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Are μ-opioid receptor polymorphisms important for clinical opioid therapy?

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Mutations in the μ-opioid receptor – the primary site of action of opioid analgesics – are candidates for the variability of clinical opioid effects. This has been substantiated by recent advances in genetic research. A common μ-opioid receptor polymorphism was associated with higher demands for alfentanil or morphine for pain relief. It also decreased the potency of morphine for pupil constriction and experimental analgesia, but its molecular mechanisms are unclear. Another opioid receptor mutation greatly impaired receptor signalling *in vitro*, but is very rare. The accumulated evidence provides a solid basis for continuing research that should address the underlying molecular mechanisms and the role and benefits of *OPRM1* genotyping for clinical pain therapy.

Introduction

Severe pain is therapeutically addressed with opioid analgesics. In addition to analgesia, these substances produce miosis, drowsiness, nausea and vomiting, constipation or respiratory depression. The degree to which these effects are observed in patients is variable. Several factors have been identified as or hypothesized to be the cause for this large inter-individual variability. With the recent advances in genetic research, inherited causes of the variability of opioid therapy have been investigated. The human μ-opioid receptor, which is coded by the *OPRM1* gene, is a primary candidate for the pharmacogenetic variability of the clinical effects of opioid analgesics [1] because it is the major site of action for most opioids that are established in clinical practice [2]. Mutations in the *OPRM1* gene, which is found on chromosome 6q24–q25, have been identified in the promoter, coding region and introns [3,4]. The mutations cause amino acid exchanges in the receptor protein (Figure 1) or possibly alternative splicing and, thus, alternative receptor variants or altered receptor expression. Recent findings of associations between *OPRM1* mutations and altered clinical opioid effects, and with the susceptibility for drug addiction, have encouraged expectations of an importance of *OPRM1* mutations for pain therapy.

A broader investigation of *OPRM1* mutations for pain therapy is complicated by the high number of naturally occurring *OPRM1* mutations. This makes it difficult to restrict the investigation to a few mutations for which sufficient cases can be gathered to judge their role in pain therapy. Twenty-four *OPRM1* mutations are reviewed here (Table 1 and Table 2). They have been selected because they meet one ore more of the following three criteria: (i) *in vitro* or human studies revealed a functional consequence, (ii) the mutation causes an amino acid exchange, thus resulting in an altered opioid receptor protein, or (iii) the single nucleotide polymorphism (SNP) has a high reported allelic frequency, so it might gain immediate clinical relevance for the administration of opioids in a larger part of the population.

Altered opioid binding and signalling in mutated μ-opioid receptors

The above selection criteria resulted in ten coding *OPRM1* polymorphisms (Table 1). For some of the mutated μ-opioid receptors, altered agonist binding or impaired receptor signalling have been shown (Box 1). The 118A>G SNP causes an amino acid exchange at position 40 of the μ-opioid receptor protein from asparagine to aspartate (N40D), leading to the loss of a putative N-glycosylation site in the extracellular receptor region. The affinity of β-endorphin was three times higher for the mutated than the non-mutated receptors in transfected AV-12 cells, whereas morphine binding was not affected [5]. However, others found no altered ligand binding by the mutated D40 μ-opioid receptors [6]. Moreover, it has been suggested that receptor signalling, measured as (D-Ala^2,N-MePhe^4,Gly-ol^5)-emkephalin (DAMGO)-stimulated GTPγS binding or cAMP accumulation, is not impaired in the mutated receptors on HEK293 cells [6,7].

In vitro evidence supports potential functional consequences of mutations affecting the second intracellular loop of the μ-opioid receptors. When replacing the threonine at position 180 of rat μ-opioid receptors with alanine, agonist-dependent receptor uncoupling was blocked. This could lead to altered receptor desensitization [8]. However, no naturally occurring mutations have been found for the threonine 182 in human μ-opioid receptors that correspond to the threonine 180 of rat receptors.

