Pharmacology Biochemistry & Behavior, Vol 38, pp 287–292 © Pergamon Press plc, 1991 Printed in the U S A 0091-3057/91 $3 00 + 00

The Effects of Medetomidine, an α-2-Adrenoceptor Agonist, and Cocaine on the Tooth Pulp-Evoked Jaw-Opening Reflex in Cat

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Received 26 March 1990

PERTOVAARA, A , P KEMPPAINEN AND T KAUPPILA *The effects of medetomidine, an α-2-adrenoceptor agonist, and cocaine on the tooth pulp-evoked jaw-opening reflex in cat* PHARMACOL BIOCHEM BEHAV **38**(2) 287–292, 1991 —In the pentobarbitone-anesthetized cat, the threshold of the tooth pulp-elicited jaw-opening reflex was elevated in a dose-dependent way (30–100 μg/kg, IP) following the administration of medetomidine, an α-2-adrenoceptor agonist This elevation was significantly reduced by atipamezole (1 mg/kg, IP), an α-2-adrenoceptor antagonist The inhibitory interaction between two successive dental stimuli applied to the same tooth (in-field inhibition) was suppressed by a lower dose of medetomidine (30 μg/kg) than the threshold elevation to single electrical pulses (55 μg/kg) Only the highest dose of medetomidine used (100 μg/kg) significantly influenced the temporally facilitated (in-field facilitation) response In comparison, cocaine, a nonspecific monoaminergic agent, did not produce a significant threshold elevation of the tooth pulp-elicited jaw-opening reflex (1–25 mg/kg, IP) It is concluded that medetomidine, through an action on α-2-adrenoceptors, can suppress a predominantly nociceptive trigeminal reflex in anesthetized cats The threshold evoked by single electric pulses, in-field inhibition, and in-field facilitation display differential sensitivities to medetomidine effects

α-2-Adrenoceptor Antinociception Atipamezole Cat Cocaine Jaw-opening reflex Medetomidine Nociception Tooth pulp

SEVERAL groups have reported that systemic clonidine, an α-2-adrenoceptor agonist, has antinociceptive properties in different behavioral tests in animals [see (10)]. Medetomidine is a new highly selective and potent α-2-adrenoceptor agonist (41). Systemic dexmedetomidine, a stereoisomeric form of medetomidine, has been shown to prolong behavioral response latencies to nociceptive tail pinch in halothane-anesthetized rats (34) However, in subanesthetic doses (up to 100 μg/kg, IP), medetomidine alone was not effective in a nociceptive test involving mainly spinal circuitry (tail flick test), but it was effective only in a nociceptive test involving highly organized behavior (formalin test) and only at doses producing sedation (30). These studies suggest that medetomidine alone at subanesthetic doses influences nociceptively evoked behavior at supraspinal levels via mechanisms related to sedation. However, when combined with other anesthetics, medetomidine may potentiate their antinociceptive effects even at low doses.

In the current study we wished to examine in pentobarbitone-anesthetized cats whether systemic medetomidine influences a disynaptic trigeminal reflex, the tooth pulp-evoked jaw-opening reflex (38). This is generally considered to be a nociceptive reflex (20), although under some conditions a liminal reflex response can be evoked at nonnoxious intensities also (20,27). A conditioning dental stimulus of liminal intensity facilitates or inhibits the jaw-opening response to the succeeding dental stimulus depending on whether the interstimulus interval is short (<20 ms) or long, respectively (13). This interaction, in-field facilitation or inhibition, can also be seen in the responses of the sensory trigeminal nucleus neurons (28). These facilitatory and inhibitory interactions provide a possibility to study drug effects on two different types of synaptic mechanisms taking place at the spinal cord level. In the current study we also determined the effect of medetomidine on in-field facilitation and inhibition to examine the contribution of α-2-adrenergic mechanisms to these synaptic interactions Atipamezole, a novel highly specific α-2-adrenergic antagonist (19, 33, 42), was used to reverse the possible medetomidine-induced effects. For comparison, we determined the effect of a nonsedative, nonspecific monoaminergic agent, cocaine, on the jaw-opening reflex Systemic cocaine has strong central antinociceptive effects in several behavioral tests in rats (17, 29–31), but its effect on a nociceptive trigeminal reflex has not been studied previously.

