Commentary

World views and Trojan horses in the sociobiology debate

1. The sociobiology debate

It is now over a quarter century since the famous sociobiology controversy began around Harvard zoologist Edward O Wilson's huge tome *Sociobiology*: *The New Synthesis*. In that book Wilson set out to document and synthesize several decades of new theoretical and empirical research on animal social behaviour. Sociobiology was defined as "the systematic study of the biological basis of all social behaviour". The idea was, that just like other features, behaviour, too, was undergoing evolution, which meant that it, too, could be included in the Neodarwinist paradigm, in which evolution is expressed as a change in gene frequencies in populations. Wilson hoped to continue the work of the architects of the Modern Synthesis, who aimed at putting evolutionary biology on a firm quantitative foundation.

There was good reason to deal with behaviour. The mystery of animal altruism had finally been cracked by people like William Hamilton, George Price, John Maynard Smith and Robert Trivers. A new "gene's eye's" perspective (made popular by George Williams' important 1966 book *Adaptation and Natural Selection*) now shifted the focus from the individual organism to groups of relatives who shared genes. With the help of cost-benefit calculations, and with an eye to the genetic relatedness between the donor and recipient of an altruistic act, it was now possible to show that from a gene's point of view it made sense for a bird, say, to sacrifice itself by letting out an alarm call, if it in this way could save a whole bunch of relatives.

What upset a large number of academics in 1975 was that Wilson went one step further than what seemed necessary. In his last chapter Wilson included also humans, and postulated hypothetical genes for all kinds of human behaviours. A group of academic critics, called the Sociobiology Study Group, which included Wilson's Harvard colleagues Stephen J Gould and Richard Lewontin, soon took action. They published a letter (Allen *et al* 1975) in the *New York Review of Books*, which linked the book to racism and Nazism and to a conservative political agenda. The most dramatic event was the 1978 meeting of the American Association for the Advancement of Science in Washington, where a group of activists from the International Committee against racism poured a pitcher of ice-water in Wilson's neck, shouting: "Racist Wilson, you can't hide, we charge you with genocide! and "Wilson, you are all wet!"

At the time many bought into the critics' view of sociobiology and Wilson's political motives. Few ever read his book, and even fewer asked about Wilson's real agenda – or, for that matter, about the critics' agenda. In 1975 it was clearly too early to even talk about the possibility of a biological basis for human behaviour. The "environmentalist" or culturalist paradigm reigned high, with people like Margaret Mead in anthropology and B F Skinner in psychology. And here now came Wilson suggesting that our human characteristics could actually have a genetic basis: all the way from sex role divisions and aggressiveness to moral concerns and even religious beliefs.

Over a quarter century the sociobiology debate has become a major transatlantic controversy over general principles of evolutionary biology, particularly such things as the unit of selection and the role of adaptation as an evolutionary force. Many of the initial players have remained, although lately it is Richard Dawkins and Steven J Gould, rather than Wilson and Lewontin, who have emerged as the chief combatants. The debate continues largely in a new guise as a conflict about "evolutionary psychology," a take-off from sociobiology. In this commentary I limit myself to one particular angle of

the complex controversy. Many more aspects of the sociobiology debate are covered in *Defenders of the Truth: The Battle for Science in the Sociobiology Debate and Beyond* (Segerstråle 2000).

2. Different views of "good science"

What attracted the participants in the sociobiology debate to this particular academic feud? In my research and interviews I have tried to document the deep-seated epistemological, metaphysical, and moral commitments that existed on both sides. My conclusion is that we had a case of total world views in conflict. Still, the protagonists were scientists first. Scientists are interested in one main thing: to promote their own view of "good science". They want to be right and to get recognition for it. And this was also the case in the sociobiology debate.

One of the important dividing lines between the two camps in the controversy had to do with different convictions about the nature of science. There was a conflict between different conceptions about the way science ought to be done, about the social utility of science and the responsibility of the scientist. But these concerns were not addressed in an explicit manner. Instead they were formulated in an indirect way, in the form of individual scientists accusing one another of doing "bad" or politically motivated science.