Agreement about the functional role of SNPs has been achieved for mutations affecting the third intracellular loop of the μ-opioid receptor. It has an amino acid sequence that is highly preserved among species, with complete conformity of the amino acids at positions 248–292 in

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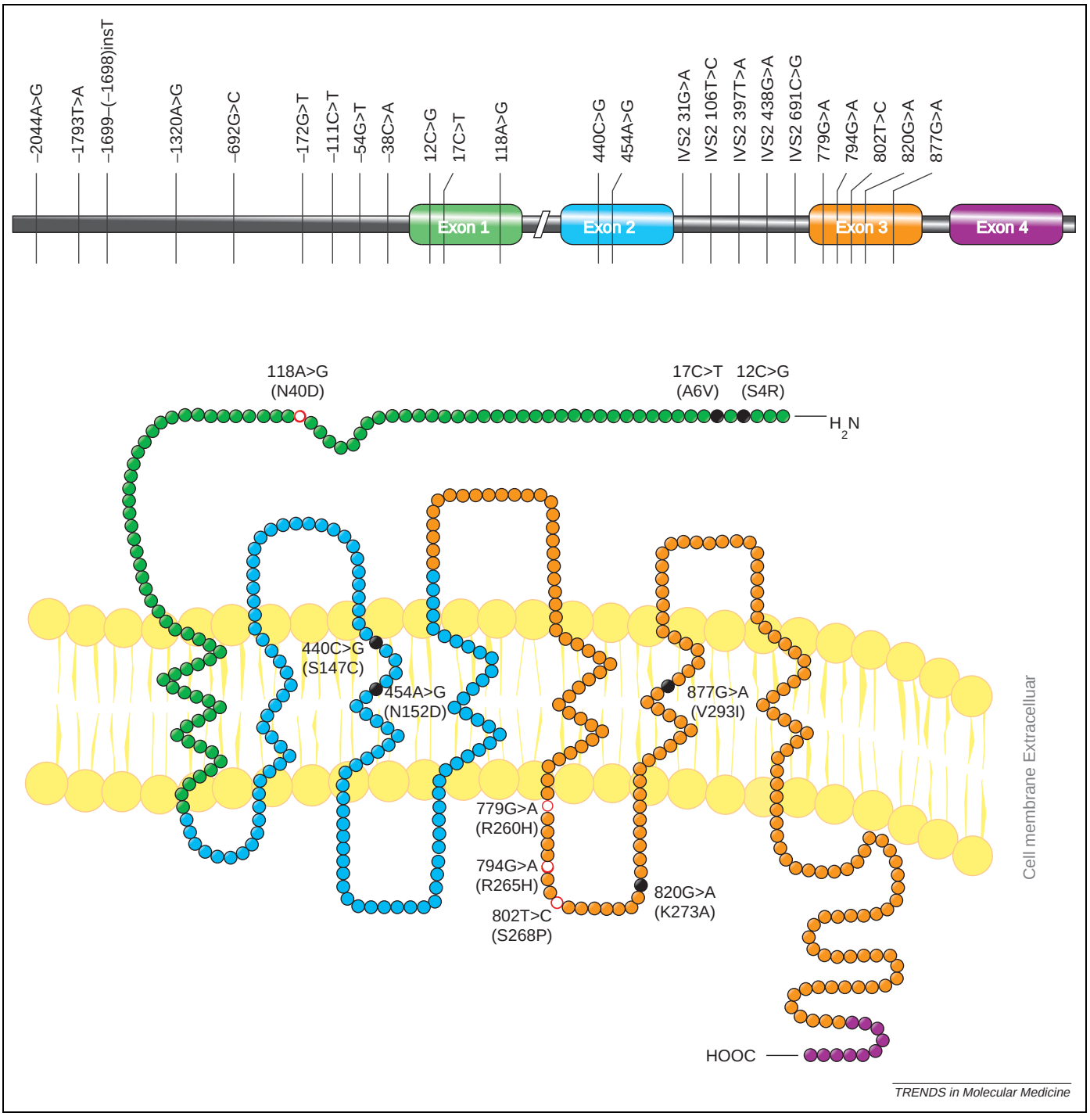

Figure 1. Reported mutations in the μ-opioid receptor related to the exonic organization of the *OPRM1* gene. Twenty-four mutations that produce an amino acid exchange and are frequently reportedly (>1%) or are proposed to have functional consequences are indicated in the gene. Amino acids are symbolized as circles, coloured according to the exons by which they are coded. Black circles represent a naturally occurring mutation at the respective position, and red circles when functional consequences are shown at molecular level. Mutations are indicated by the nucleotide exchange and the resulting amino acid exchange.