METHOD

The experiments were performed with adult cats (2 6–3.7 kg) anesthetized with sodium pentobarbital (40 mg/kg IP). Due to the

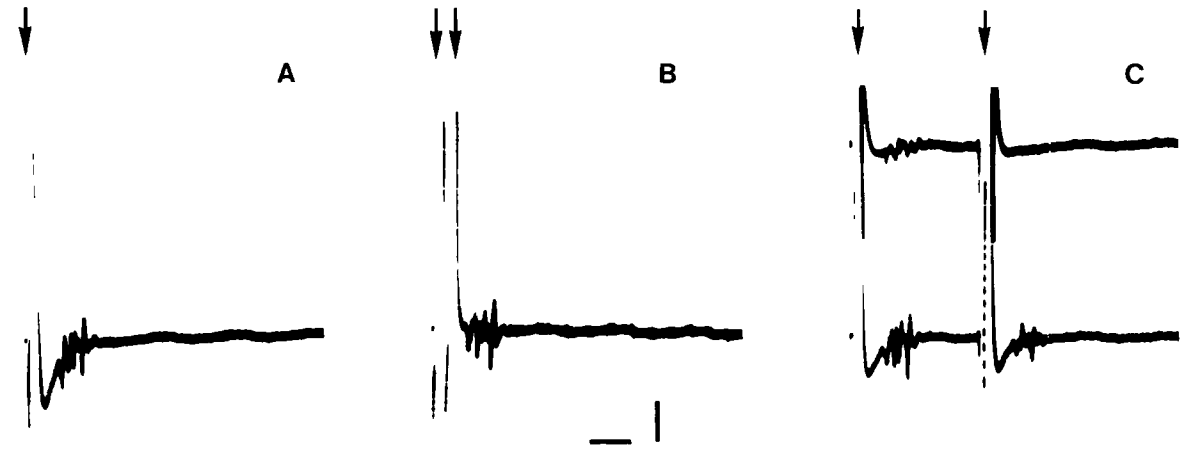

FIG. 1 Photographic examples of liminal tooth pulp-evoked reflex responses in the digastric (jaw-opening) muscle. (A) Response to a single stimulus pulse The threshold was 5 μA (B) Response to a double pulse of short (4 ms) interstimulus interval The threshold was lower (3 μA) than that to a single stimulus pulse indicating a facilitatory interaction (C) Upper beam The threshold to the first stimulus of a double pulse with a long (40 ms) interstimulus interval was equal to that to a single stimulus pulse (5 μA) Lower beam The threshold to the second stimulus of a double pulse with a long (40 ms) interstimulus interval was higher (7 μA) than that to the first stimulus indicating an inhibitory interaction The arrows indicate stimulus artifact The horizontal calibration bar represents 10 ms, and the vertical one 50 μV

short duration (less than 2 h) of the experiments, no supplementary doses were needed. The cats breathed spontaneously, but in cases of respiratory depression the end tidal CO_2 could be measured and the cat could be connected to a respirator When required, a heating lamp was used to maintain body temperature

EMG responses were recorded from the digastric muscle with a concentric bipolar needle electrode. The EMG signal was amplified (band pass 10 Hz–1 kHz) and led to a storage oscilloscope for immediate analysis and photography.

Monopolar cathodal stimulation of the tooth has been described in detail elsewhere (39). The electrode was applied to the surface of a carefully dried tooth. Constant current pulses (duration 2 ms) were applied at 0 25 Hz and the stimulus intensity was increased slowly until the first EMG response appeared. Then the stimulus intensity was decreased to zero and again slowly increased until the first EMG response appeared. If the same stimulus intensity elicited the first EMG response in at least two successive threshold determinations, the stimulus intensity was considered to be the threshold intensity. The electrode resistance was determined between each measurement to ensure a proper contact between the electrode and the tooth pulp.