Researchers in the sociobiological camp found it quite unproblematic to develop scientific models using hypothetical genes "for" social behaviour – in the same way as psychometricians felt free to posit genes "for" various personality traits or intelligence. But this was absolute anathema for many of the opponents of sociobiology, who had been trained in the experimental laboratory tradition. For them, only "real" genes existed – that is, those they themselves were studying in their laboratories. The sociobiological modelers, again, saw their own scientific strategy as a very standard one, representing normal "good science" within the prevailing Neodarwinian paradigm, while they of course hoped that there would, indeed, turn out to exist actual genes roughly corresponding to the traits in their models.

3. Planters and weeders

The Sociobiology Study Group feared that scientific claims about genetic differences between individuals would be politically abused, because in people's minds 'biological' equalled '
and biology appeared as destiny. And there was the additional need for power holders to legitimize inequality and "to exonerate their institutions of responsibility for the problems they have created" (Lewontin 1975). In such a climate, Lewontin said, "any investigations into the genetic control of human behaviours is bound to produce a pseudo-science that will inevitably be misused".[1]

The question was what to do about it. One way to proceed could surely have been to educate the general public about the fact that biology was *not* destiny and about the importance of gene-environment interactionism instead of the false old nature-nurture opposition. This is not what the critics of sociobiology typically did, however. Instead they engaged in rather unusual work in the garden of science: they became meticulous, self-appointed 'weeders'.

Weeders, a minority among scientists, regarded it as their duty to debunk what they saw as other scientists' "bad science" in fields often far away from their own. These weeders were in direct opposition to the majority of 'planters', traditional scientists who believed that the goal of science was simply to produce new "positive" knowledge. Indeed, it came as a shock and surprise to many planters to be accused of "bad science" in this way. They could not imagine that what they saw as standard

[1]Indeed, policy-wise it was possible to point to such things as earlier eugenics ambitions and sterilization programmes based on purported state-of-the art scientific knowledge which later turned out to have been mistaken; and theory-wise one had only to mention the "mismeasurement" of skulls resulting in racist and sexist theories (Gould 1981), and various biologically based theories of racial supremacy.

science in their own field was exactly what weeders (coming from other fields) regarded as "bad" and socially pernicious science.[2]

Weeders used a number of different approaches. Stephen J Gould in a 'historic' treatise warned about earlier examples of the "mismeasure of man" and advocated "debunking" as a new, positive science (Gould 1981). Lewontin and his British colleague Steven Rose in *Not In Our Genes* (Lewontin *et al* 1984) explained why the factual claims of sociobiologists and IQ researchers were wrong about human nature being "in our genes". Scientific activists within Science for the People, such as Harvard molecular biologist Jon Beckwith, were involved in direct efforts to close down various types of "dangerous" research, such as an early study at Harvard Medical School intended to diagnose and follow up boys with an XYY ("criminal") genetic constitution (Davis 1986; Segerstråle 2000, ch. 11).

4. The sociobiology debate as politics by scientific means

But there was more to the sociobiology debate than a clash of total world views. I will now turn to strategical concerns in the debate – and that on both sides. I will consider two types of suggestions that have been made about the nature of the sociobiology controversy. One is that the science of sociobiology was simply "politics by other means". The aim of Wilson and other sociobiologists was to reinforce a conservative ideology by boosting the idea of "biological determinism". The other suggestion is more interesting, since it is more counter-intuitive. That is that the controversy would actually represent the opposite: science by political means. I will explore these in turn.

