ELSEVIER

European Journal of Pharmacology 312 (1996) 273–279

ejp

Neuronal responses to Δ^9-tetrahydrocannabinol in the solitary tract nucleus

Thami Himmi, Michel Dallaporta, Jean Perrin, Jean-Claude Orsini *

Laboratoire de Neurobiologie, UPR 9024-CNRS, Université de Provence, 31 chemin Joseph Aiguier, 13402 Marseille Cédex 20, France

Received 25 March 1996; revised 10 June 1996; accepted 21 June 1996

Abstract

The effects of Δ^9-tetrahydrocannabinol on single-unit activity in the subpostremal division of the nucleus tractus solitarii were investigated by extracellular recording in rat brain slices. The spontaneous firing rate of 54.8% of the recorded neurons was significantly changed after bath applications of Δ^9-tetrahydrocannabinol. Putative nutrition-related neurons responding to a moderate increase in glucose concentration were selectively sensitive to Δ^9-tetrahydrocannabinol. The Δ^9-tetrahydrocannabinol-sensitive neurons were depressed by clonidine and are therefore likely to be adrenergic or noradrenergic. These observations suggest that some catecholaminergic, glucose-responsive neurons in the subpostremal nucleus tractus solitarii might mediate the influence of cannabinoids on feeding behaviour. Furthermore, most Δ^9-tetrahydrocannabinol-sensitive neurons in the nucleus tractus solitarii showed opposite responses to Δ^9-tetrahydrocannabinol and the 5-HT_3 receptor agonist 1-phenylbiguanide, and might therefore be involved in the nausea-reducing effects of cannabinoids.

Keywords: Δ^9-Tetrahydrocannabinol; Nucleus tractus solitarii; Nausea; Glucose; Catecholaminergic neuron; 5-HT_3 receptor

1. Introduction

Marijuana smoking and administration of its main psychoactive component, Δ^9-tetrahydrocannabinol, were reported to stimulate appetite and reduce nausea in human subjects. These incidental observations were confirmed in laboratory studies (Beal et al., 1995; Foltin et al., 1986; Mattes et al., 1994; Sallan et al., 1975) and give rise to therapeutic applications in patients with acquired immunodeficiency syndrome or under cancer chemotherapy, although the underlying neural mechanisms of these effects have not been elucidated as yet.

The effects of cannabinoids on nausea and feeding have been poorly investigated in non-human animals. Antiemetic activity of nabilone, a synthetic cannabinoid derivative, was observed (McCarthy and Borison, 1977). Unexpectedly, chronic Δ^9-tetrahydrocannabinol treatment was shown to decrease food intake in a few studies (Miller and Drew, 1974) but acute administration of low doses of Δ^9-tetrahydrocannabinol was found to stimulate eating. In the rat for example, Wayner et al. (1973) obtained an enhancement of lever-pressing for food, and proposed that lateral hypothalamic neurons might be involved in the effect. In agreement with this hypothesis is the recently reported facilitation by Δ^9-tetrahydrocannabinol of the feeding response to electrical stimulation of the lateral hypothalamus (Trojniar and Wise, 1991). In two studies on the anatomical location of the cannabinoid binding sites in the central nervous system (Herkenham et al., 1991; Mailleux and Vanderhaeghen, 1992), low densities were observed in the hypothalamus. However, both groups suggested that the receptors detected in the caudal part of the nucleus tractus solitarii, an area directly connected to the main feeding-relevant hypothalamic nuclei (Ter Horst et al., 1989), might mediate the anti-emetic action of Δ^9-tetrahydrocannabinol. In preliminary experiments, we established the existence of Δ^9-tetrahydrocannabinol-sensitive neurons in the caudal nucleus tractus solitarii at the level of the area postrema (T. Himmi et al., personal communication). The involvement of this nucleus in nutritional events similar to those induced by cannabinoids is supported by the following two sets of data.

* Corresponding author. Laboratoire de Neurobiologie, CNRS, 31 chemin Joseph Aiguier, 13402 Marseille Cédex 20, France. Tel.: +1 33 91 16 45 81; fax: +1 33 91 22 08 75; e-mail: orsini@irlnb.cnrs-mrs.fr

0014-2999/96/$15.00 Copyright © 1996 Elsevier Science B.V. All rights reserved.
PII S0014-2999(96)00490-6

On the one hand, the caudal nucleus tractus solitarii holds a key position in the brain circuitry that controls behavioural, vegetative and metabolic aspects of nutritional regulation. Some of its ascending projections towards feeding-related hypothalamic nuclei are adrenergic or noradrenergic (Cunningham and Sawchenko, 1988; Cunningham et al., 1990; Pierret et al., 1994) and might contribute to the catecholaminergic influence exerted on food intake through the latter nuclei (Leibowitz and Shor-Posner, 1986). The caudal nucleus tractus solitarii itself receives feeding-relevant information through vagal digestive afferents (Contreras et al., 1982) and local glucose-sensitive cells (Adachi et al., 1984; Mizuno and Oomura, 1984). We recently observed that a majority of the neurons recorded in this area respond to moderate changes in blood glucose concentration and might therefore be involved in the control of the body energy balance (Yettefti et al., 1995b, 1996). These glycemia-sensitive neurons, located within the catecholaminergic A_2 and C_2 cell group area, are directly sensitive to glucose molecules, and their inhibitory response to clonidine suggests that, according to a classical criterion (Moore and Guyenet, 1983; Rasmussen et al., 1986), they are noradrenergic or adrenergic. Therefore, glycemia-sensitive catecholaminergic neurons in the caudal nucleus tractus solitarii might represent a selective target able to mediate the nutritional effects of Δ^9-tetrahydrocannabinol.