The EMG threshold to single pulses (Fig 1A) was determined before and every 5 min at least for 15 min after the IP administration of each dose of medetomidine or cocaine. In case of the highest dose of cocaine, the threshold was determined every 5 min for 30 min after the cocaine administration To examine the effect of medetomidine or cocaine on the facilitatory interaction between two successive stimuli (13,28), the threshold to a double pulse (each of 2 ms duration and of equal intensity) with an interstimulus interval of 4 ms (Fig. 1B) was determined before and after each drug dose. To examine the effect of medetomidine or cocaine on the inhibitory interaction between two successive stimuli with an interval of 40 ms, the threshold for the first and second stimulus of the double pulse (Fig 1C) was determined before and after the administration of each drug dose as above. The difference in the threshold for the first (equal threshold as with single pulses) and second (higher threshold) stimulus of a pair was used as an index of in-field inhibition One-way analysis of variance (ANOVA) and Student's *t*-test (two-tailed) were used for the statistical evaluation of the data. $p<0.05$ level was considered to represent a significant difference in the results.

All the drugs were given IP When testing dose-dependence, the cumulative medetomidine (Farmos Group Ltd., Turku, Finland) doses were 30, 55, and 100 μg/kg. Dose-dependence of cocaine effects was tested using cumulative doses of 1, 10, and 25 mg/kg Atipamezole (Farmos Group Ltd.) was used to reverse the medetomidine effect at a dose of 1 mg/kg.

RESULTS

Effect of Medetomidine

The average EMG threshold for single pulses of 2 ms duration was 5.1 ± 0.7 μA (n = 8; ± S.E M.) without medetomidine. The EMG threshold to a double stimulus of a short interstimulus interval (4 ms) was on the average 3.6 ± 0.3 μA without medetomidine indicating a significant in-field facilitatory effect (reference threshold to single pulses, $p<0$ 05, *t*-test) The increase of the interstimulus interval to 40 ms suppressed the latter EMG response so that its threshold was significantly higher (8.6 ± 1 2 μA) than the threshold to a single stimulus in the control conditions ($p<0.05$, *t*-test) indicating in-field inhibition.

Medetomidine produced a dose-dependent elevation of all studied thresholds ($p<0.05$, ANOVA; Fig. 2). The threshold elevation for single pulses was significant at doses ≥55 μg/kg ($p<0.05$, *t*-test), whereas the threshold elevation for double pulses of short interstimulus interval (4 ms) or longer interstimulus interval (40 ms; the response threshold to the second stimulus of a pair) was significantly elevated only at 100 μg/kg dose (compared to the corresponding thresholds without medetomidine; $p<0.05$, *t*-test) It is noteworthy that the index of in-field inhibition (the difference in the thresholds of the first and second pulse of the pair with 40 ms interstimulus interval) decreased with increasing doses of medetomidine so that after the dose of 30 μg/kg the index (difference) was not significant ($p>0.05$, *t*-test). However, the index of in-field facilitation (the difference in the