Let's start with the critics' accusations. Was Wilson's real aim with *Sociobiology* political? Their "sandwich model" of *Sociobiology* saw Wilson as strategically putting 500 pages on animals between his two all-important first and last chapters to camouflage his real message which had to do with humans. Wilson himself maintains that he was ignorant of a broader political interpretation when he wrote his book. Rather than stirring up the Marxists, he said, his aim was to provoke the social sciences into taking biology seriously (e.g. Wilson 1991, 1994 and interview in 1981). Wilson, in turn, dismissed the critics out of hand as "tabula rasa Marxists". For him, their opposition of sociobiology was purely political, and this applied also to Gould and Lewontin. In other words, both sides accused each other of doing politics by scientific means.[3]

5. The critique of adaptationism

But now I want to closely scrutinize Gould and Lewontin (1979), who were members of the activist Sociobiology Study Group, and later turned to a more comprehensive critique of "the adaptationist program". In their famous 1979 paper "The Spandrels of San Marco and the Panglossian Paradigm: A Critique of the Adaptationist Programme" they accused evolutionists of trying to demonstrate that every trait of every animal was perfectly adapted. They charged that adaptationists were just like Dr Pangloss in Candide, presenting this as the best of all possible worlds. (The point with using the architectural notion of spandrels was to demonstrate that such pan-adaptationism is not valid: a trait may simply have come about as a by-product of evolution acting on something else, just like four "spandrels" are automatically created by two arches crossing in the ceiling of San Marco in Venice).[4]

Indeed, adaptation had from the very beginning been made to sound as a political conspiracy. Already in their first letter the Sociobiology Study Group stated: "It is a deeply conservative politics, not an understanding of modern evolutionary theory that leads one to see the wonderful operation of

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[2]Planter-type scientists may or may not have thought that all science produced by their colleagues was necessarily 'good,' but they did not feel they needed to take action beyond their traditional scientific duties. They expected possible errors to be identified and eliminated in due time by the regular scientific process, and left it to the democratic social process to decide about the ultimate use of scientific knowledge.

[3]This he stands by today. For instance, in an interview in *Times Higher Education Supplement* June 2000 he dismisses Gould and Lewontin's attack on sociobiology as clearly politically motivated.

[4]Actually, the correct architectural term for those spaces is "pendentives", not spandrels, according to Dennett (1995).

adaptation in every feature of human social organization" (Allen *et al* 1975). Others have seen Gould and Lewontin's attack as purely political (e.g. Cain 1979; Queller 1995). In other words, both Wilson and his critics have been accused of conducting politics by other means. On this view, then, both camps were using claims and counterclaims about sociobiology as a Trojan horse for smuggling in and legitimizing certain political and ideological notions. But what if the political allegations actually were window-dressing for ambitions that were fundamentally *scientific*? It is this second type of Trojan horse strategy that we might call science by political means.

6. The sociobiology debate as science by political means

In this case Gould's and Lewontin's political involvement with sociobiology would have been a strategical maneuver aiming at gaining a later hearing for their basically scientific argument about adaptation. Gould and Lewontin used the political hubbub around sociobiology as a Trojan horse to attract interest to alternatives to "the adaptationist program". Their basic problem was how to create legitimacy for a scientifically unpopular idea that might have been easily rejected out of hand by fellow scientists – and by editors. (As Gould himself described it later: "We faced a special and unusual sort of problem in gaining attention and understanding for alternatives to adaptation. . . . How can you challenge something if most people simply regard it as true. . . .? You can't initiate this sort of reform from within, Gould 1993, p. 325).

Something had to be done to rattle the received view of evolution, but a standard publication was not an option. Gould and Lewontin's position was too far from prevailing orthodoxy. But there was a way. As Gould told a Science for the People meeting in 1984, he and Lewontin "opened up the debate by taking a strong position. We took a definitive stand in order to open up the debate to scientific criticism. Until there is some legitimacy for expressing contrary opinions, scientists will shut up." Gould seems to be saying here that the sociobiology controversy was merely a vehicle to bring about what was in reality desired: a serious scientific debate about adaptation, which could never have emerged on its own. What Gould and Lewontin did was to make the anti-adaptationist critique "interesting" to scientists through its moral/political connotations. Then they used this interest to gain journal space at least for critical "opinion papers". Later, the moral/political envelope could be removed and their critique of adaptationism considered in an unsupported form.[5]

Is it possible to apply a similar analysis to Wilson? What if Wilson, too, wanted to do science by political means, using this second type of Trojan horse strategy? After all, Wilson had put in several years' worth of work in his tome. Just like other academics, he wanted recognition. What better way than through a publicity campaign around *Sociobiology*? The question is only how far this campaign went. Actually, there already exists a type of Trojan horse theory involving Wilson. Some actually suspect that Wilson's last chapter on humans was deliberately aimed to generate scandal, and through this, interest in *Sociobiology* (e.g. Mazur 1981).