Box 1. Molecular consequences of naturally occurring μ-opioid receptor mutations

- Mutations in the extracellular receptor terminal: the 118A>G SNP occurs with a 10.5–18.8% allelic frequency [4,49] and codes for N40D mutant receptors. Inconsistent findings about consequences for agonist binding and receptor signalling have been reported: increased endorphin affinity at the N40D receptors [5] is not always seen [6], and only negative reports have been published about changes in the binding affinity of morphine and morphine-6-glucuronide [5,6] and changes in receptor signalling [6,7].
- Mutations in the third intracellular loop (allelic frequency ≪1%): result in impaired receptor signalling. The 802T>C SNP, which codes for S268P-mutant receptors with impaired agonist-induced receptor signalling, results in a 75% reduction of opioid efficacy, a twofold decrease in potency (GTPγS binding assay [7]) and the loss of Ca^{2+}/calmodulin-dependent protein-kinase-II-induced receptor desensitization [10]. The SNPs 779G>A and 794G>A, which code for R260H and R265H mutant receptors, respectively, result in reduced spontaneous receptor signalling [12].

Table 1. Studies on functional associations of ten *OPRM1* mutations that cause an amino acid exchange in the receptor protein, with studies addressing opioid therapy marked in blue[a]

Refs	Effect parameter		12C>G	17C>T	118A>G	440C>G	454A>G	779G>A	794G>A	802T>C	820G>A	877G>A
	Amino acid exchange		S4R	A6V	N40D	S147C	N152D	R260H	R265H	S268P	K273A	V293I
	Reported allelic frequencies [%][b]		–	1–10	10.5–18.8	< 1	1.4	< 1	< 1	< 1	< 1	< 1
Controlled studies		**Subjects**	**Exon 1**			**Exon 2**		**Exon 3**				
[29]	Cocaine/opioid abuse	110	○	+	○	○	○	○	○	○	○	○
[60]	Alcohol dependence	1480	○	○	–	○	○	○	○	○	○	○
[5]	Opioid dependence	300	○	+	–	○	○	○	○	○	○	○
[61]	Alcohol dependence	670	○	○	–	○	○	○	○	○	○	○
[55]	Alcohol, drug dependence	520	○	–	–	○	○	○	○	○	○	○
[56]	Alcohol dependence	230	○	○	+	○	○	○	○	○	○	○
[4]	Opioid dependence	250	○	+	–	○	–	○	○	○	○	○
[62]	Heroin addiction	540	○	○	–	○	○	○	○	○	○	○
[52]	Alcohol dependence	670	○	–	–	○	○	○	○	○	○	○
[53]	Alcohol dependence withdrawal	670	○	–	+	○	○	○	○	○	○	○
[64]	Tardive dyskinesia, schizophrenia	220	○	○	+	○	○	○	○	○	○	○
[17]	Analgesia	100	○	–	+	○	○	○	○	○	○	○
[32]	Heroin addiction	300	○	○	+	○	○	○	○	○	○	○
[63]	Alcohol, drug dependence	870	○	○	–	○	○	○	○	○	○	○
[21]	M6G miosis	12	○	○	+	○	○	○	○	○	○	○
[31]	Heroin addiction	300	○	○	+	○	○	○	○	○	○	○
[54]	Idiopathic generalized epilepsy	230	○	○	+	○	○	○	○	○	○	○
[50]	Cortisol response to naloxone	40	○	○	+	○	○	○	○	○	○	○
[66]	Anxiety-related traits	1530	○	○	–	○	○	○	○	○	○	○
[57]	Substance dependence	230	○	○	+	○	○	○	○	○	○	○
[67]	Naltrexone response in alcohol dependents	80	○	–	+	○	○	○	○	○	○	○
[22]	M6G miosis, analgesia	12	○	○	+	○	○	○	○	○	○	○
[51]	Cortisol response to naloxone	130	○	○	+	○	○	○	○	○	○	○
[34]	Opioid dependence	410	○	–	–	○	○	○	○	○	○	○
[68]	Opioid addiction, pain tolerance	110	○	○	○	○	○	○	○	○	○	○
[58]	Heroin addiction	500	○	+	+	○	○	○	○	○	○	○
[33]	Alcohol, drug dependence	680	○	○	○	○	○	○	○	○	○	○
[20]	M6G analgesia	16	○	○	+	○	○	○	○	○	○	○
[59]	Response to nicotine replacement therapy	320	○	○	+	○	○	○	○	○	○	○
[65]	Obsessive compulsive disorder	50	○	○	+	○	○	○	○	○	○	○
[69]	Personality factors	780	○	○	–	○	○	○	○	○	○	○
[70]	Alcohol dependence	250	○	○	+	○	○	○	○	○	○	○
[18]	Morphine analgesia	100	○	○	+	○	○	○	○	○	○	○
Case reports												
[23]	Morphine therapy, side effects	2	○	○	+	○	○	○	○	○	○	○
[19]	Morphine therapy	2	○	○	+	○	○	○	○	○	○	○
In-vitro experiments												
[5]	Receptor binding	0	○	○	+	○	○	○	○	○	○	○
[12]	GTPγS, cAMP	0	○	○	○	○	○	+	+	+	○	○
[7]	GTPγS, cAMP	0	○	○	–	○	○	○	–	+	○	○
[6]	Receptor binding, cAMP	0	○	○	–	○	○	○	○	○	○	○
[10]	Desensitization, G-protein coupling, cAMP	0	○	○	○	○	○	–	+	+	○	○