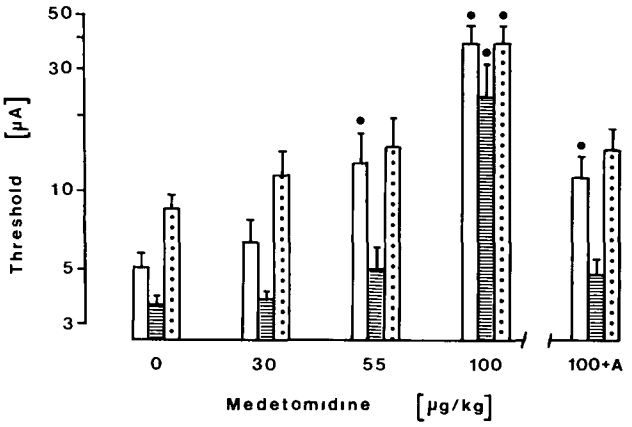

FIG 2 Medetomidine-induced dose-dependent elevation of the threshold for the tooth pulp-elicited jaw-opening reflex, and its reversal by atipamezole (A = 1 mg/kg of atipamezole) Notice that different thresholds display differential sensitivity to medetomidine The empty bar the threshold to a single stimulus pulse The striped bar the threshold to a double pulse of short (4 ms) interstimulus interval (in-field facilitated response) The dotted bar the threshold to the second stimulus of a double pulse with a long (40 ms) interstimulus interval The threshold to the first stimulus of a double pulse with a long interstimulus interval is not shown since it equals the threshold to single stimulus pulses (empty bar) Also notice that the difference between the empty bar (threshold to single pulses) and the dotted bar (threshold to the second stimulus of a pair, 40 ms interstimulus interval) is an index of in-field inhibition. The difference between the empty bar and the dotted bar (= in-field inhibition) was significant only in the first control condition (0 μg/kg) The error bars represent S E.M (n = 8, except at the dose of 30 and 55 μg/kg n = 4) The black dots above the error bars indicate a statistically significant difference from the corresponding control (= 0 μg/kg, *t*-test, $p<0$ 05) Threshold measurements were made 15 min after the application of each drug dose

threshold for single pulses and double pulses of 4 ms interstimulus interval) was still significant at the 55 μg/kg dose. Concerning the comparison of thresholds obtained at the medetomidine dose of 100 μg/kg, it should be noted that in some cases the thresholds were higher than the highest stimulus intensity used in this study (50 μA) the threshold value 50 μA has been assigned in cases the threshold was ≥50 μA. Thus due to the ceiling effect it is not possible to compare reliably the effect of 100 μg/kg medetomidine on thresholds obtained using single pulses with those obtained using double pulses. Due to the ceiling effect the threshold elevations produced by 100 μg/kg of medetomidine may be actually higher than shown in the Fig 2.

Atipamezole (1 mg/kg) produced a significant reduction of all medetomidine-induced threshold elevations ($p<0.05$, *t*-test). However, the atipamezole dose used did not produce a total reversal of all medetomidine-induced threshold elevations as revealed by the higher threshold for single pulses after atipamezole than in the predrug control conditions ($p<0.05$, *t*-test) Similarly, the index of in-field inhibition did not reach statistical significance following atipamezole.

The time course of the medetomidine effect (single dose of 100 μg/kg) and its reversal by atipamezole was separately studied in 4 cats The medetomidine effect was fully developed (in 2 cases no responses obtained at the maximal stimulus current of 50 μA) within 15 min, and the reversal of all three thresholds was significant within 15 min of the application of atipamezole (1 mg/kg, Fig. 3). In three separate cats atipamezole was not administered following the application of medetomidine. In these cats the thresholds remained high (>50 μA) for at least 30 min. This finding indicates that it was atipamezole and not the disappearance of the medetomidine effect per se that caused the reversal of thresholds shown in Fig 3.

Effect of Cocaine

The effect of cocaine was studied in 5 cats. The thresholds for single pulses and the threshold for the second pulse of the pair with a double pulse of 40 ms duration were slightly higher after cocaine, but none of these changes was significant even after the highest dose of cocaine (25 mg/kg; Fig 4).

DISCUSSION

Systemic medetomidine, an α-2-adrenoceptor agonist (41), produced a dose-dependent elevation of the threshold for the tooth pulp-elicited jaw-opening reflex in the pentobarbitone-anesthetized cat, and this elevation could be significantly reduced by ati-

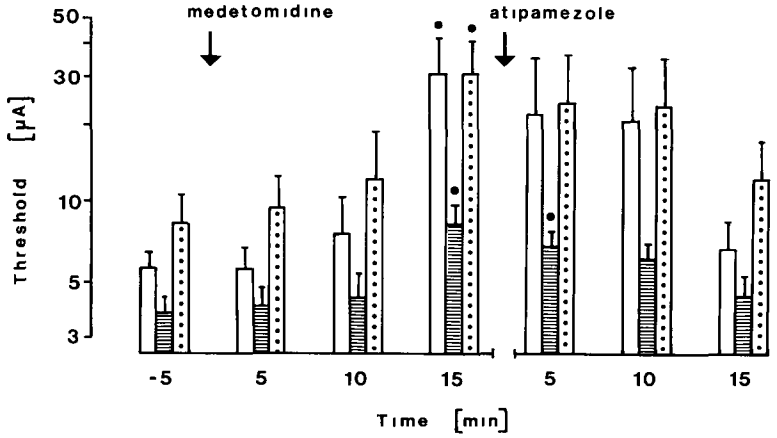

FIG 3 The time course of the effect of medetomidine (100 μg/kg) on thresholds for the tooth pulp-elicited jaw-opening reflex, and the time course of their reversal by atipamezole (1 mg/kg) n = 4 See the legend for Fig 2 for further explanations

