Pharmacology Biochemistry & Behavior, Vol. 39, pp. 383–387. © Pergamon Press plc, 1991. Printed in the U.S.A. 0091-3057/91 $3.00 + .00

Attenuation of Central α_2 Adrenergic Action in Diabetic Rats

TIAN-ZHI GUO,[1] BRADLEY MAZE[2] AND MERVYN MAZE[3,4]

Department of Anesthesia, Stanford University School of Medicine, Stanford, CA 94305
V.A. Medical Center, 3801 Miranda Avenue, Palo Alto, CA 94304

Received 8 February 1991

GUO, T.-Z., B. MAZE AND M. MAZE. *Attenuation of central α_2 adrenergic action in diabetic rats.* PHARMACOL BIOCHEM BEHAV **39**(2) 383–387, 1991.—Molecular components in transmembrane signaling may be dysfunctional in insulin-deficient states. To investigate whether the α_2 adrenergic receptor-effector mechanism is functionally altered by insulin deficiency, we determined the hypnotic response to dexmedetomidine [(+)4-[1-(2,3-dimethylphenyl)ethyl]-1H-imidazole, a highly-selective α_2 agonist, in streptozotocin-induced diabetic rats. The duration of the loss of righting reflex (sleep time) in response to dexmedetomidine, 0.25 mg·kg^{-1} IP, was measured in rats pretreated with streptozotocin, 50 mg·kg^{-1} IP. Dexmedetomidine sleep time was significantly shortened when tested 10 days (−25%), 3 (−29%), 6 (−35%) and 8 (−47%) weeks into the diabetic state. Supplementation of the diabetic rats with insulin normalized α_2 responsiveness. Acute hyperglycemia did not reduce dexmedetomidine-induced sleep time. Sleep time was also reduced when dexmedetomidine was administered via the intracerebroventricular (ICV) route at 4 (−21%) and 8 (−29%) weeks after streptozotocin. Thus the central nervous system response to the α_2 adrenergic agonist has become attenuated. The mechanism may involve a perturbation of an insulin-sensitive molecular component of the signal transduction pathway responsible for α_2 adrenoceptor-mediated anesthetic action.

Streptozotocin Diabetic Insulin deficiency Metabolism d-Glucose Hyperglycemia
Inhibitory G-protein Adrenergic receptor: α_2 Dexmedetomidine

THE α_2 adrenergic agonists potently decrease volatile anesthetic requirements (19). The profound reduction in anesthetic requirements with dexmedetomidine (34,27) raised the possibility that α_2 adrenergic agonists may be considered anesthetic-hypnotic agents. This sole anesthetic-hypnotic response was established together with the confirmation that a central α_2 adrenoceptor mediated this action (10). A pertussis toxin-sensitive G protein is involved in the signal transduction pathway for the α_2 adrenergic agonist's anesthetic action (11).

G protein-mediated transmembrane signaling of inhibitory neurotransmitter action appears to be perturbed in insulin-deficient states (32). The liver membranes from streptozotocin-induced diabetic rats exhibit a dramatic reduction (>90%) in the concentration and function of the inhibitory guanine-nucleotide-binding regulatory protein, G_i (12). This functional abnormality can be normalized by insulin therapy. Additionally, the G protein mediating the inhibitory effect of dopamine on adenylate cyclase is attenuated in the corpus striatum of alloxan-induced diabetic rats (1). Also, muscarinic inhibition of retinal adenylate cyclase activity, another function mediated via pertussis toxin-sensitive G proteins, is retarded in streptozotocin-induced diabetic rats (14).

Efficacy of drugs acting on the CNS may also be altered in the diabetic state (18,29) although this may not be obtained for hypnotic agents (9). However, Amouzadeh and Sangiah recently reported that the hypnotic action of a drug combination, which included an α_2 adrenergic agonist, was attenuated in diabetic animals (3). Because of the apparent dependence of α_2 adrenergic agonist action on pertussis toxin-sensitive G protein function (11), we investigated whether dexmedetomidine's hypnotic action is reduced in the insulin-deficient state.

METHOD

Following approval of the experimental protocol from the Animal Care and Use Committee at the Palo Alto Veterans Administration Medical Center, male Sprague-Dawley rats (starting weight 200–250 g) were selected as the experimental model.