[a]○ = not found or not screened for, + = functional association, – = not associated with the studied effect parameter

[b][4,5,28,29,33,55,60,65]

humans, bovines, pigs, mice, rats, guinea pigs and rhesus monkeys. This region has a key role for G-protein coupling and receptor signalling [9]. DAMGO-induced receptor signalling was impaired in the S268P mutant receptor expressed in HEK293 cells, with a 75% reduction of DAMGO efficacy and a two-times decrease in DAMGO potency in the GTPγS binding assay [7]. The S268P mutation lies within a putative Ca^{2+}/calmodulin-dependent protein kinase II (CaMK II) phosphorylation site and results in the loss of CaMK-II-induced receptor desensitization [10]. Reduced receptor desensitization might cause persistent adenylyl cyclase activity with the promotion of compensatory mechanisms, leading finally to opioid tolerance [11]. Other mutations affecting the third intracellular loop, such as the 779G>A SNP (coding for R260H receptors) and the 794G>A SNP (coding for R265H receptors), have been associated with reduced spontaneous receptor signalling. This might be associated

Table 2. Studies on functional associations of 14 *OPRM1* mutations that do not cause amino acid exchanges but are frequent or have been proposed to have functional consequences, with studies addressing opioid therapy marked in blue[a]

Refs	Effect parameter		−2044C>A	−1793T>A	−1699−(−1698)insT	−1320A>G	−692G>C	−172G>T	−111C>T	−54G>T	−38C>A	IVS2−31G>A	IVS2−106T>C	IVS2−397T>A	IVS2−438G>A	IVS2−691C>G
	Reported allelic frequencies [%][b]		0.8	1.4	1.4	1.4	4.3	11.4	1.4	1.4–5	-	4.2–14.3	1.4	1.4	4.3	42.9
	Controlled studies	**Subjects**	**Promoter, 5′-UTR**										**Intron 2**			
[29]	Cocaine/opioid abuse	110	○	○	○	○	○	–	○	○	○	○	○	○	○	○
[60]	Alcohol dependence	1480	○	○	○	○	○	○	○	○	○	○	○	○	○	–
[5]	Opioid dependence	300	○	○	○	○	○	○	○	○	○	○	○	○	○	○
[61]	Alcohol dependence	670	○	○	○	○	○	○	○	○	○	○	○	○	○	○
[55]	Alcohol, drug dependence	520	○	○	○	○	○	○	○	○	○	○	○	○	○	○
[56]	Alcohol dependence	230	○	○	○	○	○	○	○	○	○	○	○	○	○	○
[4]	Opioid dependence	250	○	+	+	+	–	–	+	○	–	–	–	–	–	–
[62]	Heroin addiction	540	○	○	○	○	○	○	○	○	○	○	○	○	○	–
[52]	Alcohol dependence	670	○	○	○	○	○	–	–	○	–	○	○	○	○	○
[53]	Alcohol dependence withdrawal	670	○	○	○	○	○	–	–	○	–	○	○	○	○	○
[64]	Tardive dyskinesia, schizophrenia	220	○	○	○	○	○	○	○	○	○	○	○	○	○	○
[17]	Analgesia	100	○	○	○	○	○	○	○	○	○	○	○	○	○	○
[32]	Heroin addiction	300	○	○	○	○	○	○	○	○	○	○	○	○	○	+
[63]	Alcohol, drug dependence	870	○	○	○	○	○	○	○	○	○	○	○	○	○	○
[21]	M6g miosis	12	○	○	○	○	○	○	○	○	○	○	○	○	○	○
[31]	Heroin addiction	300	○	○	○	○	○	○	○	○	○	+	○	○	○	○
[54]	Idiopathic generalized epilepsy	230	○	○	○	○	○	+	○	○	○	○	○	○	○	○
[50]	Cortisol response to naloxone	40	○	○	○	○	○	○	○	○	○	○	○	○	○	○
[66]	Anxiety-related traits	1530	○	○	○	○	○	○	○	○	○	○	○	○	○	○
[57]	Substance dependence	230	○	○	○	○	○	○	○	○	○	○	○	○	○	○
[67]	Naltrexone response in alcohol dependents	80	○	○	○	○	○	○	○	○	○	○	○	○	○	○