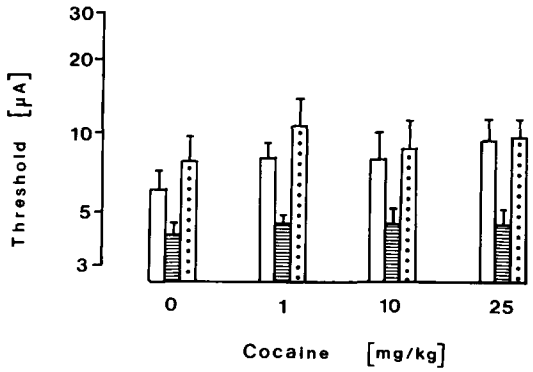

FIG. 4 Lack of significant cocaine-induced threshold elevations for the tooth pulp-elicited jaw-opening reflex n=5 For further explanations see the legend for Fig 2

pamezole, an α-2-adrenoceptor antagonist (33). This finding is in agreement with previous studies showing that systemic clonidine, a less selective α-2-adrenoceptor agonist, produces threshold elevations for tooth pulp-elicited jaw-opening responses in rodents (5,6) and dogs (12,36) as well as antinociceptive effects in various other tests (10, 12, 36). Also consistent with the present results is the finding that dexmedetomidine, a stereoisomeric form of medetomidine, potentiates the antinociceptive effect of halothane in a mechanically evoked nociceptive test in rats (34). However, in otherwise drug-free rats, the currently used medetomidine doses proved sedative but insufficient to produce a significant antinociceptive effect in a spinally organized nociceptive test (tail flick test); only a highly organized test of nociception (formalin test) was influenced (30). The currently used medetomidine doses are sedative but subanesthetic in cats (37) These findings suggest that under general anesthesia the activation of α-2-adrenoceptors, at least by medetomidine, at low (in itself sedative but subanesthetic) doses can significantly suppress spinally organized nociceptive reflexes but in awake animals higher (anesthetic) doses are needed to suppress spinally organized nociceptive reflexes (e.g , tail flick) In otherwise drug-free human subjects, experimental pain (cutaneous heat pain threshold, dental pain threshold, pain-intensity estimate of experimental ischemic pain) was not attenuated by sedative and hypotensive doses of systemic medetomidine with the exception of the affective-motivational component of experimental ischemic pain [=unpleasantness, (16)]. This finding in humans is consistent with the hypothesis that systemic medetomidine alone at subanesthetic doses predominantly suppresses nociception at supraspinal levels. Concerning the role of α-2-adrenoceptors in the effects produced by medetomidine, it should be recognized that medetomidine is an imidazole like clonidine It has been shown that imidazole receptors may be involved in some of the effects produced by clonidine (9). Thus a possibility remains that imidazole receptors are mediating some of the effects produced by medetomidine

In the current study we also tried to determine whether the response components involving synaptic inhibitory or facilitatory mechanisms have different sensitivities to medetomidine effects. Disappearance of the in-field inhibition was the most sensitive parameter of medetomidine effects in the current study Presynaptic mechanisms in the sensory part of the trigeminal nuclear complex might be involved in this in-field inhibition as shown by previous investigations (8), although we cannot exclude a contribution of postsynaptic mechanisms. The next sensitive parameter was the threshold for single electric pulses. The least sensitive parameter of medetomidine effects was the threshold to a double pulse of short (4 ms) interstimulus interval; this threshold is based on temporally summated and facilitated synaptic transmission which phenomenon can be seen at the level of the sensory trigeminal nuclear complex (28). Thus inhibitory synaptic mechanisms seem to be more sensitive to medetomidine effects than facilitatory synaptic mechanisms