Insulin deficiency was induced by injecting streptozotocin, 50 mg·kg^{-1}, diluted in 0.3 ml of 0.01 M citrate buffer, pH 4.5, intraperitoneal into rats that had been fasted for 18 hours (4). Control rats received injections of the buffer only. In the groups receiving continuous insulin or saline treatment, an osmotic minipump (Alzet®) was inserted 1 day after the streptozotocin injection and was set to deliver 14 units/kg of protamine zinc insulin daily from a solution containing 1.6% v/v glucose, 0.2%

[1]Visiting Research Scholar, Department of Anesthesiology, 3rd University Hospital, Beijing, P.R.C.
[2]Research Technician.
[3]Associate Professor.
[4]Requests for reprints should be addressed to Mervyn Maze, M.B., Anesthesiology Service (112A), PAVAMC, Miranda Ave, Palo Alto, CA 94304.

TABLE 1

BLOOD GLUCOSE AND WEIGHT IN RATS (MEAN ± SD)

	Weight (g)	Blood Glucose ($mg \cdot dl^{-1}$)
Following streptozotocin (STZ) treatment (IP* groups)		
10 days		
control (n=28)	309 ± 26	78 ± 11
STZ (n=25)	277 ± 29†	275 ± 58†
3 weeks		
control (n=7)	323 ± 22	74 ± 16
STZ (n=8)	273 ± 26†	348 ± 56†
6 weeks		
control (n=10)	376 ± 39	80 ± 7
STZ (n=9)	283 ± 24†	387 ± 43†
8 weeks		
control (n=8)	463 ± 41	90 ± 9
STZ (n=8)	287 ± 22†	342 ± 62†
Following STZ treatment (ICV‡ groups)		
10 days		
control (n=11)	310 ± 25	82 ± 8
STZ (n=9)	274 ± 21†	250 ± 34†
4 weeks		
control (n=9)	404 ± 25	85 ± 43
STZ (n=9)	283 ± 40†	345 ± 98†
8 weeks		
control (n=15)	463 ± 37	89 ± 9
STZ (n=19)	311 ± 46†	380 ± 67†
Following insulin (Ins) treatment		
10 days		
control (n=10)	341 ± 16	71 ± 8
STZ (n=10)	284 ± 23†	378 ± 29†
STZ+Ins(n=8)	323 ± 15	58 ± 34
4 weeks		
control (n=10)	353 ± 23	80 ± 7
STZ (n=11)	261 ± 20†	398 ± 39†
STZ+Ins(n=4)	351 ± 54	75 ± 8

*Animals treated with dexmedetomidine via intraperitoneal route.

†Significantly different from the control group at $p<0.05$.

‡Animals treated with dexmedetomidine via intracerebroventricular route.

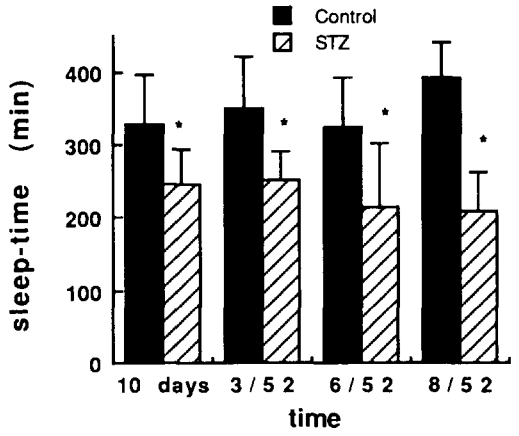

FIG. 1. Hypnotic effect of dexmedetomidine following streptozotocin (STZ) treatment. Rats were treated with STZ, 50 $mg \cdot kg^{-1}$ IP or citrate buffer (control). The duration of loss of righting reflex (sleep time) was determined 10 days (control n=28; STZ n=25), 3 (control n=7; STZ n=8), 6 and 8 (control n=8; STZ n=8) weeks later in separate cohorts of animals administered dexmedetomidine, 0.25 $mg \cdot kg^{-1}$ IP. Data are reported as mean ± SD and are analyzed by unpaired *t*-test of control vs. STZ treatment at each time course with Bonferroni correction for multiple comparison. *Significantly different from the control group at $p<0.05$.

phenol and 7 $mg \cdot ml^{-1}$ glycerol at pH 3.4, for 10 days or 4 weeks.