On the other hand, the caudal nucleus tractus solitarii is involved in the nausea reactions induced by either vagal gastrointestinal activation or several humoral cytotoxic agents. Both emetogenic stimulation of digestive afferents (Boissonade et al., 1994) and administration of emetic drugs (Miller and Leslie, 1994) evoke an intense expression of c-fos protein in this area, which is considered as the starting point of a final common pathway for the induction of emesis in vomiting species (Miller and Leslie, 1994). Interestingly, the c-fos response to cisplatin, a drug used in cancer chemotherapy, is significantly decreased after either ipsilateral vagotomy or treatment with a 5-HT_3 receptor antagonist (Reynolds et al., 1991). The latter treatment inhibits cisplatin-induced emesis (Costall et al., 1986; Miner and Sanger, 1986; Smith et al., 1988), whereas 5-HT_3 receptor agonists are emetogenic agents (Miller and Nonaka, 1992). Moreover, the highest density of 5-HT_3 receptors in the central nervous system is found in a subregion of the nucleus tractus solitarii ventrolateral to the area postrema, which has been termed the area subpostrema or the nucleus gelatinosus (Pratt et al., 1990), where the receptors are located pre-synaptically on vagal afferent terminals (Leslie et al., 1990; Pratt and Bowery, 1989; Tecott et al., 1993). These 5-HT_3 receptors might be involved in the nausea-reducing effect of cannabinoids.

The present investigation with rat brain slices was undertaken to confirm the neuronal sensitivity to Δ^9-tetrahydrocannabinol of the caudal nucleus tractus solitarii, at the level of the area postrema, i.e. the subpostremal nucleus tractus solitarii (Barraco et al., 1992). We also addressed 3 questions concerning the functional and neurochemical identity of Δ^9-tetrahydrocannabinol-sensitive neurons: are they nutrition-related? Are they adrenergic or noradrenergic neurons? Are they affected by the activation of 5-HT_3 receptors? In order to answer these questions, we tested the possible response of Δ^9-tetrahydrocannabinol-sensitive neurons to moderate changes in extracellular glucose, to clonidine, and to the 5-HT_3 receptor agonist, 1-phenylbiguanide.

2. Materials and methods

Male Wistar rats weighing 220–300 g were anesthetized by halothane inhalation (Fluothan, Coopers) and decapitated. The brain was quickly removed and placed in chilled artificial cerebrospinal fluid saturated with O_2 95%, CO_2 5%, and containing (in mM) NaCl 127.5, KCl 5, KH_2PO_4 1.25, $MgSO_4$ 2, $CaCl_2$ 3, $NaHCO_3$ 25.5, and glucose 5. The medulla oblongata was microdissected using previously described techniques (Dekin et al., 1987). Then, 300-μm-thick coronal slices were cut at the level of the area postrema with an oscillating tissue slicer (Campden Instruments) and transferred into a pre-incubation chamber filled with oxygenated artificial cerebrospinal fluid at room temperature.

More than 2 h after pre-incubation, the recording session started in a submerged type recording chamber (0.5 ml) perfused at a rate of 1.5 ml/min with oxygenated artificial cerebrospinal fluid containing 4 mM glucose. The temperature of the chamber was kept at 34°C. The bottom of the chamber was coated with Sylgard (Dow Corning), so that slices could be fixed with platinum staples. The perfusion medium entered the chamber close to the slice. A rapid switch to artificial cerebrospinal fluid containing 6 mM glucose was carried out using an inlet flow valve. The new solution reached the chamber in about 30 s (dead space time).

Bath application of drugs was performed by injection into the perfusion inlet tubing. Three drugs were used in the study: 1-phenylbiguanide (Research Biomedicals International) and clonidine hydrochloride (Sigma) were dissolved in artificial cerebrospinal fluid (final concentrations in the chamber: 110 and 2 μM, respectively), and Δ^9-tetrahydrocannabinol (Sigma) was dispersed in artificial cerebrospinal fluid using polyvinylpyrrolidone as a carrier, according to a standard procedure (Fenimore and Loy, 1971) (final concentration in the chamber: 6.36 μM). Control injections of polyvinylpyrrolidone were routinely carried out.