In the current study, systemic cocaine did not produce a significant elevation of the tooth pulp-evoked jaw-opening reflex even at the highest dose used (25 mg/kg) which dose has proved to produce strong antinociceptive effects in different behavioral tests in rats (17, 29–31). The present finding is consistent with previous electrophysiological studies in rat which showed that electrically evoked nociceptive responses in spinal flexomotoneurons (26) and sensory projection neurons (32) are suppressed very little by an analgesic dose of cocaine (25 mg/kg). At supraspinal levels, the effect of cocaine on nociceptive neuronal responses has been strong, indicating that supraspinal mechanisms may have the major role in cocaine analgesia (1, 2, 31). There is some evidence that spinally organized nociceptive reflex activity evoked by natural stimuli (which produces a less synchronized afferent volley than electric stimuli) may be significantly suppressed due to cocaine-activated descending medullo-spinal inhibitory pathways (3); thus a possibility remains that a stronger effect of cocaine had been seen with natural noxious stimuli which should evoke a less synchronous afferent volley than the currently used electric pulses. Cocaine is known to produce a reuptake inhibition of various monoamines (14). The reuptake inhibition of norepinephrine should produce a consequent activation of α-2-adrenoceptors. However, cocaine did not produce a significant suppressive effect on the jaw-opening reflex as did medetomidine, an α-2-adrenoceptor agonist. This difference in the effects of medetomidine and cocaine is difficult to explain. It may be that the activation of α-2-adrenoceptors following cocaine is not as strong as that caused by medetomidine. Moreover, a previous study has shown that cocaine-induced antinociceptive effect in rat is not attenuated by a specific α-2-adrenoceptor antagonist (30), whereas in another study specific dopamine-receptor antagonists effectively attenuated cocaine-induced antinociception indicating a major role for dopaminergic mechanisms in cocaine-induced analgesia (17).

Electrophysiological studies of primary afferent fibers indicate that the sensory innervation of the tooth pulp consists of slowly conducting A δ- and C-fibers, although some fast conducting, possibly mechanoreceptive, fibers have been encountered (4, 7, 22, 39). The tooth pulp-evoked jaw-opening reflex is generally considered to be a predominantly nociceptive reflex, although a liminal reflex response can be elicited at nonnoxious stimulus intensities (20, 22, 27). Similarly, a nonnoxious "prepain" sensation has been reported in response to low-intensity stimulation of the tooth pulp in human studies although at higher stimulus intensities only a pain sensation is reported (18, 35, 40). In the current study the reflex thresholds with medetomidine were higher than the thresholds of nociceptive intradental fibers (39) which indicates that in the current study not only the possibly nonnociceptive component of the reflex but also the nociceptive component of the reflex was suppressed by medetomidine. Since the jaw-opening reflex is a disynaptic trigeminal reflex (38), medetomidine did have a suppressive effect at the trigeminal nuclear level either directly or indirectly through the activation of descending inhibitory pathways. However, since the effects of studied drugs need not be selective on sensory (nociceptive) neurons to produce a suppression of nociceptive reflexes (25), further neurophysiological studies are needed before it is possible to conclude whether the α-2-adrenoceptor-induced suppression of the jaw-opening reflex evoked by noxious stimuli is due to effects at sensory, interneuronal, motoneuronal or at all of these levels. Interestingly, in a recent electrophysiological study it was shown

that systemic clonidine can inhibit nociceptive neuronal responses in the presumed sensory-relay neurons of the spinal dorsal horn in the rat (23). Furthermore, local intrathecal or iontophoretic applications of α-2-adrenergic agents to the spinal cord have proved to produce antinociceptive effects in several previous studies (11, 24, 43). Also intrathecal application of dexmedetomidine has had antinociceptive effects in two recent investigations (15,21). Thus it is possible that in the current study systemic medetomidine produced antinociceptive effects through the same mechanisms which are activated by spinal applications of α-2-adrenergic agonists

ACKNOWLEDGEMENTS

This study was supported by the Pro Sanitate Studiosorum Foundation, Helsinki, and the Academy of Finland