To induce acute hyperglycemia, rats were administered D-glucose, 20 $mmoles \cdot kg^{-1}$, IP in a volume of 2.5 ml containing 0.25 $mg \cdot kg^{-1}$ of dexmedetomidine (25). In these experiments control rats received either saline or the nonmetabolizable 3-O-methylglucose, 20 $mmols \cdot kg^{-1}$, IP (31). Tail blood was sampled for glucose 30, 90, and 180 min following drug administration and measured by an Accucheck II glucose analyzer.

To test blood glucose under other circumstances, rats were fasted for 4 h (between 8–noon) and tail blood samples were applied to glucose sticks and read in an Accucheck II glucose analyzer. Insulin deficiency was confirmed by a blood glucose in excess of 250 $mg \cdot dl^{-1}$; successful insulin replacement was established by a blood glucose below 150 $mg \cdot dl^{-1}$.

All testing for hypnotic response was performed between 10 a.m. and 6 p.m. in an exposure chamber in which the ambient temperature was maintained at 30°C by heating lamps and warming blankets. Hypnotic response was defined by the loss of the rat's righting reflex (LORR), and its duration was measured in minutes and referred to as sleep time. Concentrations of dexmedetomidine were adjusted in order that the volume of the injectate was 1 ml for intraperitoneal administration (except where indicated) and 10 μl for the intracerebroventricular (ICV) groups. Four days prior to administration of dexmedetomidine by the ICV route, rats were cannulated stereotaxically by siting a 24 gauge stainless steel cannula in the left lateral ventricle as previously described (11). The cannula was anchored to three bone screws with methyl methacrylate cement. On the day of testing a 30 g stainless steel needle, with polyethylene tubing, was inserted through the cannula and positioned 1 mm beyond the tip of the cannula. Confirmation of the site of injection was accomplished by injecting 10 μl of methylene blue via the cannula and documenting the presence of the dye in the CSF at necropsy.

The hypnotic response to dexmedetomidine was only tested on a single occasion in the individual animals.

Data were analyzed using unpaired Student's *t*-test with Bonferroni correction for multiple comparisons, or by ANOVA and post hoc Scheffe F-test, according to the figure legends. Computations were performed with StatView® (Abacus Concepts, Berkeley, CA 94704) software package. Level for statistical significance was established at $p<0.05$.

RESULTS

Streptozotocin treatment resulted in chronic hyperglycemia and decreased weight gain (Table 1). Dexmedetomidine sleep time was significantly shortened after streptozotocin treatment (Fig. 1). This attenuated hypnotic response to the α_2 agonist was apparent by the 10th day and progressed over time with the reduction reaching 47% by the eighth week after streptozotocin injection (Fig. 1). Chronic insulin infusion both normalized the blood glucose values in the streptozotocin-treated rats (Table 1) and the hypnotic response to dexmedetomidine at 10 days and at 4 weeks (Fig. 2).

Acute administration of D-glucose produced acute hypergly-

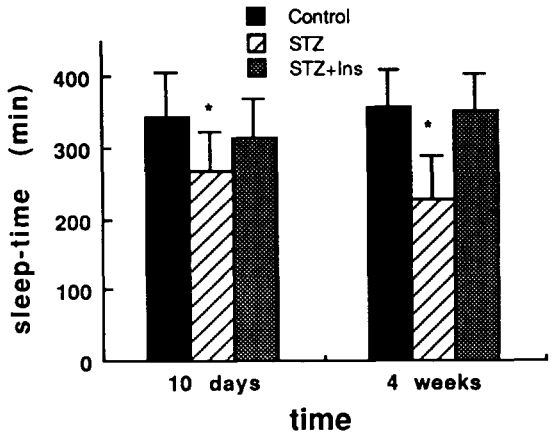

FIG. 2. Effect of insulin treatment on hypnotic effect of dexmedetomidine following streptozotocin (STZ) treatment. Rats were treated with STZ, 50 mg·kg^{-1} IP or citrate buffer (control). One day later osmotic infusion minipumps were inserted to deliver insulin (STZ-ins) or vehicle (other groups). The duration of loss of righting reflex (sleep time) was determined 10 days (control n = 10; STZ n = 10; STZ-ins n = 8) and 4 weeks (control n = 10; STZ n = 11; STZ-ins n = 4) later in separate cohorts of animals administered dexmedetomidine, 0.25 mg·kg^{-1} IP. Data are reported as mean ± SD. @ 10 d, ANOVA with 27 degrees of freedom yielded an F-test statistic of 4.4 ($p = 0.024$). @ 4 weeks, ANOVA with 24 degrees of freedom yielded an F-test statistic of 15.8 ($p = 0.0001$). *Significantly different from the control group at 95% probability by the Scheffe F-test.