Single-unit activity was recorded extracellularly with glass microelectrodes (tip diameter 2–3 μm) filled with 3 M NaCl. Electrodes were placed under microscopic observation in the subpostremal nucleus tractus solitarii, according to atlas plates (Barraco et al., 1992). Amplified spikes

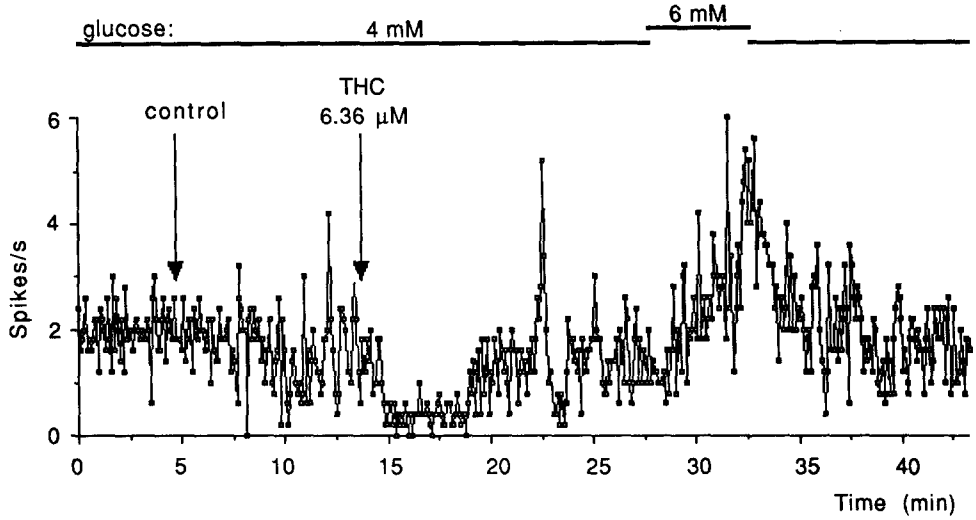

Fig. 1. Firing frequency of a neuron in the nucleus tractus solitarii: depression by Δ^9-tetrahydrocannabinol (THC) application and activation by an increase in extracellular glucose concentration. Control injection of the vehicle (polyvinylpyrrolidone) had no effect.

were observed on a storage oscilloscope and selected by a window discriminator. The number of spikes per 5 or 10 s was counted with the timer of an interface adapter board (National Instruments) inserted into a computer (Macintosh, Apple) and the time course of firing frequency was plotted on the screen. Once the spontaneous activity had become stable, drugs were injected or the glucose concentration of the bathing medium was changed. When the unit activity changed less than 5 min after the stimulus (drug application or perfusion switch), the mean discharge frequency measured during the period of altered activity was compared to that measured for a control period of 5 min immediately preceding the stimulus in order to ensure that the response was statistically significant (Student's *t*-test).

3. Results

3.1. Responses to Δ^9-tetrahydrocannabinol

Possible effects of bath application of Δ^9-tetrahydrocannabinol (6.36 μM) were reliably examined for 42 neurons. While 19 cells failed to be affected by the drug, 23 displayed changed activity after a latency of 89.1 ± 13.2 s (S.E.): 11 had a decreased firing rate (Fig. 1) and 12 were activated (Fig. 2). The activity of the responding neurons was not significantly altered after vehicle application.

The location of the 42 neurons tested within the subpostremal nucleus tractus solitarii is represented in Fig. 3.

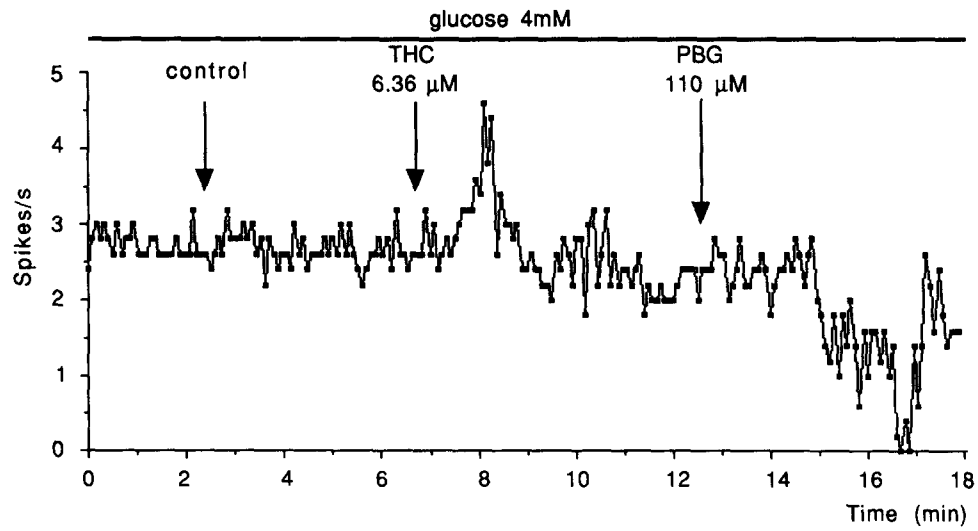

Fig. 2. Firing frequency of a neuron in the nucleus tractus solitarii: activation by Δ^9-tetrahydrocannabinol (THC) and depression by the 5-HT_3 receptor agonist, 1-phenylbiguanide (PBG).