[22]	M6G miosis, analgesia	12	○	○	○	○	○	○	○	○	○	○	○	○	○	○
[51]	Cortisol response to naloxone	130	○	○	○	○	○	○	○	○	○	○	○	○	○	○
[32]	Opioid dependence	410	○	–	–	–	○	○	○	○	○	○	○	○	○	○
[68]	Opioid addiction, pain tolerance	110	○	○	○	○	○	○	○	○	○	○	○	○	○	○
[58]	Heroin addiction	500	○	○	○	○	○	○	○	○	○	○	○	○	○	–
[33]	Alcohol, drug dependence	680	+	+	+	+	○	○	+	○	○	○	○	○	○	○
[20]	M6G analgesia	16	○	○	○	○	○	○	○	○	○	○	○	○	○	○
[59]	Response to nicotine replacement therapy	320	○	○	○	○	○	○	○	○	○	○	○	○	○	○
[65]	Obsessive compulsive disorder	50	○	○	○	○	○	○	○	○	○	○	○	○	○	○
[69]	Personality factors	780	○	○	○	○	○	○	○	○	○	○	○	○	○	○
[70]	Alcohol dependence	250	○	○	○	○	○	○	○	○	○	○	○	○	○	○
[18]	Morphine analgesia	100	○	○	○	○	○	–	○	○	○	–	○	○	○	–
Case reports																
[23]	Morphine therapy, side effects	2	○	○	○	○	○	○	○	○	○	○	○	○	○	○
[19]	Morphine therapy	2	○	○	○	○	○	○	○	○	○	○	○	○	○	○
***In vitro* experiments**																
[5]	Receptor binding	0	○	○	○	○	○	○	○	○	○	○	○	○	○	○
[12]	GTPγS, cAMP	0	○	○	○	○	○	○	○	○	○	○	○	○	○	○
[7]	GTPγS, cAMP	0	○	○	○	○	○	○	○	○	○	○	○	○	○	○
[6]	Receptor binding, cAMP	0	○	○	○	○	○	○	○	○	○	○	○	○	○	○
[10]	Desensitization, G protein coupling, cAMP	0	○	○	○	○	○	○	○	○	○	○	○	○	○	○

[a]○ = not found or not screened for, + = functional association, – = not associated with the studied effect parameter.

[b][4,5,28,29,33,55,60,65]

with altered opioid tolerance and dependence [12], but such a consequence of the mutations has not yet been shown.

Finally, the third extracellular loop of the μ-opioid receptor has an important role for ligand binding [13]. However, the only reported mutation in that receptor portion, the 942G>A SNP, does not lead to an amino acid exchange (Figure 1). For the remaining coding polymorphisms, 12C>G, 17C>T, 440C>G, 454A>G, 820G>A and 877G>A, no information about their consequences for ligand binding or receptor function has been reported.

Mutations in non-coding parts of the *OPRM1* gene have been scanned for possible consequences for μ-opioid receptor expression or transcription, although the

information on possible consequences for receptor expression or splicing is incomplete. The −1793T>A SNP is localized at a potential binding site for a yin yang-1 box (YY1) and −1699−(−1698)insT occurs at an AP-1 binding site [14]. In addition, an allelic variation at position −557, within a binding site for NF-κB, was proposed to affect the regulation of the *OPRM1* gene [15]. However, such a mutation was not found in genetic screening studies. The −995C>A SNP [4] involves the binding motif for STAT6 at nucleotide position −997 [16], which participates in interleukin-4-mediated μ-opioid receptor upregulation for peripheral opioid analgesia and immunosuppressive opioid effects. Finally, the more frequent mutation IVS2–31G>A SNP in intron 2 involves an A/TGGG motif [14], which might offer a possibility for the altered splicing of μ-opioid receptors: this remains to be demonstrated.