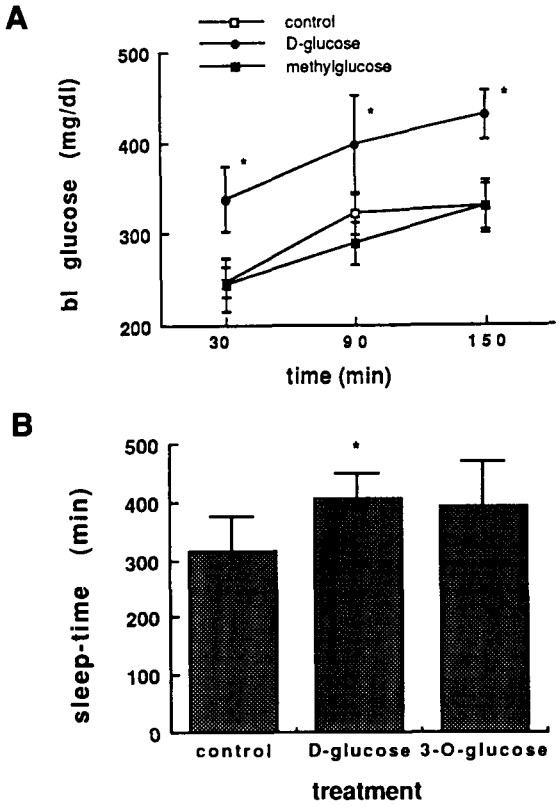

FIG. 3. Hypnotic response to dexmedetomidine during acute hyperglycemia. Rats were administered saline (n = 7), D-glucose 20 mmol (n = 8), or 3-O-methylglucose 20 mmol (n = 7) in 2.5 ml together with dexmedetomidine 0.25 mg·kg^{-1} IP. (A) Glucose was measured from tail blood at 30, 90 and 150 min following administration of dexmedetomidine. (B) Duration of loss of righting reflex was measured in the three cohorts of rats. Data are reported as mean ± SD. (A) @ 30 min: ANOVA with 21 degrees of freedom yielded an F-test statistic of 26.5 ($p = 0.0001$). @ 90 min: ANOVA with 21 degrees of freedom yielded an F-test statistic of 16.6 ($p = 0.0001$). @ 150 min: ANOVA with 21 degrees of freedom yielded an F-test statistic of 35.5 ($p = 0.0001$). (B) ANOVA with 21 degrees of freedom yielded an F-test statistic of 4.7 ($p = 0.022$). *Significantly different from the control group at 95% probability by the Scheffe F-test.

cemia in the range seen with chronic insulin deficiency and higher than that seen following the acute administration of the nonmetabolizable sugar, 3-O-methylglucose (Fig. 3A). Acute hyperglycemia without insulin deficiency *increased* the duration of dexmedetomidine-induced sleep time (Fig. 3B).

To distinguish whether the decrement in α_2 responsiveness, seen in the insulin-deficient state, was due to a pharmacodynamic or pharmacokinetic mechanism, we measured the hypnotic response to dexmedetomidine administered via the intracerebroventricular (ICV) route. There was no change in the hypnotic response at the 10th day after streptozotocin; however, sleep time to dexmedetomidine by the ICV route was reduced by 21 and 29%, at 4 and 8 weeks respectively (Fig. 4).

DISCUSSION

These data indicate that streptozotocin (STZ) treatment produces chronic hyperglycemia, and attenuates the hypnotic response to α_2 adrenergic agonists in rats. Acute hyperglycemia does not decrease responsiveness to α_2 adrenergic agonists. Normal α_2 responsiveness can be restored in STZ-treated rats with continuous insulin infusion.