Still, *Sociobiology* would probably have sold well enough even without the controversy – just like Wilson's earlier *The Insect Societies* (1971), another large coffee table book. Also, most of his biological colleagues greatly appreciated his synthetic effort.[6] In other words, Wilson did not really need a scandal – although nobody doubts that the controversy greatly boosted sales. If anyone needed a scandal, that was Gould and Lewontin.

Admittedly, an analysis in terms of Trojan horses can easily take a surrealist turn. What happens if we apply the second Trojan horse model simultaneously to both sides in the sociobiology debate? We get a situation where scientists on both sides in a controversy are doing their best to create *political* scandal in order to promote their fundamentally *scientific* agendas. This means that we would actually

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[5]Gould himself argued that the scientific criticism required a number of extrascientific props (esthetic, moral, and so on) in order to be effective; that is why he mobilized spandrels and Candide (Gould 1993). Gould was the main author and delivered the paper (Gould 1993; Segerstråle 2000, ch. 6).

[6]In 1989 the international Animal Behavior Society "rated Sociobiology the most important book on animal behaviour of all time, edging out even Darwin's 1872 classic, *The Expression of the Emotions in Man and Animals*" (Wilson 1994, pp 330–331).

have an extraordinary case of synergy between the critics of sociobiology and their targets – all while the world thought they were at each others' throats! In fact, something like this did seem true for later stages of the debate, which I have characterized as symbiosis (Segerstråle 2000, chapter 3 and 16).

7. A nested hierarchy of Trojan horses

In reality I see something like a nested hierarchy of Trojan horses on both sides, a type of Russian doll situation with both sides pursuing their own moral and scientific agendas. For instance, Wilson's ambition to make sociobiology as quantitative and mathematical as possible can be seen as aimed to serve the moral agenda contained in his inner Russian doll. Wilson wanted to provide a materialist alternative to religion with the help of evolutionary biology (Wilson 1980). His other great ambition, his wish to unite the natural and social sciences, again, ultimately served his moral and practical goal of effective management of the Earth (as became clearer with *Consilience* 1998).

Let us now take a peek into the inner one of Gould's and Lewontin's Trojan horses. Here we have a scientific truth (anti-adaptationism) which contains inside itself a moral/political truth. It is hard to believe that Lewontin is talking strictly biology when he notes that "some significant fraction of evolutionary change has occurred without creating the best of all possible worlds" or that "the race is not to the swift nor the battle to the strong nor yet bread to the wise . . . but time and chance happeneth to them all" (Lewontin 1981). Gould, meanwhile, in a similar spirit, over the years has developed a number of objections to adaptation, from punctuated equilibria (Eldredge and Gould 1972; Gould and Eldredge 1977), to the notion of "exaptation" (Gould and Vrba 1982) to the emphasis on "contingency" in evolution (Gould 1989, 1996).

We have, then, two basic types of Defenders of the Truth. There are the naturalist sociobiologists, who think it is useful to consider hypothetical genes "for" behaviour in their evolutionary models, and the critics who protest that no such genes have ever been seen and should not be speculated about – even in the case of animals, but particularly in regard to humans. The battle continues. Meanwhile, many of the defenders are bestselling authors, and continue getting prizes and honorary doctorates. Wilson has no doubt won a victory: he is increasingly internationally celebrated. But his enemy Gould is also extremely popular. In 1999 he was elected the president of the American Association for the Advancement of Science; his books are popular bestsellers. And Gould has a quite different message for the public than Wilson, with conclusions that are comforting for many. Obviously, many truths can be defended at the same time. Controversy pays.