Taken together, evidence points to the 118A>G polymorphism as being potentially important for pain therapy. Other mutations alter receptor function but are rare (e.g. those affecting the third intracellular loop) or the current knowledge about their molecular consequences is insufficient to conclude the probable therapeutic importance.

Therapeutic consequences of the 118A>G polymorphism

Several lines of evidence indicate that N40D-mutated μ-opioid receptors alter the clinical response to opioids (Box 2). Carriers of the mutated 118G allele needed more alfentanil but had less pain relief than non-carriers [17]. Patients with cancer who were homozygous for the 118G allele required higher morphine doses for pain relief than did non-carriers or heterozygous carriers of the mutation [18]. One patient who did not respond to high doses of morphine was heterozygous for the mutated *OPRM1* 118G allele [19]. In addition, morphine-6-glucuronide (M6G), which is an active metabolite of morphine, had a lower analgesic potency in 118G carriers [20]. Moreover, M6G [21] and morphine [22] constricted pupils, another opioid-related effect, with a decreased potency in 118G carriers [22]. These findings suggested that the 118A>G polymorphism results in a less effective opioid analgesia. However, a homozygous carrier of the mutated 118G allele, who had renal failure and received morphine for pain treatment, tolerated the accumulated plasma levels of M6G surprisingly well [23]. In addition, healthy carriers of the 118G allele vomited less often after M6G administration than did non-carriers of the mutation [22]. This resulted in the hypothesis that the 118A>G SNP protects against opioid side effects. Taking the clinical evidence together, there are more positive than negative reports about a therapeutic consequence of the 118A>G SNP (Table 1). Its significance for pain therapy might lie in both an increase in opioid demand to achieve analgesia and the protection against opioid toxicity, resulting in a broadened therapeutic range of opioid analgesics (i.e. a greater distance between the opioid doses producing the clinically desired effects and doses producing unwanted side effects).

The 118A>G mutation is located in exon 1 of the μ-opioid receptor gene. Interestingly, antisense targeting of exon 1 of the μ-opioid receptor genes in mice decreased the anti-nociceptive effects of morphine but not those of M6G [24]. Moreover, the inhibition of gastrointestinal transit was blocked by an antisense probe against exon 4 but not by antisense probes directed against exon 1 [24]. Thus, splice variants of the μ-opioid receptor have different consequences for opioid analgesia and for other opioid effects [25], and they have different consequences for different opioids. For the mouse μ-opioid receptor gene, ten exons and 14 splice variants have been identified and investigated for functional consequences [25]. The identification of novel splice variants [26,27] and new exons in the human *OPRM1* gene [27] suggest that the complex splicing of opioid receptors extends to humans and the current four-exon structure (Figure 1) might not be complete. In analogy to mice, this increased complexity of human opioid receptors raises the possibility that mutations of the *OPRM1* gene differently affect opioid analgesia and opioid side effects, and these pharmacogenetic modifications are not necessarily the same for all μ-opioid agonists established in clinical practice.

Box 2. Effects of the 118A>G *OPRM1* polymorphism

- Causes an amino acid exchange at position 40 from asparagine to aspartate (N40D).
- Carriers need more alfentanil for postoperative pain relief [17].
- Carriers needed more morphine for cancer pain treatment [18].
- Decreased miotic potency of morphine [22] and of the active metabolite of morphine, morphine-6-glucuronide (M6G) [21,22].
- Increased demands of M6G to produce analgesia but less frequent vomiting despite slightly higher doses of M6G [22].
- Good tolerance of high M6G plasma concentrations during morphine therapy in patients with renal failure (case report [23]).
- Decreased analgesic response to morphine (case report [19]) and M6G [20].
- Impaired responsiveness of the hypothalamic–pituitary–adrenal axis in 118G carriers [50,51].
- The increased endorphin affinity at the N40D receptors [5] is not always seen [6]. Only negative reports have been published concerning the binding affinity of morphine [5,6] and morphine-6-glucuronide [6] and of altered receptor signalling [6,7].