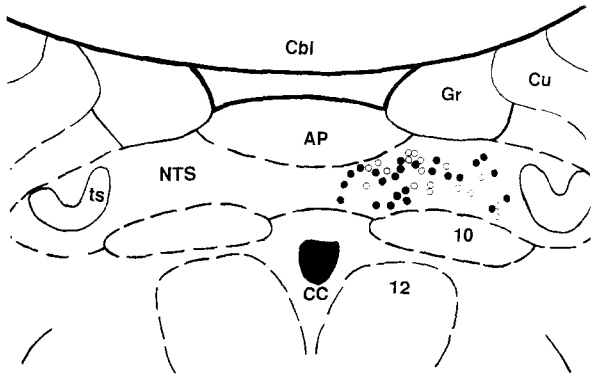

Fig. 3. Location of the 42 recorded neurons on a coronal plane passing through the area postrema. Open circles, neurons showing no response to Δ^9-tetrahydrocannabinol; filled circles, neurons that responded to Δ^9-tetrahydrocannabinol; AP, area postrema; Cbl, cerebellum; CC, central canal; Cu, nucleus cuneatus; Gr, nucleus gracilis; NTS, nucleus tractus solitarii; ts, tractus solitarius; 10, dorsal motor nucleus of the vagus nerve; 12, hypoglossal nucleus.

Most of the Δ^9-tetrahydrocannabinol-responsive neurons were located in an area that corresponds to the noradrenergic A_2 and the adrenergic C_{2d} cell groups described by Hökfelt et al. (1984), but the mapping failed to reveal any selective anatomical distribution of these cells, compared to that of the non-responsive ones, within the A_2 and C_{2d} areas.

3.2. Sensitivity to Δ^9-tetrahydrocannabinol of glucose-responsive and glucose-unresponsive neurons

Among the 37 neurons tested with a 2-mM increase in extracellular glucose concentration and Δ^9-tetrahydrocannabinol application, 29 either responded to both stimuli (Figs. 1 and 4) or did not respond to either (Table 1). The proportion of Δ^9-tetrahydrocannabinol-sensitive cells was significantly higher among the glucose-responsive population (17/23) than among the glucose-unresponsive one (2/14) ($\chi^2 = 10.11$, df = 1, $P < 0.001$).

Table 1
Comparison of the responses of nucleus tractus solitarii neurons to Δ^9-tetrahydrocannabinol application and increase in extracellular glucose

Responses to glucose	Responses to Δ^9-tetrahydrocannabinol			
	Depressed	Activated	No response	Total
Depressed	6	6	2	14
Activated	3	2	4	9
No response	0	2	12	14
Total	9	10	18	37

3.3. Effect of clonidine on Δ^9-tetrahydrocannabinol-sensitive neurons

15 neurons were tested with Δ^9-tetrahydrocannabinol and clonidine applications. Of the 9 cells which responded to Δ^9-tetrahydrocannabinol, all displayed a decrease in firing rate in response to clonidine (Fig. 4). Among the 6 Δ^9-tetrahydrocannabinol-insensitive neurons, 4 were also depressed by clonidine and 2 were unaffected by this drug.

3.4. Comparison between the effects of Δ^9-tetrahydrocannabinol and 1-phenylbiguanide

The responses of the same neuron to applications of Δ^9-tetrahydrocannabinol and 1-phenylbiguanide were compared in 24 cases (Table 2). Δ^9-Tetrahydrocannabinol modified the activity of 12 cells and had no effect on the 12 others. The proportions of 1-phenylbiguanide-responsive neurons among the Δ^9-tetrahydrocannabinol-sensitive and the Δ^9-tetrahydrocannabinol-insensitive populations

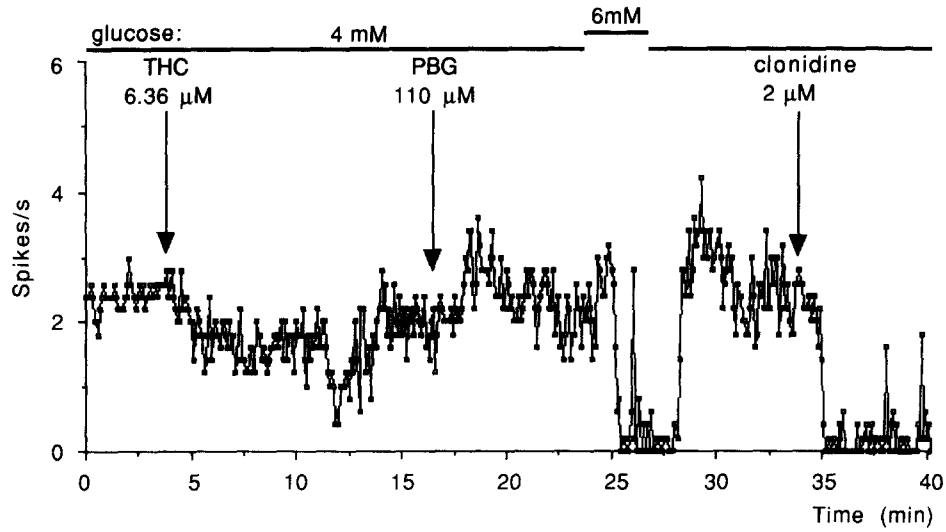

Fig. 4. Firing frequency of a neuron in the nucleus tractus solitarii: depression by increase in extracellular glucose concentration and by bath application of either Δ^9-tetrahydrocannabinol (THC) or clonidine, and activation by 1-phenylbiguanide (PBG) application.