In order to obtain parametric data from these studies, we selected a dose of dexmedetomidine (250 μg·kg^{-1}) that was large enough to induce loss of righting reflex in all animals. Thus we do not have a dose-response curve; nevertheless, the α_2 hyporesponsiveness is progressive over the time course of the experiment (Fig. 1) and presumably reflects progressive perturbation of the mediating mechanism for α_2 adrenergic agonist-induced hypnosis (see below).

Exogenously administered insulin prevented the α_2 hyporesponsiveness (Fig. 2). Plasma insulin levels were not determined; instead, we considered the insulin deficiency to be appropriately corrected when the blood glucose levels had normalized (Table 1). These data alone do not allow one to discriminate between hyperglycemia-induced vs. hypoinsulinemia-induced α_2 hyporesponsiveness. The hypnotic response to the α_2 agonist dexmedetomidine was qualitatively opposite to that seen during the chronic hyperglycemia of insulin deficiency (Fig. 3B). Thus the attenuated hypnotic response following STZ treatment is more likely to be due to the effects of insulinopenia rather than hyperglycemia per se. However, changes induced by *chronic* hyperglycemia unrelated to insulinopenia should also be considered. Parenthetically, it is noteworthy that relative hyperglycemia is produced in the saline-treated animals, too, following dexmedetomidine (Fig. 3A) which is probably due to α_2 adrenoceptor-mediated inhibition of insulin release (4).

Diabetes may affect biotransformation and pharmacokinetics of many drugs (16). We did not determine whether the pharmacokinetics of dexmedetomidine are affected in the streptozotocin-induced diabetic state because of the difficulty of assessing minute concentrations of dexmedetomidine in biologic fluids (R. Virtanen, personal communication). To try and distinguish be-

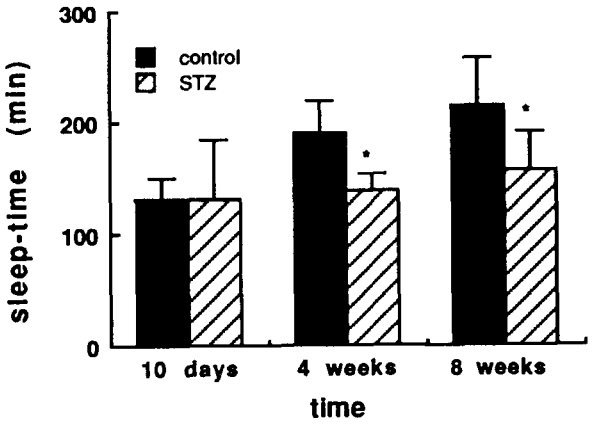

FIG. 4. Hypnotic effect of intracerebroventricular (ICV) administration of dexmedetomidine following streptozotocin (STZ) treatment. Rats were treated with STZ, 50 mg·kg^{-1} IP or citrate buffer (control). The duration of loss of righting reflex (sleep time) was determined 10 days (control n=11; STZ n=9), 4 weeks (control n=9; STZ n=9) and 8 weeks (control n=15; STZ n=19) later in separate cohorts of animals administered dexmedetomidine, 100 mg·kg^{-1} ICV via a chronically implanted cannula in the lateral ventricle. Data are reported as mean ± SD and are analyzed by unpaired *t*-test of control vs. STZ treatment at each time course with Bonferroni correction for multiple comparisons. *Significantly different from the control group at $p<0.05$.

tween a peripheral (pharmacokinetic) vs. a central (pharmacodynamic) mechanism for the α_2 hyporesponsiveness we determined the state of responsiveness in STZ-treated rats following dexmedetomidine ICV. The hypnotic response to centrally administered dexmedetomidine was also significantly attenuated but the time course and extent of attenuation did not mirror the effects seen following systemically administered dexmedetomidine (Fig. 4). The response to the centrally administered α_2 agonist should be largely insensitive to any possible diabetes-induced changes in the pharmacokinetics of dexmedetomidine establishing the likelihood that central pharmacodynamic mechanisms may be invoked. Nevertheless, the α_2 hyporesponsiveness was consistently greater in the diabetic animals administered dexmedetomidine systemically (Fig. 1) vs. those given the drug centrally (Fig. 4). These data may imply that there is also a change in the pharmacokinetics of dexmedetomidine which decreases the level of free drug in the biophase in the insulin-deficient state. Such a decrease in parent drug concentration was seen with diabetic rats administered isoflurane and enflurane (23). If one assumes that the degree of hyporesponsiveness observed following the systemically-administered dexmedetomidine is due to a combination of both kinetic and dynamic alterations, while the hyporesponsiveness following CNS administration is due exclusively to dynamic changes, it appears that the kinetic change appears by the tenth day and does not progress over time (≈20%).

