drinking when given in appropriate doses (20). Thus, amperozide could prevent the alcohol induced decline in T_b, not by a systemic effect on peripheral vasoconstrictor mechanisms but rather by a direct action on hypothalamic neurons that operate to maintain heat production. Another explanation for our findings relates to the amperozide evoked release of dopamine in the brainstem (10), which may cause a compensatory activation of hypothalamic serotonergic neurons that underlie thermogenesis and the functions for maintaining body heat (21). However, additional research is required to elucidate further the central role of 5-HT_{2A} receptors as related to the poikilothermic action of alcohol.

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REFERENCES

1. Abdel-Fattah, A.; Matsumoto, K.; El-Hady, K.; Watanabe, H.: 5-HT_{1A} and 5-HT_2 receptors mediate hypo- and hyperthermic effects of tryptophan in pargyline-pretreated rats. Pharmacol. Biochem. Behav. 52:379–384; 1995.
2. Christie, M. I.; Harper, D.; Smith, G.: Analysis of the agonist activity of fenoldopam (SKF 82526) at the vascular 5-HT_2 receptor. Br. J. Pharmacol. 107:1008–1112; 1992.
3. Finn, D.; Syapin, P.; Bejanian, M.; Jones, B.; Alkana, R.: Temperature dependence of ethanol depression in mice: Dose response. Alcohol. Clin. Exp. Res. 18:382–386; 1994.
4. Fletcher, A.; Bill, D.; Bill, S.; Cliffe, I.; Dover, G.; Forster, E.; Haskins, J.; Jones, D.; Mansell, H.; Reilly, Y.: WAY 100135: A novel, selective antagonist at presynaptic and postsynaptic 5-HT_{1A} receptors. Eur. J. Pharmacol. 237:283–291; 1993.
5. Foreman, M. M.; Fuller, R.; Nelson, D.; Calligaro, D.; Kurz, K.; Misner, J.; Garbrecht, W.; Parli, C.: Preclinical studies on LY237733, a potent and selective serotonergic antagonist. J. Pharmacol. Exp. Ther. 260:51–57; 1992.
6. Freund, G.: Ethanol-induced changes in body temperature and their neurochemical consequences. In: Majchrowicz, E.; Noble, E. P., eds. Biochemistry and pharmacology of ethanol, vol. 2. New York: Plenum Press; 1979:439–452.
7. Ginefri-Gayet, M.; Gayet, J.: Involvement of serotonin receptors in methionine sulfoximine-induced hypothermia in the rat. Eur. J. Pharmacol. 217:85–91; 1992.
8. Gudelsky, G.; Koenig, J.; Meltzer, H.: Thermoregulatory responses to serotonin (5-HT) receptor stimulation in the rat. Neuropharmacology 25:1307–1313; 1986.
9. Hadrava, V.; Blier, P.; Dennis, T.; Ortemann, C.; de Montigny, C.: Characterization of 5-hydroxytryptamine 1A properties of flesinoxan: In vivo electrophysiology and hypothermia study. Neuropharmacology 34:1311–1326; 1995.
10. Kimura, K.; Nomikos, G.; Svensson, T.: Effects of amperozide on psychostimulant-induced hyperlocomotion and dopamine release in the nucleus accumbens. Pharmacol. Biochem. Behav. 44:27–36; 1993.
11. Lopez-Valpuesta, F. J.; Nyce, J. W.; Griffin, T.; Ice, J.; Myers, R. D.: Antisense to NPY-Y1 demonstrates that Y1 receptors in the hypothalamus underlie NPY hypothermia and feeding in rats. Proc. R. Soc. Lond. [Biol.] 263:881–886; 1996.
12. Löscher, W.; Witte, U.; Fredow, G.; Ganter, M.; Bickhardt, K.: Pharmacodynamic effects of serotonin (5-HT) receptor ligands in pigs: Stimulation of 5-HT_2 receptors induces malignant hyperthermia. Naunyn Schmiedebergs Arch. Pharmacol. 341:483–493; 1990.
13. Maj, J.; Chojnacka-Wojcik, E.; Klodzinska, A.; Deren, A.; Moryl, E.: Hypothermia induced by m-trifluoromethylphenylpiperazine or m-chlorophenylpiperazine: An effect mediated by 5-HT_{1B} receptors? J. Neural Transm. 73:43–55; 1988.
14. Mazzola-Pomietto, P.; Aulakh, C.; Wozniak, K.; Hill, J.; Murphy, D.: Evidence that 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI)-induced hyperthermia in rats is mediated by stimulation of 5-HT_{2A} receptors. Psychopharmacology (Berlin) 117:193–199; 1995.
15. Meller, E.; Chalfin, M.; Bohmaker, K.: Serotonin 5-HT_{1A} receptor-mediated hypothermia in mice; Absence of spare receptors and rapid induction of tolerance. Pharmacol. Biochem. Behav. 43:405–411; 1992.
16. Millan, M.; Rivet, J.; Canton, H.; Marouille-Girardon, S.; Gobert, A.: Induction of hypothermia as a model of 5-hydroxytryptamine$_{1A}$ receptor-mediated activity in the rat: A pharmacological characterization of the actions of novel agonists and antagonists. J. Pharmacol. Exp. Ther. 264:1364–1376; 1993.
17. Myers, R. D.: Hypothalamic control of thermoregulation: Neurochemical mechanisms. In: Morgane, P.; Panksepp, J., eds. Handbook of the hypothalamus, vol. 3.New York: Marcel Dekker; 1980: 83–210.
18. Myers, R. D.: Alcohol's effect on body temperature: Hypothermia, hyperthermia, or poikilothermia. Brain Res. Bull. 7:209–220; 1981.
19. Myers, R. D.; Lankford, M. F.: Failure of the 5-HT_2 receptor antagonist, ritanserin, to alter preference for alcohol in drinking rats. Pharmacol. Biochem. Behav. 45:233–237; 1993.
20. Myers, R. D.; Lankford, M.: Suppression of alcohol preference in high alcohol drinking rats. Efficacy of amperozide vs. naltrexone. Neuropsychopharmacology 14:139–149; 1996.