8. The sociobiology debate as a Trojan horse?

Finally, of course, we might analyse the controversy itself as a Trojan horse. What would be its function in this case? One answer is: to boost interest in evolutionary biology as a science, making this field exciting and relevant to the rest of the scientific community, funding agencies, and the general public, and on a par with molecular biology in scientific significance. On this view, the twenty-five year battle would be a joint public tribute by both sides to the Modern Synthesis and the importance of evolutionary biology – at the same time as they are quarreling among themselves about the true meaning of Neodarwinism (see Segerstråle 2000, ch. 16).

Another possibility is to see the sociobiology controversy as a kind of "dry run" for the discussion that is now emerging around the human genome – both its scientific and moral and political aspects. Clearly much of the forthcoming debate will have to do with the extent to which genes can really be said to represent "blueprints" and how much predictive value there is, in fact, in knowing the genetic makeup without detailed information about how these genes get actually expressed. (Here our old combatants have taken diametrically opposite positions, see e.g. Lewontin (2000 a, b) and Wilson 1998). In other words, the sociobiology debate with its hypothetical genes could be interpreted as mere scaffolding for the really important future debate about real genes. We may here have still one more Trojan horse – the biggest of them all.

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Commentary

The enigma of morphine tolerance: recent insights

1. Introduction

Pain has been described as a necessary evil. Necessary because it is a protective reflex and evil since lives have been made miserable due to it. Morphine and its related alkaloids are still the most effective analgesics in a physician's armoury for treating pain. However, many physicians hesitate to use opioids because of side effects – the primary reason being the development of tolerance and dependence on opioids. Other, equally detrimental effects are inhibition of gastrointestinal motility and respiratory depression. However, a general consensus among physicians has emerged that opioids – particularly long-acting opioids – should form the mainstay of treatment of chronic pain of both cancerous and non-cancerous etiology (McCarberg and Barkin 2001).

2. Tolerance and dependence

From the time that opioid receptors were demonstrated in the nervous system by Pert and Snyder (1973) opioid research over the last several decades has been directed towards understanding the mechanism of tolerance and dependence. Tolerance has been defined as reduced efficacy of a drug after repeated administration, while physical dependence is revealed by the occurrence of a withdrawl response on discontinuing the drug. In humans, withdrawl responses include fever, sweating, yawning, nausea, insomnia and piloerection. Piloerection causes goose flesh and is the origin of the term "cold turkey" used to describe the effects of opioid withdrawl (Rang *et al* 1999). Behavioural dependence is manifested by a craving for the drug. The underlying mechanisms of tolerance and dependence and their interrelationships are not well understood and the relevant literature contains a number of inconsistencies and contradictions (Fleming and Taylor 1995). However, recent research has been able to structure these phenomena into more clearly separable entities.

3. Mu receptor and analgesia

Morphine binds to the μ opioid receptor on the cell surface membrane to produce analgesia as also tolerance and dependence. The endogenous ligands for the receptor, are however, endomorphins (Zadina *et al* 1997) and enkephalins (Mansour *et al* 1995). Thus, the interesting feature of these receptors is that these are activated by both nonpeptide alkaloids like morphine as also structurally distinct, native peptides (Hughes and Kosterlitz 1977).

Opioid receptors are members of the G protein-coupled receptor (GPCR) family (Chen *et al* 1993). The G proteins, specifically activated by the opioid receptors, are the G_i/G_o subtypes, which in turn, increase potassium and decrease calcium levels within neurons (Law and Loh 1999). Consequently, opioids have an inhibitory effect – both in terms of neuronal excitability and neuro-transmitter release (North 1993).