REFERENCES

1 Belczynski, C R , Jr , Pertovaara, A , Morrow, T J., Casey, K L The effect of systemic cocaine on the responses to noxious stimuli and spontaneous activity of medial bulboreticular projection neurons Brain Res 527 204–212, 1990
2 Belczynski, C R , Jr , Pertovaara, A , Morrow, T J , Casey, K L The effect of systemic cocaine on spontaneous and nociceptively-evoked activity of neurons in the medial and lateral thalamus Brain Res 517 344–346, 1990
3 Belczynski, C R , Jr , Lin, Y , Neumann, S , Morrow, T J , Casey, K L Supraspinal mediation of cocaine analgesia in the rat Soc. Neurosci Abstr 15 548, 1989
4 Cadden, S W , Lisney, S J W , Matthews, B Thresholds to electrical stimulation of nerves in cat canine tooth pulp with Aβ, Aδ, and C-fibre conduction velocities Brain Res 261 31–41, 1983
5 Curtis, A L , Marwah, J Alpha 2 adrenoceptors modulate the nociceptive jaw-opening reflex in rats Exp Neurol 91 524–531, 1986
6 Curtis, A L , Marwah, J The nociceptive jaw-opening reflex Evidence for alpha 2 adrenoceptor involvement Pharmacol Biochem Behav 26 437–444, 1987
7 Dong, W K , Chudler, E H , Martin, R F Physiological properties of intradental mechanoreceptors Brain Res 334 389–395, 1985
8. Dostrovsky, J O , Sessle, B J , Hu, J W Presynaptic excitability changes produced in brain stem endings of tooth pulp afferents by raphe and other central and peripheral influences Brain Res 218 141–160, 1981
9 Ernsberger, P , Meeley, M P , Reis, D J An endogenous substance with clonidine-like properties selective binding to imidazole sites in the ventrolateral medulla Brain Res 441 309–318, 1988
10 Fielding, S , Spaulding, T C , Lal, H Antinociceptive actions of clonidine In Lal, H , Fielding, S , eds Psychopharmacology of clonidine New York Alan R Liss, Inc , 1981 225–242
11 Fleetwood-Walker, S M , Mitchell, R , Hope, P J , Molony, V , Iggo, A An α-2-receptor mediates the selective inhibition by noradrenaline of nociceptive responses of identified dorsal horn neurones Brain Res 334 243–254, 1985
12 Hayes, A G , Skingle, M , Tyers, M B Alpha-adrenoceptor-mediated antinociception and sedation in the rat and dog Neuropharmacology 25 391–396, 1986
13 Huopaniemi, T , Pertovaara, A , Jyvasjarvi, E , Carlson, S Effect of naloxone on tooth pulp-evoked jaw-opening reflex in the barbiturate-anesthetized cat Acta Physiol Scand 134 327–331, 1988
14 Johanson, C E , Fischman, M W The pharmacology of cocaine related to its abuse Pharmacol Rev 41 3–52, 1989
15 Kalso, E , Ihalainen, J , Poyhia, R , Rosenberg, P Antinociceptive effects of intrathecal dexmedetomidine in rats Pain 5 S106, 1990
16 Kauppila, T , Kemppainen, P , Tanila, H , Pertovaara, A Effects of systemic medetomidine, an alpha-2-adrenoceptor agonist, on experimental pain in humans Anesthesiology 74 4–9, 1991
17 Lin, Y , Morrow, T J , Kiritsy-Roy, J A , Terry, L C , Casey, K L Cocaine evidence for supraspinal, dopamine-mediated, nonopiate analgesia Brain Res 479 306–312, 1989
18 McGrath, P A , Gracely, R H , Dubner, R , Heft, M W Non-pain and pain sensations evoked by tooth pulp stimulation Pain 15 377–388, 1983
19 MacDonald, E , Scheinin, H , Scheinin, M Behavioural and neurochemical effects of medetomidine, a novel veterinary sedative. Eur J Pharmacol 158 119–127, 1988
20 Mason, P A , Strassman, A , Maciewicz, R Is the jaw-opening reflex a valid model of pain? Brain Res Rev 10 137–146, 1985
21 Nagasaka, H , Yaksh, T L Effects of the alpha-2 agonists medetomidine and ST-91 on the tail-flick and cardiovascular responses to a noxious thermal stimulus Soc Neurosci Abstr 15 547, 1989