Other *OPRM1* mutations with potential clinical importance

OPRM1 mutations have been investigated for association with substance abuse or addiction and for association with neurological or psychiatric disorders (Table 1 and Table 2). Most evidence for a functional association is available for the 118A>G polymorphism. In addition, the 17C>T SNP in exon 1 (which has an allelic frequency up to 10% [5,28,29]) was more frequent in substance abusers at marginal significance levels ($p=0.054$ [5] or $p=0.05$ [29]). However, there are more negative than positive reports of a functional association with the 17C>T SNP (Table 1). For −172G>T and IVS2–691C>G, more negative than positive reports of functional associations are available, and IVS2–31G>A has rarely been included in an analysis (Table 2). As for other genetic associations [30], *OPRM1* haplotype analysis was sometimes superior to SNP analysis in the context of drug addiction [4]. Haplotypes involving mutations −1793T>A, −1699−(−1698)insT, −1320A>G, −111C>T and 17C>T [4], the 118G and

IVS2–31A alleles [31], the 118G and IVS2–691G alleles [32] or haplotypes that include the −2044A allele [33] have been associated with susceptibility for substance dependence or altered drug consumption habits in addicts. The concept of *OPRM1* haplotypes might have potential for functional associations in pain therapy. To gain clinical relevance in pain therapy, the mutations or haplotypes should be found in a relevant proportion of pain patients – for example, an allelic frequency of 5% might be a reasonable minimum – to merit the additional effort of routine genotyping. The rarity of most *OPRM1* mutations limits the number with a potentially important impact on pain therapy. Of the 24 *OPRM1* SNPs that cause an amino acid exchange in the receptor protein or were proposed to be of functional consequence or occurred frequently (Table 1 and Table 2), only five SNPs have a reported frequency of at least 5%, namely −172G>T, 17C>T, 118A>G, IVS2–31G>A and IVS2–691C>G. To this, the *OPRM1* haplotypes could be added, but because a haplotype cannot be more frequent than the rarest allele of which it is composed, the number of *OPRM1* haplotypes that are important for pain therapy is limited. In this context, ethnic differences in the distribution of *OPRM1* SNPs and haplotypes [4,34] must be regarded. Because, for example, some *OPRM1* polymorphisms are more frequent in Africans than in Caucasians [34], the number of potentially relevant alleles might increase depending on ethnicity. For example, the −1793T>A and −1320A>G SNPs had an allelic frequency of ~9% in African Americans [34]. For both alleles, associations with substance dependence have been proposed [4,33] but also denied [34].

Other factors affecting opioid therapy

From studies in laboratory animals it is known that the genetic background is important for analgesia and has a strong influence on the responses to nociceptive stimuli and their modulation by opioids (reviewed in [35–37]). For example, 11 different inbred mouse strains displayed a different pattern of nociceptive behaviour in response to 12 measures of nociception [38,39]. Genetic differences were also seen in the anti-nociceptive activity of endogenous or exogenous opioids. Distinct mouse strains differed with respect to morphine anti-nociception in different pain models [40]. Moreover, mice strains have been bred that exhibit high- or low-magnitude anti-nociception after swim stress [40] and some strains, such as CXBK mice, even displayed deficient or absent morphine anti-nociception [41]. Some of the genes involved in the different perception and processing of nociceptive stimuli or the different response to opioids have been identified. For example, polymorphisms in the *HTR1B* gene, which codes for serotonin receptors type 1B, have been proposed to be associated with differences in sensitivity to morphine anti-nociception between mouse strains [42]. Naloxone-reversible opioid anti-nociception induced by swim stress was absent in transgenic mice with a selective deficiency of β-endorphin [43]. In addition, mice lacking brain cholecystokinin-A receptors showed an enhanced anti-nociceptive response to electro-acupuncture [44]. In these and other systems relevant for nociception and pain perception, mutations in the human genome have been described. For example, individuals expressing a catechol-O-methyltransferase (COMT) with a methionine instead of a valine at protein position 158 (V158M polymorphism) showed diminished regional μ-opioid system responses to pain compared with heterozygotes [45], and these effects were accompanied by higher sensory and affective ratings of pain.

Additional genes modifying opioid therapy

The clinical response to opioids is not only subject to modified receptor activity. It might also be altered by genetic polymorphisms affecting the pharmacokinetics of the opioid by altering its metabolism or distribution. A well-known example for a mutation affecting opioid biotransformation is the inability of codeine to produce analgesia in subjects bearing mutations in the *CYP2D6* gene [46]. Owing to the inactivity of the CYP2D6 enzyme in 7% of the Caucasian population, codeine is not metabolized to morphine. Because codeine is only a very weak agonist at μ-opioid receptors [47], its clinical actions are nearly exclusively mediated by morphine. Therefore, in patients not expressing functional CYP2D6, codeine provides no pain relief. To a lesser extent, *CYP2D6* polymorphisms also affect tramadol, which is metabolized by CYP2D6 into the active O-desmethyltramadol. Patients with nonfunctional CYP2D6 needed higher tramadol doses and were more often among those patients who needed rescue analgesic medication for postoperative pain relief than patients with the fully functional enzyme [48].