Table 2
Comparison of the responses of nucleus tractus solitarii neurons to Δ^9-tetrahydrocannabinol and 1-phenylbiguanide (PBG) application

Responses to PBG	Responses to Δ^9-tetrahydrocannabinol			
	Depressed	Activated	No response	Total
Depressed	2	5	1	8
Activated	4	0	2	6
No response	0	1	9	10
Total	6	6	12	24

were significantly different ($\chi^2 = 8.4$, df = 1, $P < 0.001$): most Δ^9-tetrahydrocannabinol-insensitive neurons failed to be affected by 1-phenylbiguanide. Conversely, almost all Δ^9-tetrahydrocannabinol-sensitive neurons responded to 1-phenylbiguanide, and for most of these, the responses to the compounds were in opposite directions (Figs. 2 and 4).

4. Discussion

4.1. Effects of Δ^9-tetrahydrocannabinol on subpostremal nucleus tractus solitarii neurons

The subpostremal nucleus tractus solitarii appears to be a Δ^9-tetrahydrocannabinol-sensitive structure: about half of the neurons recorded in the present study responded to bath application of the drug at a dose similar to or lower than those already used in vitro (Caulfield and Brown, 1992; Turkanis et al., 1991). This concentration is higher than that measured in plasma after marijuana smoking (Huestis et al., 1992). However, Δ^9-tetrahydrocannabinol adheres easily to glass and plastic surfaces (Howlett et al., 1990), and this should be kept in mind before extrapolating the results of in vitro experiments to possible responses in the intact animal.

At the plasma membrane, the effect of Δ^9-tetrahydrocannabinol results from interaction with either cannabinoid-stereoselective receptors, or non-specific binding sites or both (Makriyannis, 1995). In future investigations, the first hypothesis will be supported if similar responses are evoked by high-affinity agonists and suppressed by a recently developped selective antagonist of the brain cannabinoid-1 receptors (Rinaldi-Carmona et al., 1994). A direct effect of the antagonist itself would indicate the tonic influence of endogenous cannabinoid molecules, such as anandamide (Iversen, 1994).

4.2. Response of feeding-relevant neurons to Δ^9-tetrahydrocannabinol

The location of most Δ^9-tetrahydrocannabinol-sensitive neurons within catecholaminergic areas and their depressed activity after clonidine application suggest that these neurons are noradrenergic or adrenergic, but this identity needs to be fully confirmed with immunohistochemical techniques. Considering the role played by the catecholaminergic neurons of the nucleus tractus solitarii in the control of blood circulation (Jean, 1991), the catecholaminergic identity of Δ^9-tetrahydrocannabinol-sensitive neurons would indicate their possible involvement in the complex cardiovascular effects of cannabinoids. Adrenergic and noradrenergic cells in the nucleus tractus solitarii might be involved in feeding regulation as well: their projections to the medial and lateral hypothalamus (Cunningham and Sawchenko, 1988; Cunningham et al., 1990; Pierret et al., 1994) probably contribute to supply these structures with signals stimulating and inhibiting eating, respectively (Leibowitz and Rossakis, 1978; Leibowitz and Shor-Posner, 1986). Among these putative catecholaminergic neurons, a glucose-responsive subpopulation is especially sensitive to Δ^9-tetrahydrocannabinol. These cells can be considered as glycemia-sensitive: they respond to moderate changes in extracellular glucose similar to those induced in the cerebrospinal fluid of whole animals by physiological fluctuations of blood glucose (Silver and Erecinska, 1994; Steffens et al., 1988). The fact that these neurons represent a selective target for Δ^9-tetrahydrocannabinol is consistent with the hypothesized role of the subpostremal nucleus tractus solitarii in the partial mediation of the nutritional effects of cannabinoids. In a preliminary in vivo study (Yettefti et al., 1995a), intravenous administration of nicotine, a drug that also affects nutritional functions, was found to change selectively the activity of glycemia-sensitive neurons in the caudal nucleus tractus solitarii.

4.3. Effect of 5-HT_3 activation on Δ^9-tetrahydrocannabinol-sensitive neurons

Unlike the other cells recorded in the nucleus tractus solitarii, almost all Δ^9-tetrahydrocannabinol-sensitive neurons responded to the 5-HT_3 receptor agonist, 1-phenylbiguanide. This correlation might reflect their role in a putative dependence to cannabinoids, since 5-HT_3 receptors can influence addictive processes (Grant, 1995). It might also reflect an involvement of the neurons in functions influenced by both Δ^9-tetrahydrocannabinol and 5-HT_3 receptor agonists, like nociception, cardiovascular regulations or nausea reactions.

The latter possibility, postulated in our initial hypothesis, is supported by the fact that the opposite responses of nucleus tractus solitarii neurons to these compounds parallel the opposite effects they exert on nausea: vomiting is elicited by 5-HT_3 receptor agonists, while Δ^9-tetrahydrocannabinol has anti-emetic properties. Although it is generally accepted that the nausea-relevant 5-HT_3 receptors are mainly localized in the gut wall, at the peripheral end of vagal sensory fibers (Grélot and Miller, 1994; Miller and Nonaka, 1992; Reynolds et al., 1991), the anti-emetic effects of centrally applied 5-HT_3 receptor antagonists

(Smith et al., 1988) indicate the additional involvement of central receptors. These central receptors might be those located in the area subpostrema of the nucleus tractus solitarii (Pratt et al., 1990), at the central end of vagal afferents (Leslie et al., 1990; Pratt and Bowery, 1989; Tecott et al., 1993), as suggested by the changes in c-fos expression mentioned in Section 1 (Reynolds et al., 1991).