22 Narhi, M V O The characteristics of intradental sensory units and their responses to stimulation J Dent Res 64 564–571, 1985
23 Ness, T J , Gebhart, G F Differential effects of morphine and clonidine on visceral and cutaneous nociceptive transmission in the rat J Neurophysiol 62 220–230, 1989
24 Ossipov, M H , Suarez, L J , Spaulding, T C Antinociceptive interactions between alpha-2-adrenergic and opiate agonists at the spinal level in rodents Anesth Analg 68 194–200, 1989
25 Paik, K S , Nam, S C , Chung, J M Different classes of cat spinal neurons display differential sensitivity to sodium pentobarbital J Neurosci Res 23 107–115, 1989
26 Pertovaara, A , Belczynski, C R , Morrow, T J , Casey, K L The effect of systemic cocaine on spinal nociceptive reflex activity in the rat Brain Res 438 286–290, 1988
27 Pertovaara, A , Huopaniemi, T., Aukee, K Tooth pulp-evoked jaw-opening reflex in the cat evidence for central facilitation induced by noxious discharge in the intradental nerve fibers Exp Neurol 92 207–219, 1986
28 Pertovaara, A , Huopaniemi, T , Carlson, S , Jyvasjarvi, E Response characteristics of tooth pulp-driven postsynaptic neurons in the spinal trigeminal subnucleus interpolaris of the cat comparison with primary afferent fiber, subnucleus caudalis, reflex, and sensory responses Brain Res 422 205–217, 1987
29 Pertovaara, A , Kauppila, T , Mecke, E An attempted reversal of cocaine-induced analgesia by dexamethasone Pharmacol Toxicol , in press
30 Pertovaara, A , Kauppila, T , Tukeva, T The effect of medetomidine, an α-2-adrenoceptor agonist, in various pain tests Eur J. Pharmacol 179 323–328, 1990
31 Pertovaara, A , Mecke, E , Carlson, S An attempted reversal of cocaine-induced antinociceptive effects by naloxone, an opioid antagonist Eur J Pharmacol , in press
32 Pertovaara, A , Tukeva, T Cocaine Effect on spinal projection neurons in the rat Brain Res Bull 25 1–6, 1990
33 Scheinin, H , MacDonald, E , Scheinin, M Behavioural and neurochemical effects of atipamezole, a novel α-2-adrenoceptor antagonist Eur J Pharmacol 157 35–42, 1988
34 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
35 Sessle, B J The neurobiology of facial and dental pain present knowledge, future directions J Dent Res 66 968–981, 1987
36 Skingle, M , Hayes, A G , Tyers, M B Antinociceptive activity of clonidine in the mouse, rat and dog Life Sci 31 1123–1132, 1982
37 Stenberg, D , Salven, P , Miettinen, M V J Sedative action of the α 2-agonist medetomidine in cats J Vet Pharmacol Ther 10 319–327, 1987
38 Sumino, R Central neural pathways involved in the jaw-opening reflex in the cat In Dubner, R , Kawamura, Y , eds. Oral-facial sensory and motor mechanisms New York Appleton-Century-Crofts, 1971 315–329
39 Virtanen, A Electrical stimulation of pulp nerves. comparison of monopolar and bipolar electrode coupling Pain 23 279–288, 1985
40 Virtanen, A , Huopaniemi, T , Narhi, M , Pertovaara, A , Wallgren, K The effect of temporal parameters on subjective sensations in electrical tooth stimulation Pain 30 361–371, 1987
41 Virtanen, R , Savola, J -M , Saano, V , Nyman, L Characterization

of the selectivity, specificity and potency of medetomidine as an α-2-adrenoceptor agonist Eur J Pharmacol 150 9–14, 1988
42 Virtanen, R , Savola, J -M , Saano, V Highly selective and specific antagonism of central and peripheral α-2-adrenoceptors by atipamezole Arch Int Pharmacodyn Ther 297 190–204, 1989
43 Yaksh, T L Pharmacology of spinal adrenergic systems which modulate spinal nociceptive processing Pharmacol Biochem Behav 22 845–858, 1985