In order to characterize the possible molecular mechanism for α_2 hyporesponsiveness in the diabetic state, one should consider the molecular components involved in the hypnotic response of α_2 adrenergic agonists. Using a variety of adrenergic receptor antagonists, which either cross or do not cross the blood-brain barrier, we established the involvement of central α_2 adrenoceptors for the hypnotic action to dexmedetomidine, with no mediating role of peripheral α_2 or other central adrenoceptors (10). Following pretreatment with pertussis toxin, the sleep time following dexmedetomidine administration was significantly decreased in a dose-dependent fashion. These studies indicated that pertussis toxin-mediated ribosylation of G proteins decreases the hypnotic anesthetic response to dexmedetomidine implicating a role for pertussis toxin-sensitive G proteins in the signal transduction mechanism for the α_2 hypnotic action in rodents (11).

Responses to other central nervous system depressants are decreased in diabetes. The analgesic action of opiates in both experimental animals (29,30) and in humans (21) may be reduced by the metabolic consequences of the diabetic state. Conversely, streptozotocin-induced diabetic rats were noted to exhibit a significantly *higher* pain threshold than their controls (2). Among the components of the inhibitory neurotransmitter receptor-effector mechanism which become dysfunctional in the diabetic state, Dewey's group suggested that hyperglycemia induced a decrease in agonist affinity for the opiate receptors (7). This change in efficacy of opiate agonists has been attributed to hyperglycemia by some (25,31) but not all (24) investigators. The role of hyperglycemia in attenuating the antinociceptive response to opiates is further confounded by the apparent paradox that α_2-adrenergic agonists both enhance the opiate antinociceptive effect (28) and produce hyperglycemia due to inhibition of insulin release (4). It is important to reiterate that in our studies we observed no diminution in α_2-adrenergic responsiveness during acute hyperglycemia, a finding corroborated by others in chronic hyperglycemia (5). Among other factors cited for the decrease in antinociceptive action of opiates include a decrease in axonal transport of opiate receptors (17) and altered modulation through the disruption of monoaminergic pathways (6, 8, 33).

The inhibitory neurotransmitter receptors, including opiate, dopamine and α_2 adrenergic, are coupled via a family of guanine nucleotide binding regulatory proteins (G proteins) to their effector systems (13). Insulin may interact with the G proteins to inhibit the accumulation of second messengers (15) an action which would likely promote the action of inhibitory neurotransmitters. The liver membranes from streptozotocin-induced diabetic rats exhibit a dramatic reduction (>90%) in the concentration of the inhibitory guanine-nucleotide-binding regulatory protein, G_i (12). The activity in the inhibitory limb of the adenylate cyclase pathway is attenuated in the insulin-deficient state but can be normalized by insulin therapy (12). Both muscarinic (14) and dopaminergic (1) inhibition of adenylate cyclase activity, which are mediated by pertussis toxin-sensitive G proteins, are retarded in streptozotocin-induced diabetic rats. These recent biochemical findings have not been extended to the α_2 adrenergic receptor-effector mechanism but one can appreciate that a similar disruption of the inhibitory G protein which mediate dexmedetomidine's hypnotic response may produce a functional state equivalent to that seen following in vivo treatment with pertussis toxin (11). This suggestion is consistent with the time course of the α_2 hyporesponsiveness since a progressive lesion develops in G_i/G_o function over a similar period (1).

STZ-treated animals failed to gain weight at the same rate as the control animals (Table 1). Since the mass of drug administered was scaled down according to the animals weight, the STZ-treated animals received less dexmedetomidine. In a preliminary series of experiments we have found that the hypnotic response to a barbiturate, a class of drug for which no G protein role has been established, is *increased* even with the same "scaling down" for the differences in weight (data not shown). Therefore, we think it unlikely that the change in α_2 responsiveness is due to an artefact of their failure to thrive.

In conclusion, we now report that insulin deficiency induces hyporesponsiveness in the α_2 adrenoceptor-effector mechanism which adds to the growing list of perturbed inhibitory neurotransmitter function in the diabetic state.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the technical assistance of Drs.