4. Receptor turnover

In the normal course of agonist binding to a G protein-coupled receptor, initial desensitization occurs by phosphorylation (Freedman and Lefkowitz 1996). Phosphorylation of the receptor by G protein-

coupled receptor kinases or GRKs is sufficient to produce a small degree of desensitization (or loss of function) but substantial desensitization occurs only when a cytoplasmic protein called *b*-arrestin binds to the receptor (Kavoor *et al* 1997). There are at least 6 members of the GRK gene family, whose products phosphorylate serine and threonine residues on the GPCRs carboxyl tail (Freedman and Lefkowitz 1996). Threonine at position 394 of the *m* receptor is the primary recognition site for GRKs (Pak *et al* 1997). All GRKs share a common structural organization with a poorly conserved N-terminal domain of ~ 185 residues, a conserved protein kinase catalytic domain of ~ 270 residues and a variable length C-terminal domain of 105–230 residues (Krupnick and Benovic 1998).

The arrestins bind to phosphorylated G protein-coupled receptors and cause desensitization by uncoupling the signal transduction system. The arrestins are a class of soluble proteins that function in concert with GRKs. Visual arrestin was the first to be discovered (Kuhn *et al* 1984). Later, *b*-arrestin1 was identified, which could regulate signalling by the *b*-adrenergic receptor after phosphorylation (Benovic *et al* 1987). *b*-arrestin2 was cloned from bovine brain and was noted to be ubiquitiously distributed like *b*-arrestin1 (Sterne-Marr *et al* 1993). It appears that many of these kinases and arrestins are not receptor specific, inactivating many hundreds of different G protein receptors (Fain 1999).

Generally, for any G protein-coupled receptor, like the *b*-adrenergic receptor, *b*-arrestin directs the agonist-receptor complex to specific clathrin-coated pits for endocytosis (Ferguson *et al* 1996; Oakley *et al* 1999). However, it differs for the *m* receptor, depending on the agonist used. This has been shown in cultured human embryo kidney (HEK) cells transfected with *m* opioid receptor. Binding of etorphine, a nonselective opioid agonist to the receptor, results in the usual *b*-arrestin directed internalization. However, when morphine binds to the receptor, there is hardly any internalization of the receptor (Arden *et al* 1995). This was thought to be due to the lack of phosphorylation of the morphine-*m* receptor complex and *b*-arrestin binding (Zhang *et al* 1998).

5. Importance of internalization of GPCRs

The internalized receptors, sequestered within intracellular vesicles, dissociate from the agonist. The receptors are dephosphorylated by specific membrane associated phosphatases and returned back to the cell surface – a process known as resensitization. Again, *b*-arrestin plays a central role in this regard (Zhang *et al* 1997). It was thus thought that the absence of resensitization of the *m* receptor, upon morphine binding, might lead to receptor blockade and tolerance.

However, in between, an important finding went unnoticed. As long back as 1994, it was reported that following chronic morphine treatment in rats, there was an increase in G protein-coupled receptor kinase2 (GRK2) and *b*-arrestin levels in the locus coeruleus (Terwilliger *et al* 1994). *m* receptors are known to be expressed in the locus coeruleus (Mansour *et al* 1988). It was also shown by Zhang *et al* (1998) that overexpression of GRK2 leads to increased internalization of the *m* receptors ($51 \pm 3\%$) as compared to controls ($5 \pm 4\%$) on binding to morphine. It therefore appears that both GRK2 and *b*-arrestin may have a role in the desensitization of *m* receptors.

6. Recent insights

A paper by Bohn *et al* (1999) had earlier reported that in mice lacking the *b*-arrestin2 gene ($barr2^{-/-}$), the analgesic effect of morphine was more potent and prolonged as compared to controls. The *b*-arrestin2 knockout mice was generated by inactivating the concerned gene through homologous recombination. The generation of transgenic mice deficient in an identified gene, known as knockout mice, was first reported towards the end of the 1980s (Capecchi 1989). An altered and nonfunctional variant of a target gene is synthesized and transfected into pluripotent embryonic stem cells. Identical sequences shared by the native and foreign genes allow recombination to occur, with a chance for intergration of the nonfunctional transgene into some of the embryonic cells. The recombinant stem cells are injected into a blastocyst which is then implanted into a host mother (Nicholls *et al* 2001). The data, presented in the report demonstrated that *b*-arrestin2 does play a role in the eventual desensitization of the receptor. According to Bohn *et al* (1999), the earlier finding by Zhang *et al* (1998) which showed minimum phosphorylation and *b*-arrestin2 binding to the *m* receptor, may have been due to cultured cells being used in the latter study.