Concluding remarks

Many mutations of the human μ-opioid receptor gene have been reported. Clinical evidence indicates that the 118A>G SNP is an *OPRM1* polymorphism with consequences for opioid therapy. Its allelic frequency of 12%, with 3% homozygous carriers, makes it relevant for one in eight patients, because its effects are already present in heterozygous carriers. Patients carrying the 118A>G polymorphism might require higher opioid doses to achieve similar analgesia to non-carriers but could benefit from the mutation by a broader therapeutic range of opioid analgesics, at least for some opioid effects. So far, clinical evidence supporting this hypothesis is limited to a small number of opioids, to a limited number of clinical effects and has been obtained in a small sample size. Moreover, the findings regarding the molecular consequences of this polymorphism do not satisfactorily explain the clinical observations. However, with the recent advances in *OPRM1* pharmacogenetics, both clinical evidence and a molecular basis might be provided in the near future. A role for other *OPRM1* SNPs in opioid therapy has not yet been shown. Based on allelic frequency, only a few candidate *OPRM1* mutations (Box 3) merit closer interest with respect to their consequences for opioid therapy. Furthermore, *OPRM1* haplotypes, which so far have not been related to pain therapy, should be investigated and, in the context of ethnic differences, the addition of more polymorphisms is possible. With the current information available, the role of *OPRM1* genetics for pain therapy is likely to be resolved in the near future.

Box 3. Selected *OPRM1* polymorphisms with reported allelic frequency of at least 5%

- **–172G>T**: (allelic frequency 3.4–11.4% [4,49]) located in the 5′ untranslated region. The molecular consequences are unknown, but it does not appear to be associated with substance abuse [4,29,52,53]. It is associated with idiopathic absence epilepsy, especially when in a haplotype together with the 118A>G mutation [54].
- **17C>T**: (allelic frequency 1–10% [5,49]) located in exon 1 and causes an amino acid exchange from alanine to valine at receptor protein position six of the extracellular receptor terminal. It has been reported to occur in a higher overall proportion of opioid-dependent persons [5], but the majority of studies have reported no correlation with substance abuse [34,52,53,55]. It is not associated with decreased alfentanil analgesia [17].
- **118A>G**: (allelic frequency 10.5–18.8% [5]) located in exon 1 and causes an amino acid exchange from asparagine to aspartate at receptor protein position 40 of the extracellular receptor terminal. It has been both positively [32,53,56–59] and negatively [4,5,34,52,55,60–63] associated with substance abuse and is associated with other psychiatric and neurological disorders [54,64,65] and decreased opioid effects [17,21,22,50,51].
- **31G>A**: (allelic frequency 4.2–14.3 [4,31]) located in intron 2, involving an A/TGGG motif [14]. It is often found in a haplotype with the IVS2 691C>G polymorphism, and both the presence and absence of an association with substance abuse have been reported [31,62].
- **691C>G**: (allelic frequency 43% [4,60]) located in intron 2. Has not been associated with substance abuse [56,58,60,62].

This will provide the basis to judge whether, and to what extent, *OPRM1* genotyping could be a useful addition to pain therapy with opioids. It must also be noted that *OPRM1* is only one gene involved in pain treatment, and a genetically controlled analgesic therapy will probably have to include a variety of other genes that are important for opioid metabolism, distribution and pain perception and processing.

In conclusion, enough evidence has been accumulated during the last few years to indicate that μ-opioid receptor mutations cause inter-individual variability of the clinical effects of opioids. This provides a solid basis for continuing research. Investigations should address the underlying molecular mechanisms, especially those of the 118A>G *OPRM1* polymorphism, for which clinical evidence shows a functional relevance but *in vitro* studies have so far failed to provide a basis for this observation. Furthermore, clinical studies should address the role of *OPRM1* genotyping in the context of pain therapy, to identify patient populations that will benefit from a pharmacogenetically guided pain therapy.

References cited in Tables 1 and 2 but nowhere else in this article

Refs. [66–70].

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