21. Myers, R. D.; Lee, T.: Neurochemical aspects of thermoregulation. In: Wang, L., ed. Advances in comparative and environmental physiology. Heidelberg: Springer Verlag; 1989:161–203.
22. Myers, R. D.; Ruwe, W. D.: Is alcohol induced poikilothermia mediated by 5-HT and catecholamine receptors or by ionic setpoint mechanisms in the brain? Pharmacol. Biochem. Behav. 16: 321–327; 1982.
23. Myers, R. D.; Lankford, M.; Björk, A.: Selective reduction by the 5-HT antagonist amperozide of alcohol preference induced in rats by systemic cyanamide. Pharmacol. Biochem. Behav. 43:661–667; 1992.
24. Myers, R. D.; Lankford, M.; Björk, A.: 5-HT_2 receptor blockade by amperozide suppressed ethanol drinking in genetically preferring (P) rats. Pharmacol. Biochem. Behav. 45:741–747; 1993.
25. Nakane, T.; Kawai, K.; Chiba, S.: Mechanism of pindolol-induced vasoconstriction in isolated and perfused dog coronary arteries. Jpn. J. Pharmacol. 62:67–74; 1993.
26. Nash, J.; Meltzer, H.; Gudelsky, G.: Selective cross-tolerance to 5-HT_{1A} and 5-HT_2 receptor-mediated temperature and corticosterone responses. Pharmacol. Biochem. Behav. 33:781–785; 1989.
27. O'Connell, M.; Sarna, G.; Curzon, G.: Evidence for postsynaptic mediation of the hypothermic effect of 5-HT_{1A} receptor activation. Br. J. Pharmacol: 106:603–609; 1992.
28. Paez, X.; Myers, R. D.: Alcohol-induced poikilothermia, sleep and motor impairment: Actions on brain of EGTA and verapamil. Alcohol 6:489–498,1989.
29. Paez, X.; Myers, R. D.: Differential actions of RO15-1788 and diazepam on poikilothermia, motor impairment and sleep produced by ethanol. Pharmacol. Biochem. Behav. 36:915–922; 1990.
30. Parsons, A. A.; Whalley, E. T.: Characterization of the 5-hydroxytryptamine receptor which mediates contraction of the human isolated basilar artery. Cephalalgia (Suppl.) 9:47–51; 1989.
31. Rawadi, C.; Davy, M.; Midol-Monnet, M.; Cohen, Y.: Biochemical characterization of the mechanisms involved in the 5-hydroxytryptamine-induced increase in rat atrial rate. Biochem. Pharmacol. 48:683–688; 1994.
32. Salmi, P.; Karlsson, T.; Ahlenius. S.: Antagonism by SCH 23390 of clozapine-induced hypothermia in the rat. Eur. J. Pharmacol. 253:67–73; 1994.
33. Schmidt, C.; Black, C.; Abbate, G.; Taylor, V.: Methylenedioxymethamphetamine-induced hyperthermia and neurotoxicity are independently mediated by 5-HT_2 receptors. Brain Res. 529: 85–90; 1990.
34. Scott, P. A.; Chou, J.; Tang, H.; Frazer, A.: Differential induction of 5-HT_{1A}-mediated responses in vivo by three chemically dissimilar 5-HT_{1A} agonists. J. Pharmacol. Exp. Ther. 270:198–208; 1994.
35. Sufka, K. J.; Stratton, D.; Giordano, J.: Regional differences in serotonergic contractile sensitivity mediated by 5-HT_2 receptors in rat aorta. Artery 18:47–53; 1990.