However, Sternini *et al* (1996) reported an *in vivo* study where there was no internalization of the *m* receptor in myenteric neurons of the guinea pig ileum after intraperitoneal administration of morphine. In contrast, etorphine triggered significant internalization. Myenteric neurons naturally express the receptor (Sternini *et al* 1995). A more recent study by Sternini *et al* (2000) also noted failure of *m* receptor endocytosis by morphine in ileal muscle-myenteric plexus preparations. It remains to be seen whether phosphorylation and *b*-arrestin2 binding to the *m* receptor is possible without internalization. Bohn *et al* (1999) also suggested that there could be other genetic variants of the *m* receptor, amenable to phosphorylation and *b*-arrestin binding. It was previously shown that the rat *m* receptor isoform rMOR (rat *m* opioid receptor)1 was more easily desensitized than rMOR1B (Hollt *et al* 1997).

Bohn *et al* (2000) recently reported that mice lacking the *b*-arrestin2 gene (*barr2*$^{-/-}$) as before, did not develop tolerance to both acute and chronic administration of morphine. As expected, the intracellular signal transduction mechanism was preserved in these *b*-arrestin2 knockout mice after morphine administration as was evident from [^{35}S]GTP*g*S binding. [^{35}S]GTP*g*S binding provides a functional measure of the efficacy of the signalling pathway after agonist occupation of *m* receptors (Traynor and Nahorski 1995). Notably, there was significant uncoupling in wild type mice. Uncoupling of the receptor from G proteins leads to disruption of the signal transduction mechanism, typically seen in morphine tolerance (Heyliger *et al* 2000). Morever, no significant differences were noted in the density of *m* receptors in brainstem-membrane preparations after chronic morphine administration, both in the wild type and *b*-arrestin2 gene knockout mice. We also observed no significant difference in *m* receptor density between morphine treated and control mice (Ray and Wadhwa 2001). Perhaps the most important finding by Bonn *et al* (2000) was that both groups of mice developed dependence to morphine as shown by an increase of adenylyl cyclase activity, a biochemical marker of dependence (Nestler and Aghajanian 1997).

The elegant series of experiments by Bonn *et al* (2000) have highlighted the role of *b*-arrestin2 in the mechanism of morphine tolerance and also shown that the molecular mechanisms of tolerance and dependence are different. However, developmental compensations are possible in specific gene knockout mice and it may not provide an answer to all problems which the traditional pharmacological approach has left unresolved (Kitchen 1999). Also some inconsistencies exist between different studies, which have to be addressed. For example, opioid receptor-like 1(ORL1) receptor knockout mice show attenuation of tolerance to morphine (Ueda *et al* 1997). Arden *et al* (1995) had reported a small increase of phosphorylation of the *m* receptor on morphine binding (1·8-fold) and the existence of basal phosphorylation, even in the absence of agonist.

It is possible that the role of *b*-arrestin2 is only part of the story, as earlier studies have shown that there are multiple converging cellular events leading to opiate tolerance (Dewey 2001). Other factors could be alterations in intracellular Ca^{2+} (Smith *et al* 1999), increased activity of anti-opioid peptides like nociceptin (Yuan *et al* 1999), increased glutamate in locus coeruleus (Aghajanian *et al* 1994), changes in NR1 subunit of NMDA receptor (Zhu *et al* 1999) and melatonin (Raghavendra and Kulkarni 1999). The ability to reverse morphine tolerance has important implications, which should lead to a better understanding of the mechanisms involved in its development (Dewey 2001). Further studies in this direction thus have great clinical potential.

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