Christiane Correa Sales, Markku Salonen, Mas Fujinaga and Ms. Kristina Reid; the advice of Drs. Timothy Meyer and Brian Hoffman; and the supply of dexmedetomidine from Dr. Risto Lammintausta, Farmos Research Group, Turku, Finland. This work was supported in part by the NIH (GM 30232 to M.M.) the Department of Veterans Affairs and the Molecular Research Institute.

REFERENCES

1. Abbrachio, M. P.; di Luca, M.; Di Giulio, A. M.; Cattabeni, F.; Tenconi, B.; Gorio, A. Denervation and hyperinnervation in the nervous system of diabetic animals: III. Functional alterations of G proteins in diabetic encephalopathy. J. Neurosci. Res. 24:517–523; 1989.
2. Akunne, H. C.; Soliman, K. F. The role of opioid receptors in diabetes and hyperglycemia-induced changes in pain threshold in the rat. Psychopharmacology (Berlin) 93:167–172; 1987.
3. Amouzadeh, H. R.; Sangiah, S. Effects of streptozotocin-induced diabetes on xylazine-ketamine anesthesia. Vet. Hum. Toxicol. 32: 19–22; 1990.
4. Angel, I.; Langer, S. Z. Adrenergic-induced hyperglycemia in anaesthetized rats: involvement of peripheral α_2-adrenoceptors. Eur. J. Pharmacol. 154:191–196; 1988.
5. Bansinath, M.; Ramabadran, K.; Turndorf, H.; Puig, M. M. Effect of yohimbine on nociceptive threshold in normoglycemic and streptozotocin-treated hyperglycemic mice. Pharmacol. Biochem. Behav. 33:459–463; 1989.
6. Bitar, M.; Koulu, M.; Rapoport, I.; Linnoila, M. Diabetes-induced alteration in brain monoamine metabolism in rats. J. Pharmacol. Exp. Ther. 236:432–437; 1986.
7. Brase, D. A.; Han, Y-H.; Dewey, W. L. Effects of glucose and diabetes on binding of naloxone and dihydromorphine to opiate receptors in mouse brain. Diabetes 36:1173–1177; 1987.
8. Broderick, P. A.; Jacoby, J. H. Serotonergic function in diabetic rats: Psychotherapeutic implications. Biol. Psychiatry 24:234–239; 1988.
9. Danhof, M.; Hisaoka, M.; Levy, G. Kinetics of drug action in disease states. VI. Effects of experimetal diabetes on phenobarbital concentration in rats at onset of loss of righting reflex. J. Pharmacol. Exp. Ther. 232:435–438; 1985.
10. Doze, V. A.; Chen, B.-X; Maze, M. Dexmedetomidine produces a hypnotic-anesthetic action in rats via activation of central α_2 adrenoceptors. Anesthesiology 71:75–79; 1989.
11. Doze, V. A.; Chen, B.-X; Tinklenberg, J. A.; Segal, I. S.; Maze, M. Pertussis toxin and 4-aminopyridine differentially affect the hypnotic-anesthetic action of dexmedetomidine and pentobarbital. Anesthesiology 73:304–307; 1990.
12. Gawler, D; Milligan, G; Spiegel, A. M.; Unson, C. G.; Houslay, M. D. Abolition of the expression of inhibitory guanine nucleotide redulatory protein G_i activity in diabetes. Nature 327:229–232; 1987.
13. Gilman A. G. G proteins: transducers of receptor-generated signals. Annu. Rev. Biochem. 56:615–649; 1987.
14. Hadjiconstantinou, M.; Qu, Z-X.; Moroi-Fetters, S. E.; Neff, N. H. Apparent loss of G_i protein activity in the diabetic retina. Eur. J. Pharmacol. 149:193–194; 1988.
15. Houslay, M. D. Insulin, glucagon and the receptor-mediated control of cyclic AMP concentrations in liver. Biochem. Soc. Trans. 14: 183–193; 1986.
16. Kato, R. Drug metabolism under pathologic and abnormal physiological states in animals and man. Xenobiotica 7:25–92; 1977.
17. Laduron, P. M.; Janssen, P. F. Impaired axonal transport of opiate and muscarinic receptors in streptozotocin-diabetic rats. Brain. Res. 380:359–362; 1986.