Changes in nucleus tractus solitarii neuronal activity after activation of the pre-synaptic 5-HT_3 receptors result mainly from a depolarisation-induced modulation of glutamate and γ-aminobutyric acid release by vagal terminals (Glaum et al., 1992). The opposite modulation might be exerted at the same site by cannabinoids: many cannabinoid receptors in the central nervous system are located on nerve terminals (Herkenham, 1995) and inhibition of calcium channels by cannabinoid receptor agonists suggests that they could decrease neurotransmitter release (Caulfield and Brown, 1992; Mackie and Hille, 1992). Indeed, an influence of cannabinoids on synaptic processes has been described in various brain structures, such as substantia nigra (Miller and Walker, 1995). In a recent patch-clamp study, whole-cell recording of nodose ganglion cells showed the inhibition by cannabinoid receptor agonists of the inward current induced by 5-HT_3 receptors in cell bodies of vagal sensory neurons (Fan, 1995). In the caudal nucleus tractus solitarii, a similar interaction could occur at the central endings of the same neurons.

The transmission to the brain of nausea-inducing stimuli originating in the gut might thus be controlled by both serotonin and cannabinoids, and these modulatory influences might be mediated by 5-HT_3 receptors localized at various levels of the vagal afferent neurons, including their endings in the nucleus tractus solitarii. Serotonergic afferents to the nucleus tractus solitarii arise both from the periphery, through vagal afferent fibers (Gaudin-Chazal et al., 1982) and from the central nervous system, mainly from the raphe magnus and raphe obscurus nuclei (Schaffar et al., 1988). Serotonin might also be released in the nucleus tractus solitarii by interneurons of the area postrema (Reynolds et al., 1991), a structure which constitutes a major chemo-sensitive trigger zone for the emetic reflexes in vomiting species (Miller and Leslie, 1994). Unlike the case of serotonergic afferents, the existence, nature and possible origin of endogenous cannabinoid inputs to the caudal nucleus tractus solitarii is currently unknown, and should be the matter of future investigations.

Acknowledgements

This study was supported by the CMIFM (AI No. 91/573) and in part by the MESR (No. 94.G.0085), and by a fellowship to T. Himmi from the Communauté Marseille-Provence Métropole. Thanks are due to Dr. L. Grélot for helpful advice.

References

Adachi, A., N. Shimizu, Y. Oomura and M. Kobashi, 1984, Convergence of hepatoportal glucose-sensitive afferent signals to glucose-sensitive units within the nucleus of the solitary tract, Neurosci. Lett. 46, 215.

Barraco, R., M. Elridi, E. Ergene, M. Parizon and D. Bradley, 1992, An atlas of the rat subpostremal nucleus-tractus-solitarius, Brain Res. Bull. 29, 703.

Beal, J.E., R. Olson, L. Laubenstein, J.O. Morales, P. Bellman, B. Yangco, L. Lefkowitz, T.F. Plasse and K.V. Shepard, 1995, Dronabinol as a treatment for anorexia associated with weight loss in patients with AIDS, J. Pain Sympt. Manag. 10, 89.

Boissonade, F.M., K.A. Sharkey and J.S. Davison, 1994, Fos expression in ferret dorsal vagal complex after peripheral emetic stimuli, Am. J. Physiol. 266, R1118.

Caulfield, M.P. and D.A. Brown, 1992, Cannabinoid receptor agonists inhibit Ca current in NG108-15 neuroblastoma cells via a pertussis toxin-sensitive mechanism, Br. J. Pharmacol. 106, 231.

Contreras, R.J., R.M. Beckstead and R. Norgren, 1982, The central projections of the trigeminal, facial, glossopharyngeal and vagus nerves: an autoradiographic study in the rat, J. Auton. Nerv. Syst. 6, 303.

Costall, B., A.M. Domeney, R.J. Naylor and F.D. Tattersall, 1986, 5-Hydroxytryptamine M-receptor antagonism to prevent cisplatin-induced emesis, Neuropharmacology 25, 959.

Cunningham, E.T. and P.E. Sawchenko, 1988, Anatomical specificity of noradrenergic inputs to the paraventricular and supraoptic nuclei of the rat hypothalamus, J. Comp. Neurol. 274, 60.

Cunningham, E.T., M.C. Bohn and P.E. Sawchenko, 1990, Organization of adrenergic inputs to the paraventricular and supraoptic nuclei of the hypothalamus in the rat, J. Comp. Neurol. 292, 651.

Dekin, M.S., P.A. Getting and S.M. Johnson, 1987, In vitro characterization of neurons in the ventral part of the nucleus tractus solitarius. I. Identification of neuronal types and repetitive firing properties, J. Neurophysiol. 58, 195.

Fan, P., 1995, Cannabinoid agonists inhibit the activation of 5-HT3 receptors in rat nodose ganglion neurons, J. Neurophysiol. 73, 907.

Fenimore, D.C. and P.R. Loy, 1971, Injectible dispersion of delta-9-tetrahydrocannabinol in saline using polyvinylpyrrolidone, J. Pharm. Pharmac. 23, 310.

Foltin, R.W., J.V. Brady and M.W. Fishman, 1986, Behavioral analysis of marijuana effects on food intake in humans, Pharmacol. Biochem. Behav. 25, 577.

Gaudin-Chazal, G., N. Seyfritz, S. Araneda, D. Vigier and J.J. Puizillout, 1982, Selective retrograde transport of 3H-serotonin in vagal afferents, Brain Res. Bull. 8, 503.

Glaum, S.R., P.A. Brooks, K.M. Spyer and R.J. Miller, 1992, 5-Hydroxytryptamine-3 receptors modulate synaptic activity in the rat nucleus-tractus-solitarius in vitro, Brain Res. 589, 62.

Grant, K.A., 1995, The role of 5-HT3 receptors in drug dependence, Drug Alcohol Depend. 38, 155.

Grélot, L. and A.D. Miller, 1994, Vomiting – its ins and outs, News Physiol. Sci. 9, 142.

Herkenham, M., 1995, Localization of cannabinoid receptors in brain and periphery, in: Cannabinoid Receptors, ed. R.G. Pertwee (Academic Press, London) p. 145.

Herkenham, M., A.B. Lynn, M.R. Johnson, L.S. Melvin, B.R. Decosta and K.C. Rice, 1991, Characterization and localization of cannabinoid receptors in rat brain – a quantitative in vitro autoradiographic study, J. Neurosci. 11, 563.

Hökfelt, T., R. Martensson, A. Björklund, S. Kleinau and M. Goldstein, 1984, Distributional maps of tyrosine-hydroxylase-immunoreactive neurons in the rat brain, in: Handbook of Chemical Neuroanatomy, Vol. 2: Classical Transmitters in the CNS, eds. A. Björklund and T. Hökfelt (Elsevier, Amsterdam) p. 277.

Howlett, A.C., M. Bidaut-Russel, W.A. Devane, L.S. Melvin, M.R. Johnson and M. Herkenham, 1990, The cannabinoid receptor: bio-

chemical, anatomical and behavioral characterization, Trends Neurosci. 13, 420.

Huestis, M.A., A.H. Sampson, B.J. Holicky, J.E. Henningfield and E.J. Cone, 1992, Characterization of the absorption phase of marijuana smoking, Clin. Pharmacol. Ther. 52, 31.

Iversen, L., 1994, Pharmacology – endogenous cannabinoids, Nature (London) 372, 619.

Jean, A., 1991, Le noyau du faisceau solitaire. Aspects neuroanatomiques, neurochimiques et fonctionnels, Arch. Int. Physiol. Bioch. Biophys. 99, A3.

Leibowitz, S.F. and C. Rossakis, 1978, Pharmacological characterization of perifornical hypothalamic beta-adrenergic receptors mediating feeding inhibition in the rat, Neuropharmacology 17, 691.

Leibowitz, S.F. and G. Shor-Posner, 1986, Hypothalamic monoamine systems for control of food intake. Analysis of meal patterns and macronutrient selection, in: Pharmacology of Eating Disorders, Theoretical and Clinical Developments, eds. M.O. Carruba and J.E. Blundell (Raven Press, New York) p. 29.

Leslie, R.A., D.J.M. Reynolds, P.L.R. Andrews, D.G. Grahame-Smith, C.J. Davis and J.M. Harvey, 1990, Evidence for presynaptic 5-hydroxytryptamine recognition sites on vagal afferent terminals in the brainstem of the ferret, Neuroscience 38, 667.

Mackie, K. and B. Hille, 1992, Cannabinoids inhibit N-type calcium channels in neuroblastoma glioma cells, Proc. Natl. Acad. Sci. USA 89, 3825.

Mailleux, P. and J.J. Vanderhaeghen, 1992, Distribution of neuronal cannabinoid receptor in the adult rat brain – a comparative receptor binding radioautography and in situ hybridization histochemistry, Neuroscience 48, 655.

Makriyannis, A., 1995, The role of cell membrane in cannabinoid activity, in: Cannabinoid Receptors, ed. R.G. Pertwee (Academic Press, London) p. 87.

Mattes, R.D., K. Engelman, L.M. Shaw and M.A. Elsohly, 1994, Cannabinoids and appetite stimulation, Pharmacol. Biochem. Behav. 49, 187.

McCarthy, L.E. and H.L. Borison, 1977, Anti-emetic activity of nabilone, a cannabinol derivative, reversed by naloxone in awake cats, Pharmacologist 19, 230.

Miller, A.D. and R.A. Leslie, 1994, The area postrema and vomiting, Front. Neuroendocrinol. 15, 301.

Miller, A.D. and S. Nonaka, 1992, Mechanisms of vomiting induced by serotonin-3 receptor agonists in the cat: effect of vagotomy, splanchniceotomy or area postrema lesion, J. Pharmacol. Exp. Ther. 260, 509.

Miller, A.S. and J.M. Walker, 1995, Effects of a cannabinoid on spontaneous and evoked neuronal activity in the substantia nigra pars reticulata, Eur. J. Pharmacol. 279, 179.

Miller, L.L. and W.G. Drew, 1974, Cannabis review of behavioral effects in animals, Psychol. Bull. 81, 401.

Miner, W.D. and G.J. Sanger, 1986, Inhibition of cisplatin-induced vomiting by selective 5-hydroxytryptamine M-receptor antagonism, Br. J. Pharmac. 88, 497.