18. Marshall, J. F. Further analysis of the resistance of the diabetic rat to d-amphetamine. Pharmacol. Biochem. Behav. 8:281–286; 1977.
19. Maze, M.; Vickery, R. G.; Merlone, S. C.; Gaba, D. M. Anesthetic and hemodynamic effects of the α_2-adrenergic agonist, azepexole, in isoflurane-anesthetized dogs. Anesthesiology 68:689–694; 1988.
20. Maze, M.; Birch, B.; Vickery, R. G. Clonidine reduces halothane MAC in rats. Anesthesiology 67:868–870; 1987.
21. Morley, G. K.; Mooradian, A. D.; Levine, A. S.; Morley, J. E. Mechanism of pain in diabetic peripheral neuropathy: the effect of glucose on pain perception in humans. Am. J. Med. 77:79–83; 1984.
22. Mueller, R. A.; Smith, R. D.; Spruill, W. A. Central monoaminergic neuronal effects on minimal alveolar concentrations (MAC) of halothane and cyclopropane in rats. Anesthesiology 42:142; 1975.
23. Pantuck, E. J.; Pantuck, C. B.; Conney, A. H. Effect of streptozotocin-induced diabetes in the rat on the metabolism of fluorinated volatile anesthetics. Anesthesiology 66:24–28; 1987.
24. Ramabadran, K.; Bansinath, M.; Turndorff, H.; Puig, M. M. Hyperglycemia as a factor affecting k-opiate agonist-induced inhibition of the gastrointestinal transit in mice. J. Pharm. Pharmacol. 41:496–498; 1989.
25. Raz, I.; Hasdai, D.; Seltzer, Z.; Melmed, R. N. Effect of hyperglycemia on pain perception and on efficacy of morphine analgesia in rats. Diabetes 37:1253–1259; 1988.
26. Roizen, M. F.; White, P. F.; Eger, E. I., II. Effects of ablation of serotonin or norepinephrine brain stem areas on halothane and cyclopropane MAC's in rats. Anesthesiology 49:252–255; 1978.
27. Segal, I. S.; Vickery, R. G.; Walton, J. K.; Doze, V. A.; Maze, M. Dexmedetomidine diminishes halothane anesthetic requirements in rats through a postsynaptic α_2 adrenergic receptor. Anesthesiology 69:818–823; 1988.
28. Sherman, S. E.; Loomis, C. W.; Milne, B.; Cervenko, F. W. Intrathecal oxymetazoline produces analgesia via spinal α-adrenoceptors and potentiates spinal morphine. Eur. J. Pharmacol. 148:371–380; 1988.
29. Simon, G. S.; Dewey, W. L. Narcotics and diabetes. I. The effects of streptozotocin-induced diabetes on the antinociceptive potency of morphine. J. Pharmacol. Exp. Ther. 218:318–323; 1981.
30. Simon, G. S.; Borzelleca, J.; Dewey, W. L. Narcotics and diabetes. II Streptozotocin-induced diabetes selectively alters the potency of certain narcotic analgesics. Mechanism of diabetes: Morphine interaction. J. Pharmacol. Exp. Ther. 218:324–329; 1981.
31. Singh, I. S.; Chatterjee, T. K.; Ghosh, J. J. Modification of morphine antinociceptive response by blood glucose status: possible involvement of cellular energetics. Eur. J. Pharmacol. 90:437–439; 1983.
32. Strassheim, D.; Milligan, G.; Houslay, M. D. Diabetes abolishes the GTP-dependent but not the receptor-dependent inhibitory function of the inhibitory guanine-nucleotide-binding regulatory protein (G_i) on adipocyte adenylate cyclase activity. Biochem. J. 266:521–526; 1990.
33. Trulson, M. E.; Himmel, C. D. Decreased brain dopamine synthesis rate and increased [^{3}H]spiroperidol binding in streptozotocin-diabetic rats. J. Neurochem. 40:1456–1459; 1983.
34. Vickery, R. G.; Sheridan, B. C.; Segal, I. S.; Maze, M. Anesthetic and hemodynamic effects of the stereoisomers of medetomidine, an α_2 adrenergic agonist, in halothane-anesthetized dogs. Anesth. Analg. 67:611–615; 1988.