Mizuno, Y. and Y. Oomura, 1984, Glucose responding neurons in the nucleus tractus solitarius of the rat, in vitro study, Brain. Res. 307, 109.

Moore, S.D. and P.G. Guyenet, 1983, Alpha-receptor-mediated inhibition of A2 noradrenergic neurons, Brain Res. 276, 188.

Pierret, P., A. Christolomme, O. Bosler, J. Perrin and J.C. Orsini, 1994, Catecholaminergic projections from the solitary tract nucleus to the perifornical hypothalamus, Brain Res. Bull. 35, 153.

Pratt, G.D. and N.G. Bowery, 1989, The 5-HT3 receptor ligand, [3H]BRL 43694, binds to presynaptic sites in the nucleus tractus solitarius of the rat, Neuropharmacology 28, 1367.

Pratt, G.D., N.G. Bowery, G.J. Kilpatrick, R.A. Leslie, N.M. Barnes, R.J. Naylor, B.J. Jones, D.R. Nelson, J.M. Palacios, P. Slater and J.M. Reynolds, 1990, Consensus meeting agrees distribution of 5-HT3 receptors in mammalian hindbrain, Trends Pharmacol. Sci. 11, 135.

Rasmussen, K., D.A. Morilak and B.L. Jacobs, 1986, Single unit activity of locus coeruleus neurons in the freely mooving cat. I. During naturilistic behaviors and in response to simple and complex stimuli, Brain Res. 371, 324.

Reynolds, D.J.M., N.A. Barber, D.G. Grahame-Smith and R.A. Leslie, 1991, Cisplatin-evoked induction of c-fos protein in the brainstem of the ferret: the effect of cervical vagotomy and the anti-emetic 5-HT3 receptor antagonist granisetron (BRL 43694), Brain Res. 565, 231.

Rinaldi-Carmona, M., F. Barth, M. Héaulme, D. Shire, B. Calandra, C. Congy, S. Martinez, J. Maruani, G. Néliat, D. Caput, P. Ferrara, P. Soubrié, J.C. Brelière and G. Le Fur, 1994, SR 141716A, a potent and selective antagonist of the brain cannabinoid receptor, FEBS Lett. 350, 240.

Sallan, S.E., N.E. Zinberg and E. Frei, 1975, Antiemetic effect of delta-9-tetrahydrocannabinol in patients receiving cancer chemotherapy, N. Engl. J. Med. 293, 795.

Schaffar, N., J.P. Kessler, O. Bosler and A. Jean, 1988, Central serotonergic projections to the nucleus tractus solitarii: evidence from a double labelling study in the rat, Neuroscience 26, 951.

Silver, I.A. and M. Erecinska, 1994, Extracellular glucose concentration in mammalian brain. Continuous monitoring of changes during increased neuronal activity and upon limitation in oxygen supply in normo-, hypo-, and hyperglycemic animals, J. Neurosci. 14, 5068.

Smith, W.L., E.M. Callaham and R.S. Alphin, 1988, The emetic activity of centrally administered cisplatin in cats and its antagonism by zacopride, J. Pharmac. Pharmacol. 40, 142.

Steffens, A.B., A.J.W. Scheurink, D. Porte and S.C. Woods, 1988, Penetration of peripheral glucose and insulin into cerebrospinal fluid in rats, Am. J. Physiol. 255, R200.

Tecott, L.H., A.V. Maricq and V. Julius, 1993, Nervous system distribution of the serotonin 5-HT3 receptor mRNA, Proc. Natl. Acad. Sci. USA 90, 1430.

Ter Horst, G.J., P. De Boer, P.G.M. Luiten and J.D. Van Willigen, 1989, Ascending projections from the solitary tract nucleus to the hypothalamus. A phaseolus vulgaris lectin tracing study in the rat, Neuroscience 31, 785.

Trojniar, W. and R.A. Wise, 1991, Facilitory effect of delta-9-tetrahydrocannabinol on hypothalamically induced feeding, Psychopharmacology 103, 172.

Turkanis, S.A., R. Karler and L.M. Partlow, 1991, Differential effects of delta-9-tetrahydrocannabinol and its 11-hydroxy metabolite on sodium current in neuroblastoma cells, Brain Res. 560, 245.

Wayner, M.J., I. Greenberg, S. Fraley and S. Fisher, 1973, Effects of delta9-tetrahydrocannabinol and ethyl alcool on adjunctive behavior and the lateral hypothalamus, Physiol. Behav. 10, 109.

Yettefti, K., J.C. Orsini and J. Perrin, 1996, Characteristics of the neurons sensitive to moderate glycemic variations in the nucleus tractus solitarius. Possible involvement in nutritional regulations, Physiol. Behav. (in press).

Yettefti, K., A. Boyer, J.C. Orsini and J. Perrin, 1995a, Etude des effets de la nicotine sur les neurones du noyau du faisceau solitaire, Alcoologie 17, 76.

Yettefti, K., J.C. Orsini, T. El Ouazzani, T. Himmi, A. Boyer and J. Perrin, 1995b, Sensitivity of nucleus tractus solitarius neurons to induced moderate hyperglycemia, with special reference to catecholaminergic regions, J. Auton. Nerv. Syst. 51, 191.